Studies Directed Toward the Synthesis of Palau'amine and Axinellamines A-D

Thesis by

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To my parents

Acknowledgements

For the past four years Professor Erick Carreira has played the central role in my education. His enthusiastic teaching and consistently high expectations inspired me to learn and accomplish more than I thought I could. He opened my mind to the vast possibilities of synthetic chemistry and challenged me to think on my feet and approach problems with an intelligent eye and a creative mind. In so doing, he instilled in me great confidence in my ideas and the fortitude to argue for them. I will forever remember his unique and invaluable contribution to my career and to my life.

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Abstract

The use of spiro[2.4]hepta-4,6-diene-1-methanol **7** as a general precursor for the synthesis of highly functionalized cyclopentyl rings is described. Diene **7** was converted to its silyl protected 4-nitrile derivative **24** in 46% overall yield. The cyclopropyl ring of **24** reacted with soft carbanionic nucleophiles to give ring opened homo-conjugate addition products **25a-h** in 76-97% yield without loss of optical purity. The addition products could be further manipulated by selective mono-hydrogenation to give 1,2 substituted cyclopentenes **26a-e** in 85-96% yield.

Diene **7** was used as a starting material for studies directed toward the synthesis of the stereochemically dense chloro-cyclopentyl core of palau'amine **1**. Two advanced intermediates **50** and **72** were synthesized. Attempts to effect intramolecular chlorine transfer with **50** were unsuccessful. Attempted intramolecular chlorine transfer with **72** led, instead, to an oxygenated species resulting from oxygen radical trapping.

The enantioselective synthesis of the stereochemically dense chloro-cyclopentyl core of axinellamines A-D **2-5** starting from **7** is also described. The core is synthesized in 4.6% yield over 24 steps. Nakamura's radical dehalogenative hydroxylation is applied for the first time to a cyclopropyl carbinyl iodide to give the ring-opened product in 86% yield. Bolm's *meso*-anhydride desymmetrization is used to introduce asymmetry in a norbornene intermediate. The final step is a diastereoselective intermolecular chlorination using Barton's methodology to achieve chlorine transfer in 76% yield.

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List of Abbreviations

Ac = acetyl

AIBN = azobisisobutyronitrile

Bu = n-butyl

BuLi = n-butyl lithium

Bn = benzyl

Bz = benzoyl

cat. = catalytic amount of

Cbz = benzyloxycarbonyl

*m*CPBA = *meta*-chloroperbenzoic acid

Dbp = 4,5-dibromopyrrole-2-carboxyl

DEAD = diethylazodicarboxylate

$(DHQD)_2Pyr$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether

DMAP = 4-*N,N*-dimethylaminopyridine

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDC = 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

Et = ethyl

FTIR=Fourier Transfor Infrared Spectroscopy

equiv. = equivalents of

HOBt = *N*-hydroxybenzotriazole

HPLC = high performance liquid chromatography

HRMS=high resolution mass spectroscopy

Hünig's base = ethyldiisopropylamine

Hz = Hertz

J = coupling constant

L = liter

LAH = lithium aluminum hydride

LDA = lithium diisopropylamide

M= molar concentration

Me = methyl

MeOH = methanol

MHz = megahertz

min = minute

mL = milliliter

mmol = millimole

mol = mole

mol. sieves = molecular sieves

MOM = methoxymethyl

MP = melting point

N = normal (concentration)

NMR = nuclear magnetic resonance spectroscopy

PhCl = chlorobenzene

PhH = benzene

PhMe = toluene

PCC = pyridinium chlorochromate

Ph = phenyl

Pht = phthaloyl

PhtN = phthalimide

ppm = parts per million

Pr = n-propyl

pyr = pyridine

R_f = retention factor

TCA = trichloroacetyl

TCACl = trichloroacetyl chloride

TBS = *tert*-butyldimethylsilyl

TEA = triethyl amine

Tf = trifluoromethanesulfonyl

TFAA = trifluoroacetic anhydride

THF = tetrahydrofuran

TIPS = triisopropylsilyl

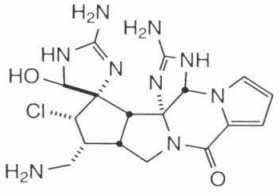
TLC = thin layer chromatography

TMS = trimethylsilyl

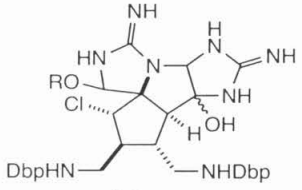
TPP = triphenylphosphine

I. General Introduction

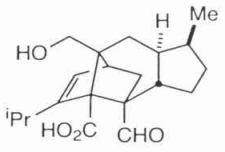
Substituted cyclopentanes are abundant in nature and are prominent substructures of natural products such as the alkaloids palau'amine **1**[1] and axinellamines A-D **2-5**,[2] the diterpene sordaricin **6**,[3] the aminocyclopentitol trehazolin **8**[4] (Figure 1), and others.[5] Identifying and developing new methodologies for the construction of complex cyclopentanes, therefore, increases the accessibility of these and other natural products via total synthesis.



1
palau'amine



2-5
axinellamines A-D



6
sordaricin

Figure 1. Cyclopentane containing natural products.

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[1] (a) Kinnel, R. B.; Gehrken, H. P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (b) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

[2] Urban, S.; Leone, P. D.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.

[3] (a) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595. (b) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 5718. (c) Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002. (d) SCH-57404: Coval, S. J.; Puar, M. S.; Phife, D. W.; Terraciano, J. S.; Patel, M. *J. Antibiot.* **1995**, *48*, 1171.

[4] Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R. *J. Antibiot.* **1991**, *44*, 1168.

[5] (a) allosamidin: Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 2475. (b) azadirachtin: Kraus, K.; Bokel, M.; Klenk, A.; Pohnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435. (c) bilobalide: Corey, E. J.; Su, W. -g. *J. Am. Chem. Soc.* **1987**, *109*, 7534. (d) mannostatin A: Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 882. (e) petiodial: Nakatsu, T.; Ravi, B. N.; Faulkner, D. J.; *J. Org. Chem.* **1981**, *46*, 2435. (f) streptazolin: Yamada, H.; Aoyagi, S.; Kibiyashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054.

A novel strategy employed by the Carreira laboratory involved optically active spiro[2,4]hepta-4,6-diene-1-methanol **7** as a template for stereoselective amination and hydroxylation reactions leading to the total synthesis of trehazolin **8** (Figure 2).[6] Despite its ease of synthesis and rich functionality, **7** had seen only limited application in synthetic efforts prior to this work. Most notably, Corey used racemic **7** in his synthesis of the 12-methylprostaglandin A_2.[7]

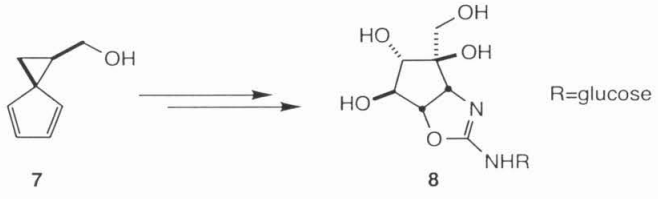
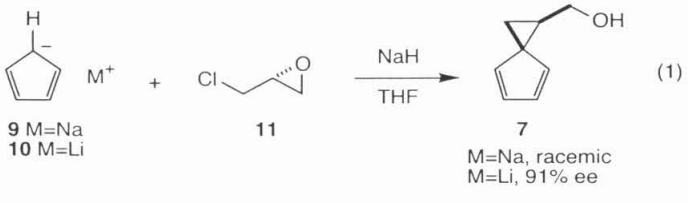


Figure 2. Carreira's synthesis of trehazolin.

In the trehazolin synthesis it was discovered that **7** could be made in non-racemic form by the use of optically active epichlorohydrin **11** and Li-cyclopentadienide **10** (Equation 1).[6] Use of Na-cyclopentadienide **9** with optically active **11** led to racemic **7** due to the poor regioselectivity of the initial nucleophilic addition step. The Li counterion presumably activates the epoxide of **11** for addition in preference to the alkyl chloride. Subsequent intramolecular opening of the resultant epoxide then gives non-racemic **7** in 91% ee.



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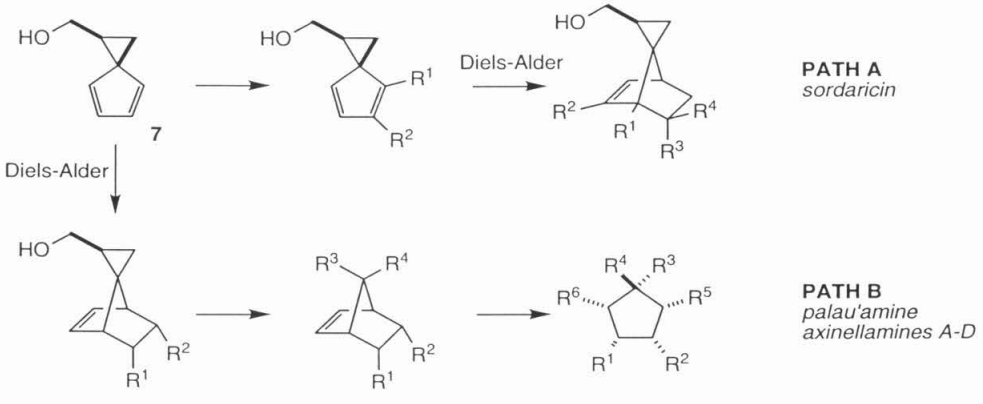
[6] Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811.

[7] (a) Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R. *Tetrahedron Lett.* **1975**, 1161. see also: (b) Corey, E. J.; Cheng, X.- M. *The Logic of Chemical Synthesis*, pg 291; **1989**, John Wiley & Sons: New York.

Our interest in capitalizing on this discovery led to the initiation of research directed at expanding the scope of **7** as a general precursor for the asymmetric synthesis of natural products containing complex cyclopentane cores. In particular, we focused on structures requiring functionalization with carbon substituents in hopes of complementing the methodology developed in the trehazolin synthesis for carbon-heteroatom bond formation.[6]

It was hypothesized that a Diels-Alder reaction could either follow (path A) or precede (path B) functionalization steps to provide access to a wide variety of cyclopentane structures from **7** as shown in Scheme 1.

Scheme 1



Contemporaneous with our own work, North and co-workers reported a similar strategy to that shown in path B for the general synthesis of highly substituted cyclopentanes containing up to five substituents (Scheme 2).[8] Their strategy relied on the Diels-Alder reaction of maleic anhydride with cyclopentadiene or TMS-cyclopentadiene to generate the meso-norbornene anhydrides **14** and **15**. A sequence of

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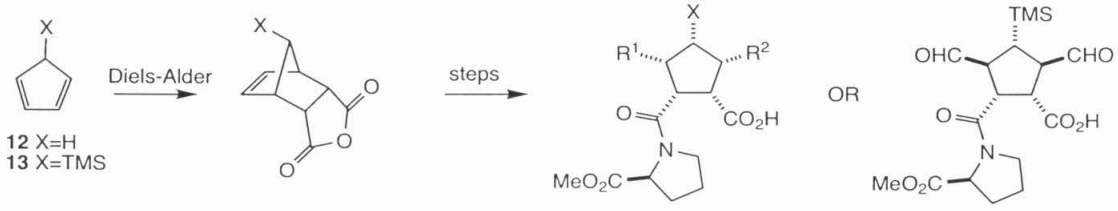
[8] Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Mali, K. M. A.; North, M. *J. Org. Chem.* **1999**, *64*, 5413.

asymmetric anhydride opening (with proline Me ester) followed by oxidative cleavage of the endocyclic olefin and subsequent functional group manipulations provided access to a wide variety of highly substituted cyclopentanes **16-18** in optically active form. When X=TMS, alternative stereochemistries were accessible by mild base promoted epimerization (K_2CO_3) of the aldehyde groups, exemplified by **18**.

Scheme 2



To explore these reaction pathways with **7**, synthetic studies inspired by sordaricin **6** and palau'amine **1** were initiated. During the course of that work, axinellamines A-D **2-5**[2] were reported and, due to their similarity to palau'amine **1**, their syntheses were investigated as well. The results of these studies are reported herein and are organized into sections according to the three natural products of interest.

Initial investigations into the nucleophilic and electrophilic functionalization of **7** (path A) are reported in section II. Further studies on the functionalization of post-Diels-Alder adducts of **7** (path B) are discussed in sections III and IV in the context of studies directed toward the syntheses of palau'amine **1** and axinellamines A-D **2-5**. A short conclusion is presented in section V and experimental procedures and data for sections II-IV follow in section VI. The sum of the work presented herein supports the hypothesis that **7** can be used as a general scaffold for the stereoselective synthesis of

complex, highly substituted cyclopentane compounds of relevance to natural products synthesis.

II. Nucleophilic Additions to Spiro[2.4]hepta-4,6-diene 1-methanol-4-nitrile.*

To expand the scope of spiro[2.4]hepta-4,6-diene-1-methanol **7** as a useful starting material for complex molecule synthesis, we undertook the synthesis of diene **20**, a possible intermediate in the synthesis of the antibiotic diterpene sordaricin **6** (Figure 3).[3] A late stage radical ring closure and a Diels-Alder reaction were key steps we envisioned could take advantage of the unique array of functionality provided by **7**. Entry into this synthetic plan thus began with an exploration of carbon-carbon bond forming reactions that could install the carbinol and isopropyl substituents of **20**.

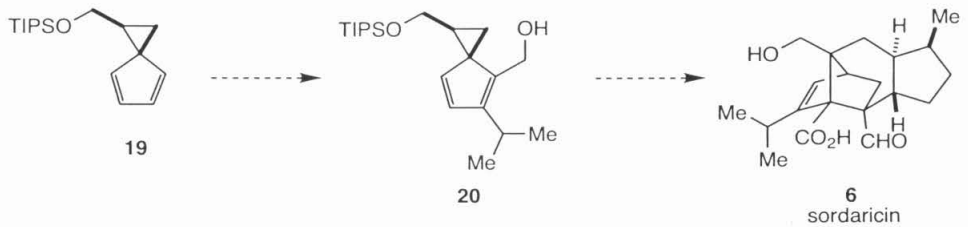


Figure 3. Key intermediates in a sordaricin synthesis.

It was found that triisopropylsilyl (TIPS) ether **19** reacted readily in [2+2] fashion with π-electrophilic agents to give the corresponding four member ring annulated products (Scheme 3).[9] Dimethyl ketene, generated in-situ (isovaleroyl chloride, TEA, DMF), reacted with **19** to give a chromatographically inseparable 1:1:1:1 mixture of the expected cyclobutanone products **21** in 66% yield whereas chlorosulfonyl

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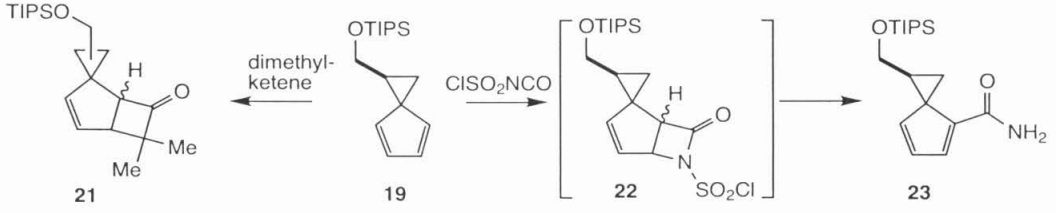
* The work reported in this section has been published. See: Starr, J. T.; Baudat, A.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 5675.

[9] Ketenes reacting with cyclic dienes: (a) Ohshiro, Y.; Ishida, M.; Shibata, J. I.; Minami, T.; Agawa, T. *Chem. Lett.* **1982**, 587. (b) Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311. Other ketene cycloadditions: (c) Baeckström, P.; Li, L.; Polec, I.; Unelius, R.; Wimalasiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358. (d) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (e) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 2920. (f) Xu, S. L.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094. (g) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752.

isocyanate (CSI) reacted with **19** to give the single 4-carboxamide **23** after hydrolytic cleavage of the intermediate chlorosulfonimide **22**.[10] The regioselectivity of addition is indicative of greater stabilization (through resonance) of the incipient cationic character at the 5 position during the cycloaddition and is consistent with the known regioselectivity of addition of CSI to dienes.[10]

Scheme 3



Conversion of carboxamide **23** to the corresponding 4-cyano derivative **24** was straightforward; however, **24** displayed unexpected reactivity towards nucleophiles (Table 1). Treatment of **24** with organo-magnesium or lithium reagents in the presence of CuI in attempts to perform ordinary conjugate addition led, instead, to chemoselective homoconjugate addition furnishing the corresponding ring-opened cyclopentadienes **25a-h** in 76-97% yield (Scheme 4).[11] The product dienes subsequently underwent selective reduction (H_2/10% Pd/C) to yield the 1,2-substituted cyclopentenes **26a-e**.[12]

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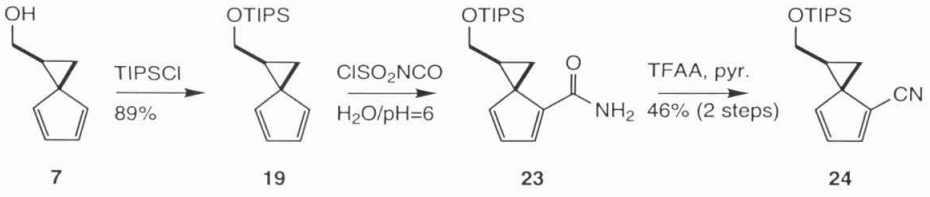
[10] Chemistry of chlorosulfonyl isocyanate: (a) Hassner, A.; Rasmussen, J. K. *Chem. Rev.* **1976**, *76*, 389. (b) Graf, R. *Angew. Chem., Int. Ed. Eng.* **1968**, *7*, 172. (c) Kaluza, Z.; Abramski, W.; Belzecki, C.; Grodner, J.; Mostowicz, D.; Urbanski, R.; Chmielewski, M. *Synlett* **1994**, 539. (d) Barton, T. J.; Rogido, R. J. *J. Chem. Soc., Chem. Commun.* **1972**, 878. (e) Bestian, H.; Biener, H.; Clauss, K.; Heyn, H. *Liebigs An.. Chem.* **1968**, *718*, 94.

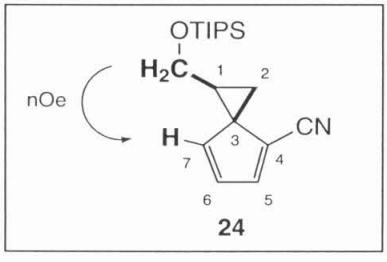
[11] Schlosser, M. *Organometallics in Synthesis*, ch. 4; John Wiley & Sons: New York, **1994**.

[12] For a discussion of solvent effects in Pd^0 catalyzed hydrogenation see: Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; pp 16, 45; Academic Press: New York, **1979**.

Although this unexpected reaction did not advance the synthesis of **20**, our interest in developing methods to functionalize **7** through carbon-carbon bond formation led to a more detailed examination of this reaction.

Scheme 4



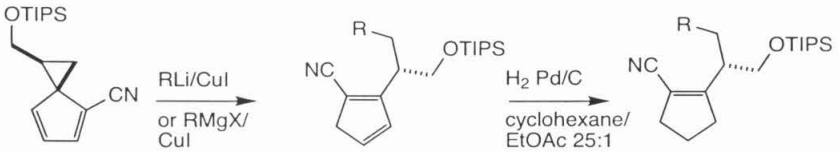


Thus, using the procedure we had previously described, the reaction of cyclopentadiene and epichlorohydrin furnished **7**, which was subsequently protected as its derived TIPS ether **19** (89%). Reaction of **19** with chlorosulfonyl isocyanate followed by aqueous workup at pH=6 afforded a mixture of diastereomers (89:11) from which primary amide **23** was obtained in 41% yield after purification on silica gel. Treatment of **23** with trifluoroacetic anhydride (TFAA) and pyridine in THF at -78 °C according to the procedure of Campagna furnished nitrile **24** in 72% yield.[13] A more efficient protocol was developed for the direct conversion of **19** to nitrile **24**; thus, the two-step sequence (**19** → **23** → **24**) could be conducted, without purification of the intermediate amide **23**, to afford the desired nitrile **24** in 46% overall yield for both steps ([2+2] cycloaddition and dehydration $RCONH_2 \rightarrow RCN$).

Analysis of the ^{1}H-NMR spectral data for **24** confirmed the formation of the C-4 regioisomer and the relative stereochemistry of the nitrile and the silyloxymethylene substituent of the cyclopropane moiety was determined by the observation of a homonuclear ^{1}H-NMR nOe between the C-1 methylene and C-7 vinyl proton in **24** (Scheme 4).

In our initial examination of the chemistry of **24** we observed reluctance by this nitrile diene to undergo simple conjugate addition to the carbon-carbon double bonds under a variety of conditions. In lieu of conjugate addition, **24** preferentially underwent nucleophilic homoconjugate addition to furnish ring-opened adducts **25a-f** in 76-97% yield.

Table 1



24 **25a-h** **26a-e**

Entry	R	Product	Yield	Product	Yield
1	Me	**25a**	76	**26a**	93
2	Et	**b**	83	**b**	85
3	^{i}Pr	**c**	83	**c**	86
4	Bu	**d**	90	**d**	96
5	Ph	**e**	97	**e**	96
6	^{i}propenyl	**f**	82	**f**	na
7	allyl	**g**	decomp.	**g**	na
8	vinyl	**h**	decomp.	**h**	na

The ^{1}H-NMR spectral data for products formed in each of the addition reactions was consistent with the formation of the single 1-cyano-2-substituted conjugated

[13] Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

cyclopentadiene isomers **25**. For one adduct, the structure of the diene was unambiguously established by single crystal X-ray crystallographic analysis of the p-nitrobenzoate derivative of **25e**. The structures of the other adducts were assigned by analogy.

Cyclopentadiene nitriles **25a-e** prepared from the addition of alkyl and aryl soft carbanions were amenable to selective monoreduction to give the α,β-unsaturated nitriles **26a-e**. Under optimized conditions, reduction of dienes **25a-e** in a suspension of 10% Pd/C in 25:1 cyclohexane/ EtOAc under an atmosphere of hydrogen furnished cyclopentenes **26a-e** in 85-96% yield.[12]

Although the reactions shown in Table 1 were conducted with racemic material, a test-substrate was chosen to determine whether the nucleophilic additions could be conducted with optically active **24** to furnish chiral cyclopentadienes and cyclopentenes as building blocks for enantioselective synthesis. The asymmetric synthesis of (*S*)-**7** was conducted following the procedure we have previously documented utilizing lithium cyclopentadienilide and (*R*)-epichlorohydrin.[6] When (*S*)-**24** was treated with MeMgBr/CuI and the adduct subjected to selective monohydrogenation, the isolated product **25a** was shown to have been formed without loss of optical purity by analysis of the derived (*R*)-Mosher ester by gas chromatography.

While the studies of carbon-carbon bond formation on **7** did not provide the desired diene **20**, they did lead to the discovery of a novel homoconjugate addition reaction and a new pathway for accessing unusual substituted cyclopentene structures. Further investigations of carbon-carbon bond forming reactions on **7** are described in the subsequent sections of this dissertation.

III. Studies Directed Toward the Synthesis of Palau'amine.**

Background and Introduction

Palau'amine **1** is one of a class of hexacyclic bisguanidine marine natural products isolated from the Belau sponge *Stylotella aurantium*.[1] Its congeners include brominated isomers **27** and **28**, and the styloguanidines **29-31**.[14] Palau'amine **1** possesses low acute toxicity (LD_{50} = 13 mg/kg in mice) and exhibits anti-cancer activity against P-388 (0.1μg/mL) and A549 (0.2μg/mL) cell lines as well as antibiotic activity against *Staphylococcus aureus* and *Bacillus subtilis* (10μg/disk) and antifungal activity against *Penicillium notatum* (50μg/disk). Its pharmaceutical properties are currently under evaluation in preclinical trials.[15] The structure and relative stereochemistry of **1** was determined by extensive NMR studies and mass spectral methods and was reported by Scheuer and co-workers in 1993.

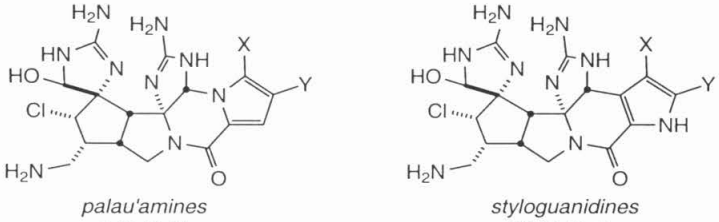


Figure 4. Palau'amine and its congeners.

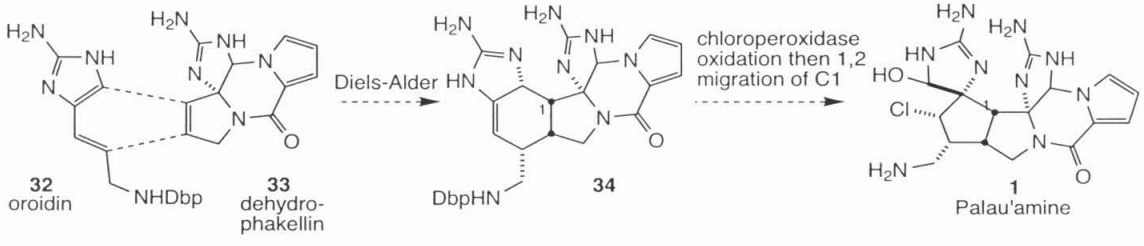
** Portions of the work reported in this section and section IV have been published: Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *in press*.

[14] Kato, T.; Shiruzi, Y.; Isumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133. See also ref. 1.

[15] European Patent Application no. 94302779.6 (as reported in ref. 1)

Palau'amine **1** can be divided into two substructures corresponding to the nitrogen rich "phakellin segment" and a stereochemically dense cyclopentane core. Scheuer recognized this compartmental architecture and proposed a biosynthetic pathway in which a Diels-Alder reaction brings together dehydrophakellin **33** with oroidin **32** to give a putative precursor **34**. Chloroperoxidase oxidation and concomitant 1,2 migration of C-1 would give **1** after hydration and hydrolysis of the dibromopyrrole-carboxamide.

Scheme 5



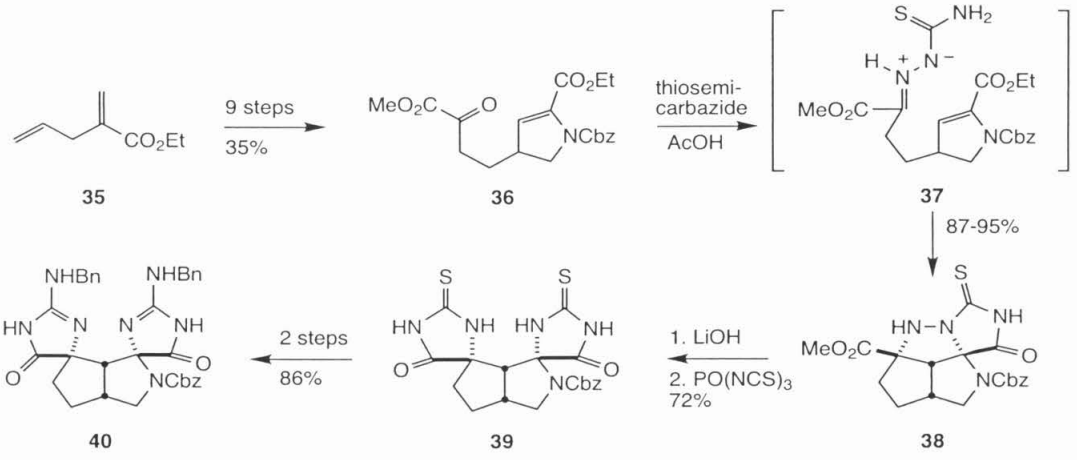
The novel heterocyclic fused ring structure containing two guanidine moieties, a chloro- substituent, and a stereochemically dense cyclopentane core make palau'amine **1** a challenging synthetic target requiring the development of methodologies for the stereoselective construction of complex carbocyclic and heterocyclic systems. No synthesis of **1** or a related natural product has been reported.

A model study reported by Overman[16] in 1997 demonstrated the synthesis of tetracyclic bisguanidine **40** representing a midsection of **1** including both guanidine rings but lacking the chloro- and aminomethyl- substituents of the natural product (Scheme 6). In an elegant synthesis, the intramolecular [3+2] azomethine imine cycloaddition of **37** quickly assembled the cyclopentane core and set the relative

[16] Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159.

stereochemistries of the cyclopentane-pyrrolidine ring fusion and the spirofused guanidine rings. Hydrolysis of **38** followed by treatment with $PO(NCS)_3$ then gave the desired thiohydantoin **39** with concomitant N-N bond cleavage. Further manipulation led to the advanced model compound **40**. To our knowledge, this methodology has not been applied to a fully functionalized palau'amine intermediate.

Scheme 6



Progress toward the synthesis of the phakellin portion of **1** was realized by Büchi[17] over a decade before palau'amine **1** was discovered (Scheme 7). The phakellins are natural products possessing the general structure of dibromophakellin **44**, differing from each other in the level of bromination at the 4 and 5 positions of the pyrrole.[18] A *de novo* synthesis of the parent structure, phakellin (**45**; X=H), has not been reported; however, it is known to be accessible from dibromophakellin **44** by simple reduction.[19] In 1982, Büchi synthesized racemic dibromophakellin **44** by the oxidative cyclization of

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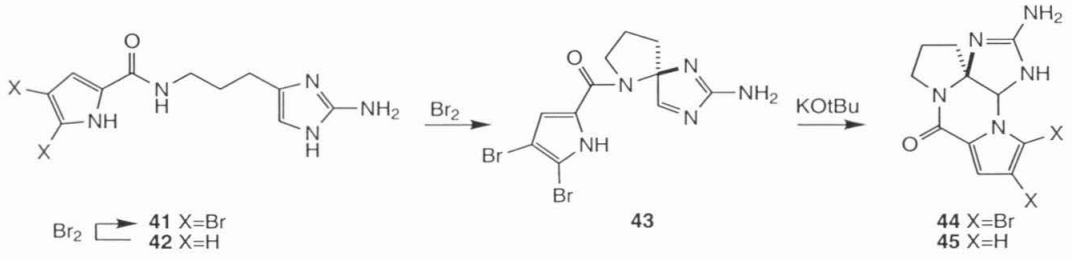
[17] Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776.

[18] Sharma, G. M.; Burkholder, P. R. *J. Chem. Soc., Chem. Commun.* **1971**, 151.

[19] Sharma, G. M.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118.

dihydrooroidin **41** with Br_2 in a biomimetic synthesis. Unfortunately, the cyclization precursor **42** did not undergo cyclization under the same conditions suggesting Büchi's route was not applicable to a synthesis of phakellin **45** except via the known reduction of dibromophakellin **44**.

Scheme 7



The cyclopentane core **46** encompasses the stereochemistry problem inherent in a synthesis of **1** (Figure 5). A viable core intermediate would possess five contiguous stereocenters with correct relative stereochemistry and appropriate substitution to provide synthetic handles for elaboration of the heterocyclic portion of the natural product. Any approach to the synthesis of **1** would have to consider the severe steric demands of the cyclopentane ring **46**. Methods involving late stage formation of the carbon-chlorine bond would necessarily have to work against crowding caused by the adjacent quaternary carbon and amino methylene groups to bring the chlorine atom in on the *more* hindered face as it is oriented in the natural product.

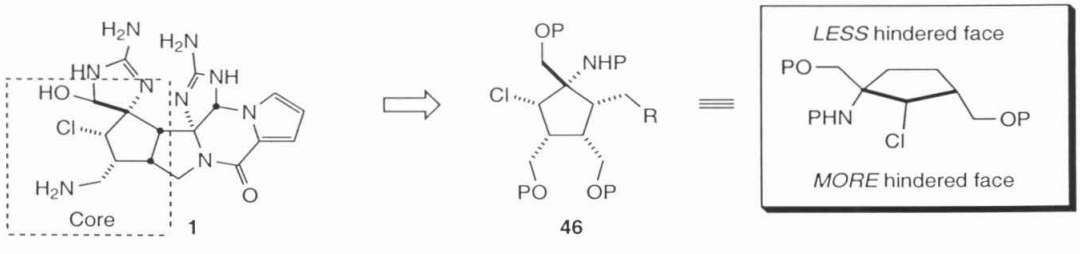


Figure 5. Defining the palau'amine core.

Preliminary investigations in the Carreira group directed at the synthesis of **1** were conducted by Dr. Guido Koch[20] and focused on stereocontrolled formation of the carbon-chlorine bond in a fully functionalized intermediate **47** (Figure 6). Koch's retrosynthesis called for radical abstraction of a chlorine atom from a neighboring trichloroacetamide moiety to ensure stereoselective bond formation on the more hindered face of the cyclopentane core. It was postulated that the radical precursor **48** could be formed by the fragmentation of a norbornane derived intermediate,[21] such as **50**, wherein the requisite oxygen radical **49** would be formed via light induced decomposition of an I-O bond according to Suarez's method using hypervalent iodine as an oxidant.[22] The norbornane skeleton would be synthesized in a stereocontrolled fashion from the appropriate Diels-Alder adduct of **7**.

In an effort to take advantage of the previously described utility of diene **7** for the synthesis of complex cyclopentane structures,[6] the Diels-Alder reaction between *N*-phenylmaleimide and *tert*-butyldimethylsilyl (TBS) ether **51** was explored as the starting point of the synthesis which provided rapid access to the substituted norbornene **52** in

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[20] Syntheses of compounds **50** through **69** were first performed by Dr. Guido Koch as part of a post-Doctoral fellowship in the Carreira laboratory from March 1996 until September 1997.

[21] For a discussion of the reactivity of alkoxy radicals in bridged bicyclic systems see: Brun, P.; Waegell, B. in *Reactive Intermediates,vol.3*; ch. 6; Abramovitch, ed.; Plenum: New York, 1983.

[22] (a) For a review of hypoiodite chemistry see: Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501. (b) For a review of intramolecular free radical reactions see: Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095. (c) Boto, A.; Freire, R.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **1997**, *62*, 2975. (d) Martin, A.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1996**, *61*, 3999. (e) Hernandez, R.; Melian, D.; Prange, T.; Suarez, E. *Heterocycles* **1995**, *41*, 439. (f) de Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 772. (g) Dorta, R. L.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Chem. Res.* **1990**, 240.

large quantities (Scheme 8).[23] Successful elaboration of **52** to the desired precursor **50** and attempts to convert **50** to the palau'amine core **47** are described below and served as the foundation for subsequent work presented in this dissertation.

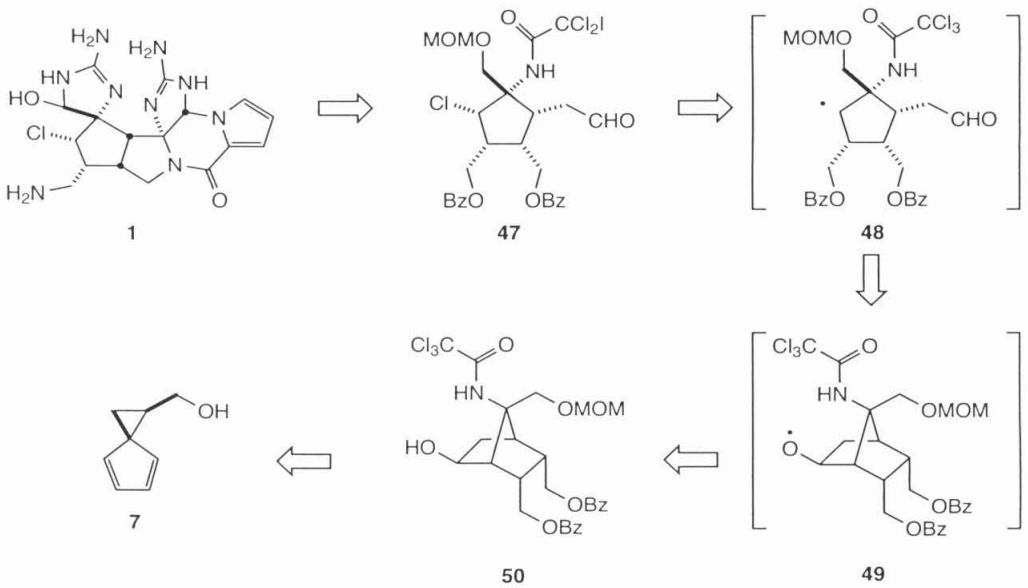


Figure 6. Koch retrosynthesis of palau'amine.

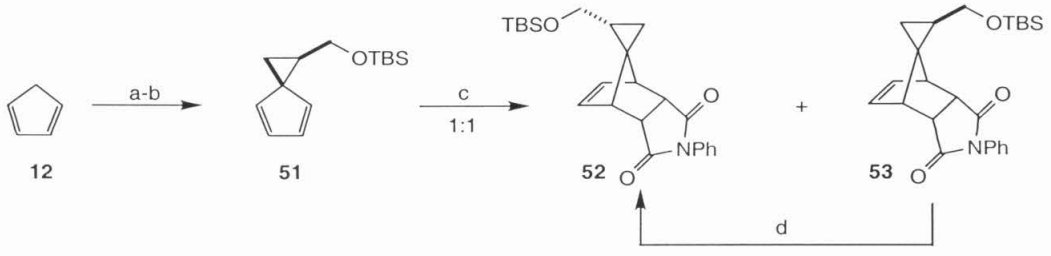
Results and Discussion

Diene **7** was prepared from cyclopentadiene and epichlorohydrin according to the literature procedure[7] then protected in quantitative yield as its derived TBS ether **51** using TBSCl, and triethylamine in DMF (Scheme 8). The exothermic Diels-Alder reaction of *N*-phenylmaleimide with **51** proceeded in CH_2Cl_2 to give a 1:1 mixture of facial diastereomers (ice bath cooling was required to prevent boiling of solvent). In a fortuitous discovery, it was found that diastereomer **52** crystallized from the crude

[23] For examples of Diels-Alder cycloaddition of *N*-phenyl maleimide with substituted cyclopentadienes see: (a) Klaerner, F.-G.; Breitkopf, V. *Eur. J. Org. Chem.* **1999**, 2757. (b) Wellman, M. A.; Burry, L. C.; Letourneau, J. E.; Bridson, J. N.; Miller, D. O.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 939. (c) Garratt, P. J.; Hollowood, F. *J. Org. Chem.* **1982**, *47*, 68.

mixture of products by dissolving it in boiling cyclohexane and allowing the solution to cool.[24]

Scheme 8



Conditions: a) NaH, epichlorohydrin; b) TBSCl, DMF, TEA, quant.; c) CH_2Cl_2, 0 °C; d) reflux ClPh, then recrystallize from cyclohexane; 74% after 3 cycles c + d.

The balance of the material, obtained by evaporation of the mother liquor, was then heated to reflux in chlorobenzene (PhCl) to induce retro-Diels-Alder and regeneration of the 1:1 diastereomeric mixture from which an additional crop of **52** could be obtained by recrystallization. Repeating this cycle three times afforded a 74% yield of the single diastereomer **52** in a 200g scale reaction.

Koch next endeavored to demonstrate the potential of the stereogenic carbon on the cyclopropyl ring to control functionalization of norbornene **52**. The olefin of **52** proved unreactive to standard hydroboration attempts; however, success was realized in the rhodium catalyzed (Wilkinson's catalyst) hydroboration with catechol borane and the product, after oxidation and hydrolysis, was found to be exclusively the exo-alcohol **54** (Scheme 9).[25] With the successful synthesis of **54**, an enantioselective synthesis of **54**

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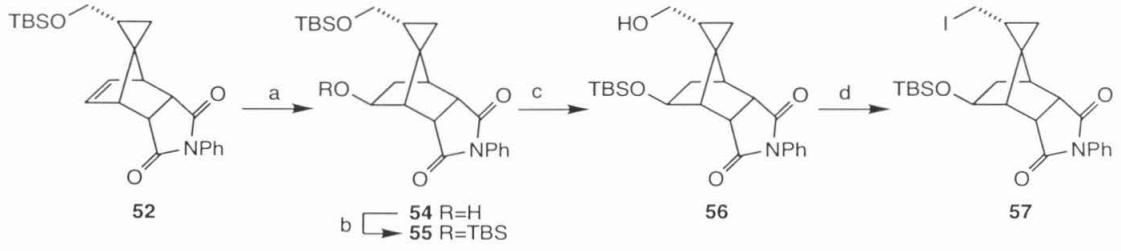
[24] The identity of **52** was confirmed by ^{1}H NMR NOE analysis.

[25] For a review: (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. See also: (b) Burgess, K.; van der Donk, W. A.; Westcott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9350. (c) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. (d) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679. (e) Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1990**, *55*, 2280. (f) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5179. (g) Männig, D.; Nöth, H. *Angew. Chem. Int. Ed. Eng.* **1985**, *24*, 878.

from optically active **7** was shown to be possible. Carreira and Ledford had previously reported the synthesis of non-racemic diene **7** in 91% ee from enantiomerically pure epichlorohydrin in the context of their synthesis of trehazolin **8**.[6] This report greatly expanded the attractiveness of **7** as a general precursor and its ease of synthesis and ready availability of both enantiomers of epichlorohydrin in pure form made it an ideal starting material for the palau'amine studies.

Scheme 9



Conditions: a) catechol borane, $RhCl(PPh_3)_3$, THF; b) TBSOTf, lutidine; c) DCA; d) I_2, PPh_3, imidazole, 73% (from **52**).

The secondary alcohol **55** was then protected as its derived TBS ether using TBSOTf and lutidine, then the primary TBS ether was selectively protodesilylated using dichloroacetic acid in CH_2Cl_2/MeOH according to the procedure developed by Carreira and Du Bois to accomplish a similar selective monodesilylation.[26] The resulting alcohol **56** was treated with PPh_3, I_2, and imidazole in ether-acetonitrile to give iodide **57** in 73% combined yield for the four step sequence (**52** → **57**).[27]

Radical fragmentation of the cyclopropane was next examined. Initial studies focused on Curran's hexabutylditin catalyzed atom transfer process to generate the

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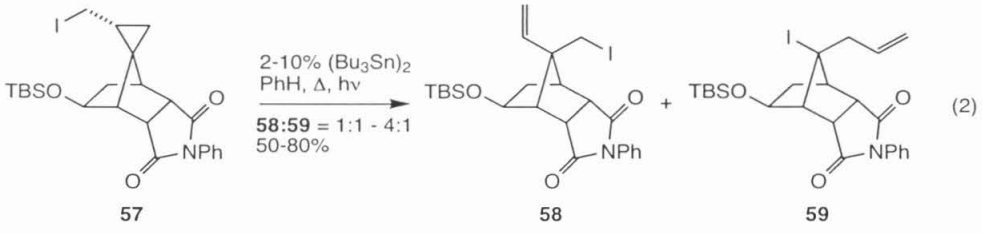
[26] Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

[27] (a) Corey, E. J.; Nagata, R. *Tetrahedron Lett.* **1987**, *28*, 5391. (b) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (c) Soll, R. M.; Seitz, S. P. *Tetrahedron Lett.* **1987**, *28*, 5391. (d) Millar, J. G.; Underhill, D. W. *J. Org. Chem.* **1986**, *51*, 4726.

cyclopropylcarbinyl radical from iodide **57** (Equation 2).[28] Thus, treatment of **57** with catalytic amounts of hexabutylditin in refluxing benzene resulted in the expected cleavage of the cyclopropane ring and formation of iodide products; however, **57** showed a propensity to rearrange through a tertiary carbon radical to give varying yields of the undesired tertiary iodide **59**. Only modest selectivity was observed in the formation of desired primary iodide **58** over the undesired iodide **59** and the ratio of products ranged from 1:1 to 4:1 with a combined yield ranging from 50-80%.



57 **58** **59**

In hopes of finding a more reliable fragmentation process, Nakamura's aerobic conversion of alkyl halides to their corresponding alcohols with excess tributyltin hydride was investigated.[29] The unexpected compatibility of oxygen and Bu_3SnH in a radical process makes Nakamura's reaction practical and its scope has been amply demonstrated in recent reports. The radical process is initiated by oxygen abstraction of

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[28] (a) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. For general information regarding cyclopropylcarbinyl radical fragmentation see: (e) Furxhi, E.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 4064. (f) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710. (g) Martin-Esker, A. A.; Johnson, C. C.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **1994**, *116*, 9174. (h) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347. For discussions of the 7-norbornenyl radical see: (i) Sauers, R. R. *Tetrahedron* **1998**, *54*, 5143. (j) Bakuzis, P.; Kochi, J. K.; Krusic, P. J. *J. Am.Chem. Soc.* **1970**, *92*, 1434. (k) Cristol, S. J.; Noreen, A. L. *J. Am. Chem. Soc.* **1969**, *91*, 3969. (l) Russell, G. A.; Lamson, D. W. *J. Am. Chem. Soc.* **1969**, *91*, 3968.

[29] (a) Sawamura, M.; Kawaguchi, Y.; Nakamura, E. *Synlett* **1997**, 801. (b) Sawamura, M.; Kawaguchi, Y.; Sato, K.; Nakamura, E. *Chem. Lett.* **1997**, 705. (c) Nakamura, E.; Sato, K.; Imanishi, Y. *Synlett* **1995**, 525. d) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.

H from tributyltin hydride and proceeds through the typical pathway of organotin mediated abstraction of the halide and concomitant carbon-radical formation (Figure 7).

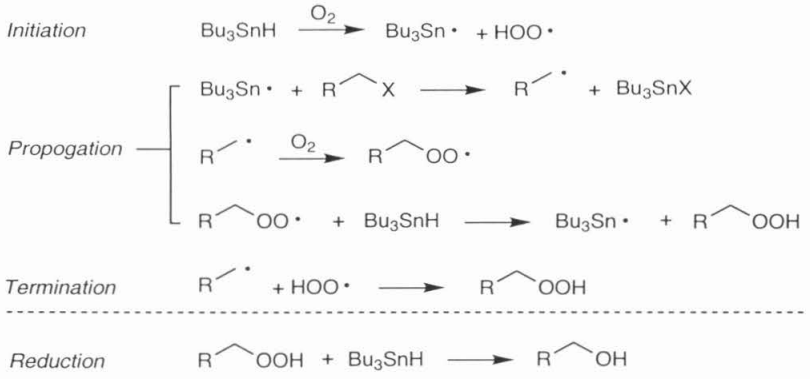
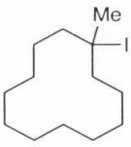
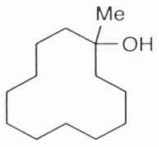
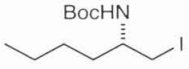
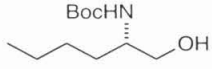
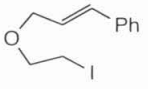
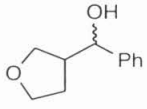
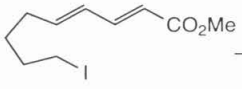
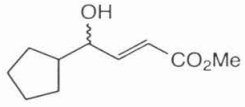


Figure 7. General mechanism of Nakamura's radical hydroxylation.

The carbon radical is then trapped by dissolved oxygen to give a hydroperoxide species that is reduced to the desired hydroxyl by a second equivalent of tributyltin hydride. A selection of substrates examined by Nakamura (Table 2) highlights the utility of the process and hints at its potential for initiating and terminating more complex molecular rearrangements involving formation of new carbon-carbon bonds (entries 3 and 4) with direct installation of a useful hydroxyl function at the final radical terminus. To our knowledge, this methodology has not previously been applied to the formation and fragmentation of a cyclopropylcarbinyl radical.

Entry	Iodide	Yield	Alcohol
1.		70%	
2.		65%	
3.		84%	
4.		69%	

Conditions: 0.2 M in toluene at 0-20 °C with 2.1-2.5 eq Bu_3SnH bubbled with dry air for 5-24 h.

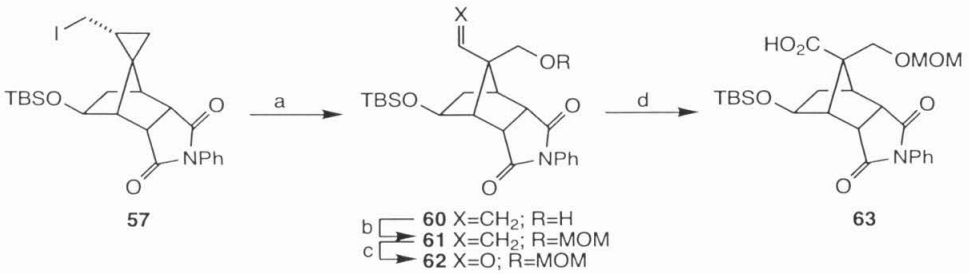
Table 2. Selected examples of Nakamura's hydroxylation.

It was found that treatment of iodide **57** with 2.5 eq. Bu_3SnH in vigorously aerated toluene lead predominantly to the desired cyclopropylcarbinyl radical fragmentation product **60** after complete reduction of the corresponding intermediate hydroperoxide with added PPh_3 (Scheme 10). Addition of Bu_3SnH in one portion to a solution of **57** in aerated toluene at 0 °C followed by slow warming to room temperature was found to be the optimum protocol affording a 69% yield of **60** after chromatographic purification to remove tin and phosphorous byproducts. Primary alcohol **60** was protected in 67% yield as its derived methoxymethyl (MOM) ether **61** using MOMCl, and Hünig's base.[30] Then, ozonation of **61** gave aldehyde **62** in 90%

[30] Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

yield after PPh_3 reduction of the ozonide. Quantitative oxidation to the carboxylic acid **63** was achieved using Masamune's pH=7 buffered $KMnO_4$ protocol.[31]

Scheme 10



Conditions: a) Bu_3SnH, air, toluene, PPh_3, 69%; b) MOMCl, Hünig's base, 67%; c) O_3/O_2, PPh_3, 90%; d) $KMnO_4$, pH=7, quant.

Curtius rearrangement was implemented according to the three step procedure of acid chloride formation with oxalyl chloride and DMF followed by acylazide formation with NaN_3 in DMSO then heating the acylazide in benzene to give the isocyanate **64** (Scheme 11).[32] Crude **64** was heated to 110 °C in benzyl alcohol solvent to give the benzyloxycarbonyl (Cbz) protected amine **65** in 58% yield (from aldehyde **62**). Hydrolysis of imide **65** with LiOH followed by refluxing the crude regioisomeric mixture of acid-amides in toluene resulted in expulsion of aniline and closure to the cyclic anhydride **66** in 83% yield for the two steps.

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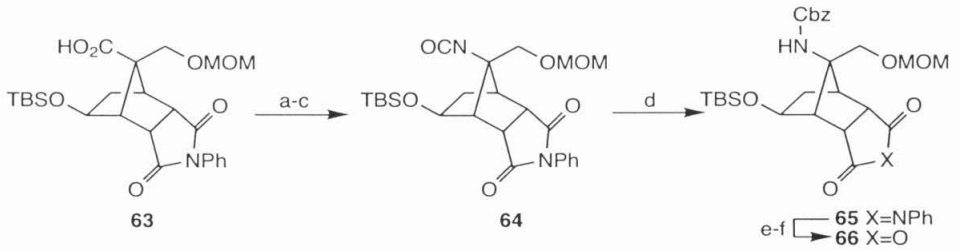
[31] Abiko, A.; Roberts, J. C.; Takewasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

[32] For examples of synthetic application: (a) Roth, G. A.; McClymont, E. L. *Synthetic Commun.* **1992**, *22*, 411. (b) Lemmens, J. M.; Blommerde, W. W. J. M.; Thijs, L.; Zwanenburg, B. *J. Org. Chem.* **1984**, *49*, 2231. (c) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515. (d) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38. (e) Chorev, M.; Rubini, E.; Gilon, C.; Wormser, U.; Selinger, Z. *J. Med. Chem.* **1983**, *26*, 129. (f) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.- T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962. (g) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (h) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

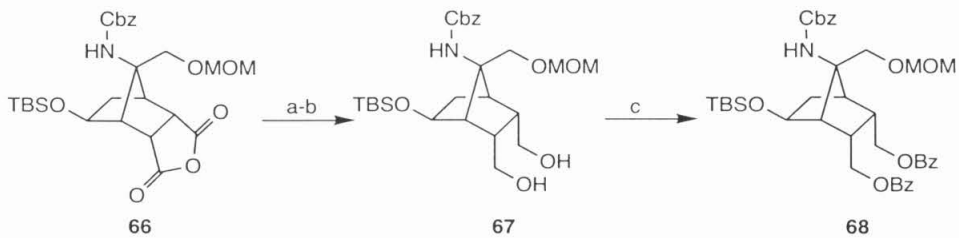
Scheme 11



Conditions: a) $(COCl)_2$; b) NaN_3, DMSO; c) PhH, reflux; d) BnOH, 100 °C, 58% (from **62**); e) LiOH, THF; f) toluene, reflux, 83% (from **65**).

The Cbz-amine function was not compatible with complete reduction of anhydride **66** using LAH so stepwise reduction began with treatment of **66** with LAH at -78 °C to give a mixture of regioisomeric lactones (Scheme 12). Complete reduction of the lactones was then realized with $LiBH_4$ to give diol **67** in 67% overall yield.[33] Double acylation of **67** with benzoyl chloride and pyridine gave dibenzoate **68** in 91% yield. Interestingly, diol **67** resisted attempts to activate both alcohols for displacement with nitrogen nucleophiles, invariable giving the cyclized furanoid species as the major product. Presumably, once one of the alcohols was activated, the intramolecular cyclization was entropically favored over any intermolecular displacement with a suitable nitrogen nucleophile.

Scheme 12

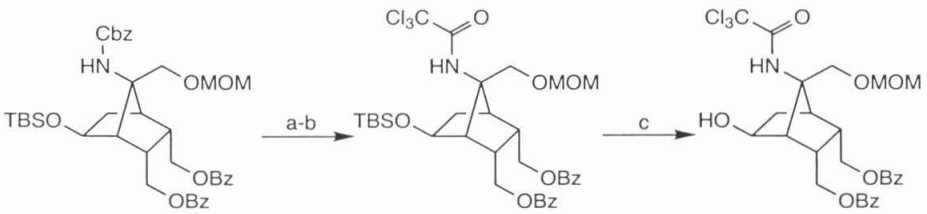


Conditions: a) LAH, -78 °C; b) $LiBH_4$, THF, 0 °C, 67% (from **66**); c) BzCl, pyr., 91%.

[33] Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23 and refs therein.

Thus, the diol was left protected as its derived dibenzoate diester **68** that could be unmasked in a later intermediate possessing the required internal nitrogen nucleophile to form the pyrrolidine ring of palau'amine **1**. Hydrogenolytic removal of the Cbz protecting group was achieved with 1 atm H_2 and Pearlman's catalyst ($Pd(OH)_2$)[34] and the resulting amine was immediately acylated with trichloroactyl chloride and TEA to give trichloroacetamide **69** in 65% yield for the two step sequence (Scheme 13). Desilylation of the TBS ether with HF-pyridine gave the desired chlorine transfer precursor **50** in 86% yield.[35]

Scheme 13



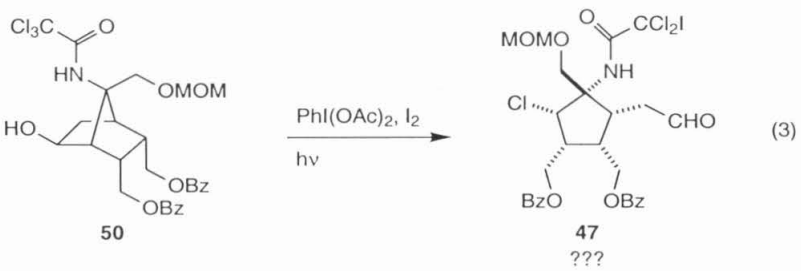
68 **69** **50**

Conditions: a) H_2, Pearlman's catalyst; b) TCACl, TEA, 65% (from **68**); c) HF-pyr., 86%.

It was Koch's intention to convert **50** to the fully functionalized palau'amine core **47** via the radical pathway shown in Figure 6. In the proposed mechanism, an alkoxy radical **49** would be formed by photolytic decomposition of the in-situ formed hypoiodite according to Suarez's method using $PhI(OAc)_2$ and I_2.[22] Fragmentation of **49** to give the more stable secondary radical species **48** would be followed by stereoselective intramolecular transfer of chlorine from the neighboring trichloroacetamide group to give a dichloro-acyl radical. The final radical species would be trapped by I_2 to give the palau'amine core **47**. Unfortunately, attempts to implement

[34] (a) For use of $Pd(OH)_2$ for deprotection of Cbz a protected amine see: Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019. (b) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663.

Suarez's chemistry in this way did not yield a product that could be unambiguously assigned structure **47** (Equation 3).



(3)

However, aldehyde products were observed as evidenced by their characteristic proton shifts in the ^{1}H-NMR (9-10 ppm), but attempts to characterize them or their derivatives were unsuccessful. The ambiguous outcome of the key chlorine transfer step prompted a re-evaluation of the mode of radical generation in hopes of designing a system wherein the desired radical could be formed directly at the cyclopentane ring without relying on the fragmentation of an alkoxy radical intermediate.

Second Generation Palau'amine Core

Introduction and Retrosynthesis

Although the Suarez chemistry[22] did not yield usable results for Koch's transformation (**50** → **47**), we felt the underlying hypothesis of that transformation still merited further study in the form of a simplified, yet still fully functionalized, core. Thus, the core synthesis was redesigned to accommodate a more reliable, milder, method for directly generating the desired secondary radical, as in **48**, while retaining the useful transformations discovered and worked out by Koch in his synthesis of **50**.

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[35] Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.

To meet this goal, we sought to utilize either the well known Barton-McCombie[36] deoxygenation of **70** or the equally well precedented homolytic decarboxylative decomposition of the Barton ester of **72** to generate the desired radical (Figure 8).[37] Because these two methods suggested entirely different syntheses, the deoxygenation approach was investigated first.

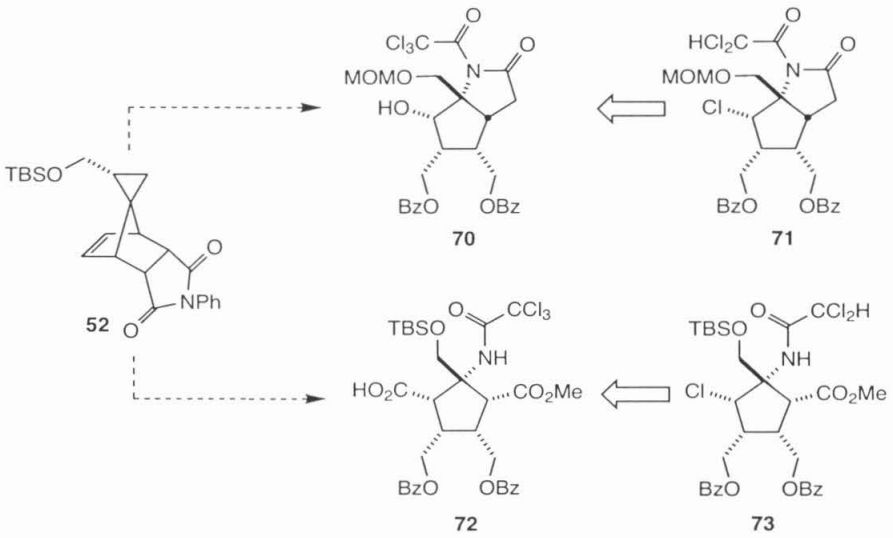


Figure 8. Retrosyntheses utilizing Barton radical methodology in the key step.

Results and Discussion

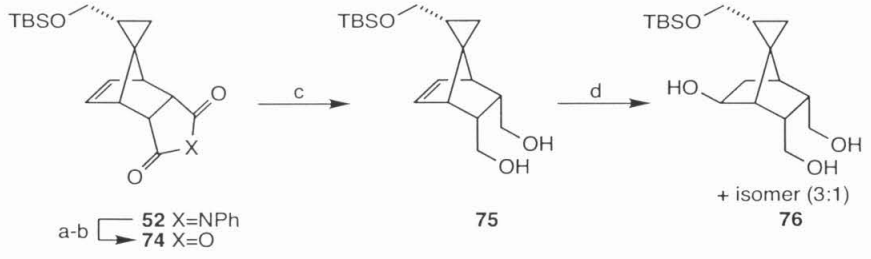
Diels-Alder adduct **52** was converted to anhydride **74** in 95% yield using the protocol of LiOH hydrolysis followed by dissolution in refluxing toluene (Scheme 14). Exhaustive reduction of **74** with LAH in ether then gave diol **75** in 89% yield. Hydroboration of **75** with BH_3-THF followed by oxidative workup under neutral

[36] (a) For a review see: Chatgilialoglu, C.; Ferreri, C. *Res. Chem. Intermediat.* **1993**, *19*, 755. See also: (b) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329. (c) Barton, D. H. R., Crich, D. *J. Chem. Soc. Perk. Trans. 1* **1986**, 1603.

[37] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

conditions reported by Evans and Fu[25] gave triols **76** in 98% yield of 3:1 regioisomeric mixture that was carried through subsequent steps together. The identity of the major isomer of **76** was confirmed by comparison to authentic material prepared from **55** (Scheme 9).

Scheme 14



Conditions: a) LiOH, THF/H_2O; b) toluene, reflux, 95% (from **52**); c) LAH, 89%; d) BH_3-THF, then H_2O_2/pH=7, 98%.

Benzoylation of **76** with benzoic acid, EDC, and DMAP occurred selectively at the two primary alcohols to give dibenzoates **77** in 97% yield (Scheme 15).[38] Oxidation of **77** with PCC[39] gave *two* ketones **78** in 71% yield confirming the minor isomeric product of hydroboration (**75** → **76**) was indeed a regioisomer. Desilylation with HF-CH_3CN (5% solution of 48% HF in CH_3CN) gave keto-alcohols **78** in 97% yield. Baeyer-Villiger oxidation of **78** with mCPBA in CH_2Cl_2 then gave exclusively the desired regioisomeric lactones **79** in 99% yield.[40]

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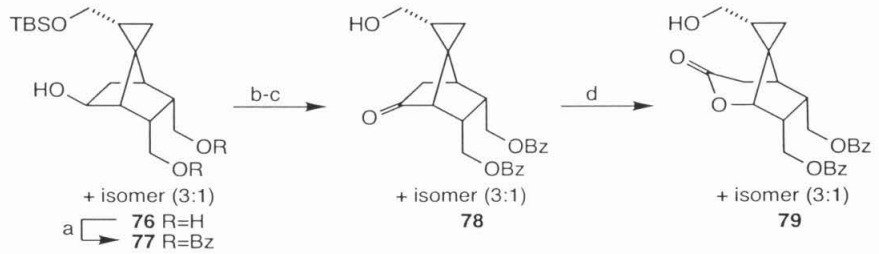
[38] (a) Skotnicki, J. S.; Kearney, R. M.; Smith, A. L. *Tetrahedron Lett.* **1994**, *35*, 197. (b) Boger, D. L.; Wysocki, R. J.; Ishizaki, T. *J. Am. Chem. Soc.* **1990**, *112*, 5230.

[39] (a) Kasmai, H. S.; Mischke, S. J.; Blake, T. J. *J. Org. Chem.* **1995**, *60*, 2267. (b) Bonadies, F.; Fabio, R. D.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703.

[40] For a review covering Baeyer-Villiger oxidation of norbornyl ketones see: (a) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697. For other examples in norbornyl systems see: (b) Hamley, P.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1793. (c) Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2055. (d) Grudzinski, Z.; Roberts, S. M.; Howard, C.; Newton, R. F. *J. Chem. Soc. Perkins Trans. 1* **1978**, 1182. (e) Takano, S.; Kubodera, N.; Ogasawara, K. *J. Org. Chem.* **1977**, *42*, 786.

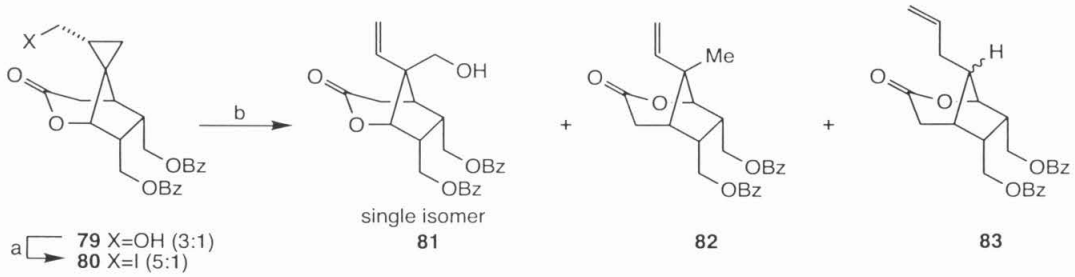
Scheme 15



Conditions: a) BzOH, EDC, DMAP, 97%; b) PCC, 71%; c) HF-CH_3CN, 97%; d) mCPBA, 99%.

Iodination of **79** (Scheme 16) with I_2, PPh_3, and imidazole gave iodides **80** in 82% yield.[27] Interestingly, iodides **80** were obtained as a 5:1 mixture of diastereomers (from the 3:1 mixture in starting material) indicating some selective decomposition of the minor iodide or an intermediate leading to the minor iodide had occurred during the iodination.

Scheme 16



Conditions: a) I_2, PPh_3, imidazole, 82%; b) Bu_3SnH, air, PhH, PPh_3, 30% of **81**.

Fragmentation of **80** using the modified Nakamura[29] procedure (2.5 eq Bu_3SnH, toluene, PPh_3, air) provided the desired alcohol **81** in a disappointing 20% yield accompanied by undesired side products **82** and **83** resulting from competitive reduction and fragmentation pathways. Performing the reaction in benzene was found to improve

the yield of **81** to 30%;[41] however, competitive generation of **82** and **83** was still problematic.

It was hypothesized that subtle changes in the substitution on the bicyclic structure had significant impact on whether the initially formed cyclopropyl carbinyl radical **84** fragmented to give the desired primary radical **85** or the undesired tertiary radical **86** (Figure 9). In particular, it was believed that substitution which caused the intermediate tertiary radical **86** to be more highly strained would lead to preferential fragmentation of **84** to the less strained primary radical **85**. In our analysis, the less flexible the bridged ring of **84** was, the more favored would be the desired pathway.

Figure 9. Strategy for controlling radical fragmentation selectivity.

By applying the criteria outlined in Figure 9, we predicted the most successful fragmentation would occur with **87** which has two ring carbons tied together by the imide ring and two sp^2 carbons on the ring (Table 3). By comparison, intermediate **57**, which fragmented to **60** in 69% yield, lacked the endocyclic olefin but retained the imide ring. Iodide **80** had even greater ring flexibility than **57,** due to its 7 member ring and lack of the cyclic imide substituent, and it fragmented in only 30% yield under

[41] Solubility of O_2 is 9.08 x 10^{-3} M in PhH and 8.70 x 10^{-3} M in PhMe, calculated from mole fractions measured at 298.15 K: 8.10 x 10^{-4} (PhH) and 9.23 x 10^{-4} (PhMe) reported in Battino, R.; Rettich, T. R.; Tominaga, T. *J. Phys.Chem. Ref. Data* **1983**, *12*, 163.

optimized conditions. A trend was emerging that linked ring system flexibility with fragmentation to the undesired tertiary radical.

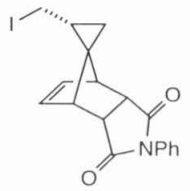
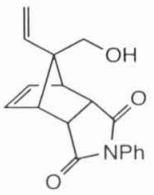
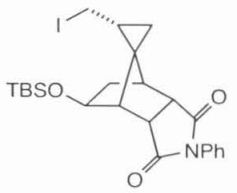
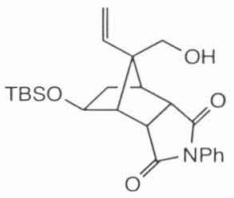
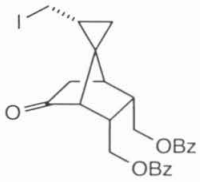
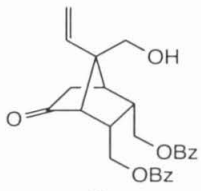
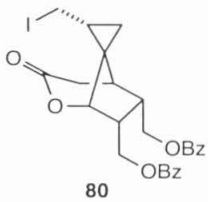
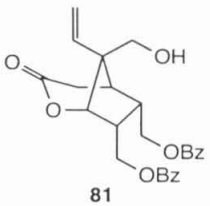
Entry	Iodide	yield	product	structural comparison
1.	 **87**	84%	 **88**	2 sp^2 carbons cyclic imide 6 member ring
2.	 **57**	69%	 **60**	no sp^2 carbons cyclic imide 6 member ring
3.	 **89**	45%	 **90**	1 sp^2 carbon no cyclic imide 6 member ring
4.	 **80**	30%	 **81**	1 sp^2 carbons no cyclic imide 7 member ring

Table 3. Effect of structure on radical fragmentation outcome.

To provide further evidence of this correlation, iodides **87** and **89** were fragmented using the modified Nakamura conditions to give the corresponding alcohols **88** and **90** in 86% and 45% yield respectively. In accord with our predictions, iodide **89** fragmented in intermediate yield and iodide **87** performed best of the four, reproducibly providing alcohol **88** in excess of 80% yield. The finally optimized protocol was as

follows: A solution of iodide **87** in benzene was vigorously aerated for 15 min. A 50 v/v% solution of 2.5 eq. Bu_3SnH in benzene was then added dropwise via addition funnel over 2 hours while aeration continued. The reaction was monitored by TLC until complete consumption of starting material was observed, at which point aeration was discontinued and the yellow to orange reaction was allowed to stir an additional 15 h for complete reduction of the intermediate hydroperoxide to occur. Over this time a white precipitate formed. The reaction was then diluted to three times its volume with hexanes to induce precipitation of **88** as a copious white solid. Filtration of the opaque mixture gave 60-80% yield of pure **88**, free of organotin contamination. The balance of product could be isolated from the mother liquor by evaporation *in vacuo* and silica gel chromatography of the residue. This procedure benefits from allowing time for complete reduction to occur after consumption of **87** is observed by TLC and obviates the need for a second reductant (PPh_3) which complicates purification by generating unwanted Ph_3PO byproduct.

With a reliable and high yielding fragmentation procedure in hand for iodide **87**, the palau'amine core synthesis was redesigned around imide-alcohol **88**, targeting precursor **72** indicated by the Barton decarboxylation strategy (Figure 8).[37] Retrosynthetic analysis of **72** called for Schreiber's non-reductive ozonation[42] of meso-**91** which would be derived from the optimized Nakamura fragmentation product **88** by a sequence of functional group modifications analogous to those performed by Koch in his synthesis of **50** (Figure 10).

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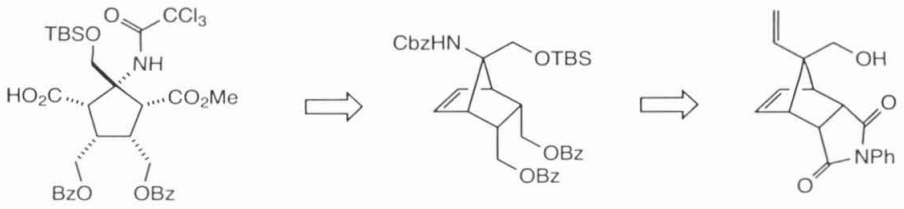
[42] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

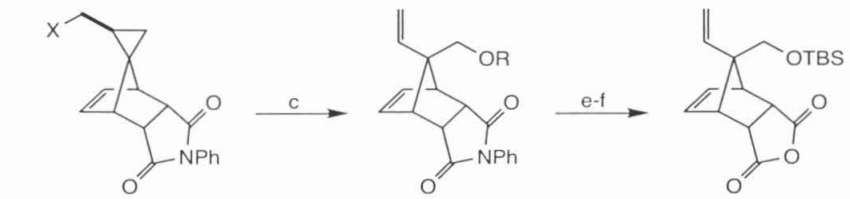


72 91 88

Figure 10. Retrosynthesis of the decarboxylation precursor **72**.

Desilylation of **52** proceeded in quantitative yield by treatment with HF-CH_3CN (48% HF 5:95:1 HF/CH_3CN/H_2O) in THF and was followed by conversion of the resulting alcohol to iodide **87** using I_2, PPh_3, and imidazole in CH_2Cl_2 in 93% yield after chromatography (Scheme 17).[27] Fragmentation of **87** afforded alcohol **88** in 86% yield as described above. Silylation of **88** in DMF using TBSCl and TEA was followed by LiOH hydrolysis of the imide and closure to the anhydride in 87% yield overall for the three steps. The hydrolysis product of **92** proved particularly facile in the conversion to **93** and could readily be cyclized simply by dissolving it in toluene at room temperature.

Scheme 17

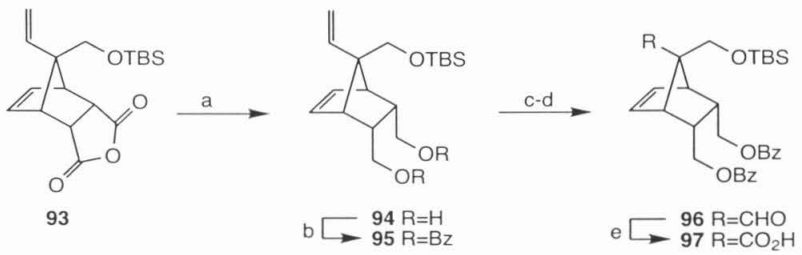


Conditions: a) HF-CH_3CN, quant.; b) I_2, PPh_3, imidazole 93%; c) Bu_3SnH, air, PhH, 86%; d) TBSCl, TEA DMF, 92%; e) LiOH; f) PhMe, 95%.

Reduction of **93** with LAH in ether gave diol **94** in 98% yield that was dibenzoylated using BzCl, TEA to give **95** in 92% yield (Scheme 18). No attempt was made to convert diol **94** to the more desirable diamine derivative because it was felt that **94** was not sufficiently different from diol **67** upon which reasonable attempts at double

amination met with failure. Thus, selective oxidative cleavage of the terminal olefin of **95** was investigated using osmium tetroxide as the active oxidant. To this end, an attempted "one-pot" LeMieux-Johnson[43] procedure (OsO_4, $NaIO_4$) consumed starting material but generated a complex mixture of products presumably from the non-selective oxidation of both olefins and subsequent formation of hydrates and lactols. We reasoned that a stepwise LeMieux-Johnson could improve selectivity if the diol moiety produced in the dihydroxylation served to sterically impede the endocyclic olefin from being oxidized.

Scheme 18



Conditions: a) LAH, 98%; b) BzCl, TEA, 92%; c) OsO_4, K_3FeCN_6, $(DHQD)_2Pyr$,, 79%; d) $NaIO_4$, K_2CO_3, 93%; e) $KMnO_4$, pH=7.

Efforts to dihydroxylate **95** using NMO or K_3FeCN_6 as stoichiometric oxidants in the absence of a ligand promoter were ineffective and returned essentially all starting material plus a small amount of highly polar colored material. Success was finally achieved with the use of the chiral ligand promoter $(DHQD)_2Pyr$ with K_3FeCN_6 as the oxidant.[44] In the event, diene **95** was reacted with 5 mol% OsO_4 in the presence of 5

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[43] (a) Schroder, M. *Chem. Rev.* **1980**, *80*, 187 and refs therein. (b) Pappo, R.; Allen, Jr., D. A.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

[44] (a) For a review see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 243. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. See also ref 44a.

mol% $(DHQD)_2Pyr$, 300 mol% K_3FeCN_6, 300 mol% K_2CO_3 in 1:1:1 ^tBuOH/THF/water to give, after workup and chromatography, the desired diol in 79% yield. Although the asymmetric ligand was required for dihydroxylation to occur at a reasonable rate it imparted only modest enantioselectivity, giving the diol in 20% ee. Nevertheless, we were hopeful that once the later steps had been worked out, this asymmetric dihydroxylation could be optimized to provide entry into an enantioselective synthesis of the palau'amine core in a subsequent version of the synthesis.

Attempted periodate cleavage of the dihydroxylation product under neutral or unbuffered conditions resulted in the formation of a mixture of **96** and a hydroxyaldehyde side product.[45] Therefore, efficient cleavage of the diol was performed using $NaIO_4$ in THF-H_2O in the presence of K_2CO_3 (3 eq) to give **96** in 93% yield. Then oxidation of **96** to the corresponding carboxylic acid **97** with $KMnO_4$ proceeded uneventfully using the pH=7 buffered conditions of Masamune.[31]

Conversion of **97** to the derived HOBt ester with EDC and HOBt was followed by heating the crude ester to reflux in benzene with 1.5 eq of $TMSN_3$ (Scheme 19).[46] The resulting isocyanate **98** was obtained in 65% yield after direct chromatographic purification of the reaction mixture. Use of a larger excess of $TMSN_3$ led to appreciable formation of carbamoyl azide **99** as a side product.[47] Conversion of **98** to Cbz-amine **91** was accomplished by heating **98** to 110 °C in BnOH with 10 mol% DMAP to give **91** in

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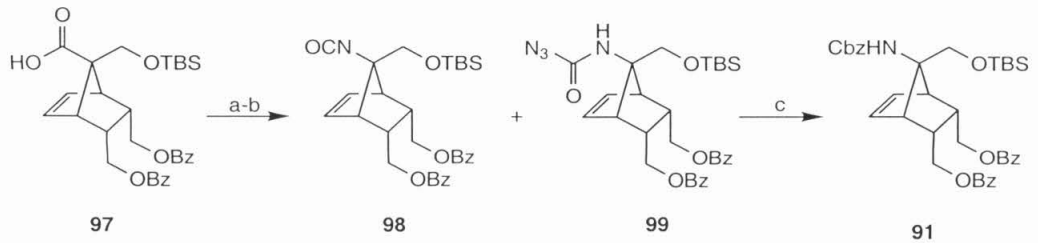
[45] For examples in natural products syntheses see: (a) Evans, D. A.; Sims, C. L. *Tetrahedron Lett.* **1973**, 4691. (b) Kido, F.; Kitahara, H.; Yoshikoshi, A. *J. Org. Chem.* **1986**, *51*, 1478. See also ref 44b.

[46] (a) Skotnicki, J. S.; Kearney, R. M.; Smith, A. L. *Tetrahedron Lett.* **1994**, *35*, 197. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

[47] For example: Froyen, P. *Synthetic Commun.* **1996**, *26*, 4549.

93% yield (from **96**). Interestingly, **99** also could be converted to Cbz-amine **91** under the same conditions.

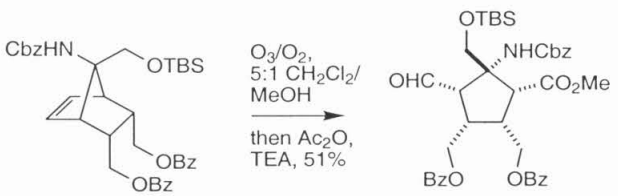
Scheme 19



97 **98** **99** **91**

Conditions: a) EDC, HOBt; b) $TMSN_3$, PhH, 80 °C, 65%; c) BnOH, 110 °C, DMAP, 93%.

Ozonolysis of **91** in 5:1 CH_2Cl_2/MeOH was followed by Shreiber's non-reductive workup (Ac_2O, TEA) to give aldehyde-methyl ester **100** (Equation 4).[42] The yield of the ozonation was highly variable (10%-51%) and rigorous purification of solvent and reagents did not improve the outcome or reliability of the procedure in our hands.



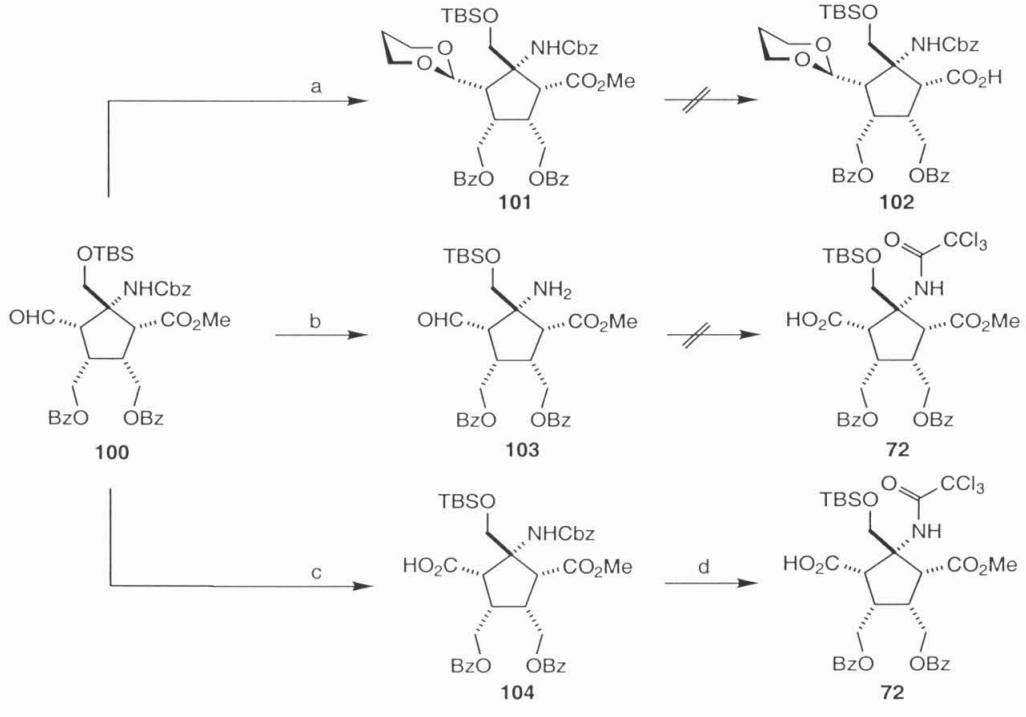
91 **100** (4)

Several stepwise approaches to a viable palau'amine core precursor from **100** were attempted (Scheme 20). First, conversion of aldehyde **100** to its derived propane-diol ketal **101** was straightforward, but LiOH hydrolysis of the methyl ester only returned starting material. More forcing hydrolytic conditions (i.e., NaOH, KOH, heating, or Bu_2SnO[48]) ultimately lead to decomposition of **101** to give an unidentified highly polar product that retained the characteristic methyl singlet of the ester (^{1}H-

NMR)! This outcome is testament to the highly hindered nature of this position on the cyclopentyl ring system.

Next, the Cbz protecting group of **100** was removed under standard hydrogenolytic conditions (H_2 10% Pd/C) to give a putative amino aldehyde **103** which proved too unstable to isolate or characterize. Presumably, **103** would be prone to retro-Mannich ring-opening decomposition and subsequent polymerization. Attempts to trap the amino aldehyde **103** as the trichloroacetamide in-situ, en route to **72**, were similarly unsuccessful yielding no characterizable products.

Scheme 20



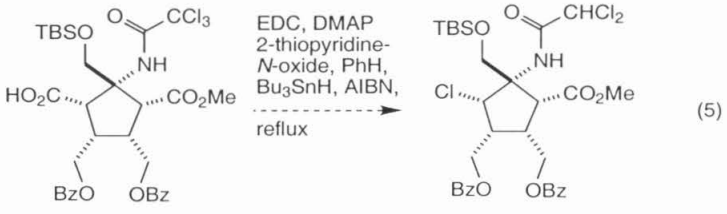
Conditions: a) 1,3-propane diol, PPTS, 51%; b) H_2, Pd/C; c) $KMnO_4$ pH=7; d) i. H_2, Pd/C, ii. TCACl, TEA,40% (from **100**)

---

[48] For use of distannoxane catalysts for transesterification see: (a) Otera, J.; Dan-oh, N.; Nozaki, H. *Tetrahedron* **1993**, *49*, 3065. (b) Otera, J.; Dan-oh, N.; Nozaki, H. *Tetrahedron* **1992**, *48*, 1449. (c) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. (d) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.

Finally, having learned some of the pitfalls of this system, a successful route to **72** was devised. Aldehyde **100** was oxidized to carboxylic acid **104** using Masamune's pH=7 buffered $KMnO_4$ procedure[31] and the unpurified acid was hydrogenolytically deprotected (H_2 10% Pd/C) to give the corresponding free β-amino acid. Treatment of the crude amino acid with TCACl and TEA then gave the desired chlorine transfer precursor **72** in 40% yield for the 3 step sequence.

The initial attempt to convert **72** to **73** followed the procedure reported by Barton for radical decarboxylative hydrogenation (Equation 5).[37] Acid **72** was converted to Barton ester **105** using EDC, DMAP, and 2-thiopyridine-*N*-oxide. The yellow ester was then heated in PhH with Bu_3SnH and AIBN resulting in rapid decolorization of the reaction and consumption of starting material. Unfortunately, only unidentifiable highly polar products were observed. In hopes of effecting the transfer under milder conditions, recourse was sought in Barton's conditions of intermolecular chlorination.

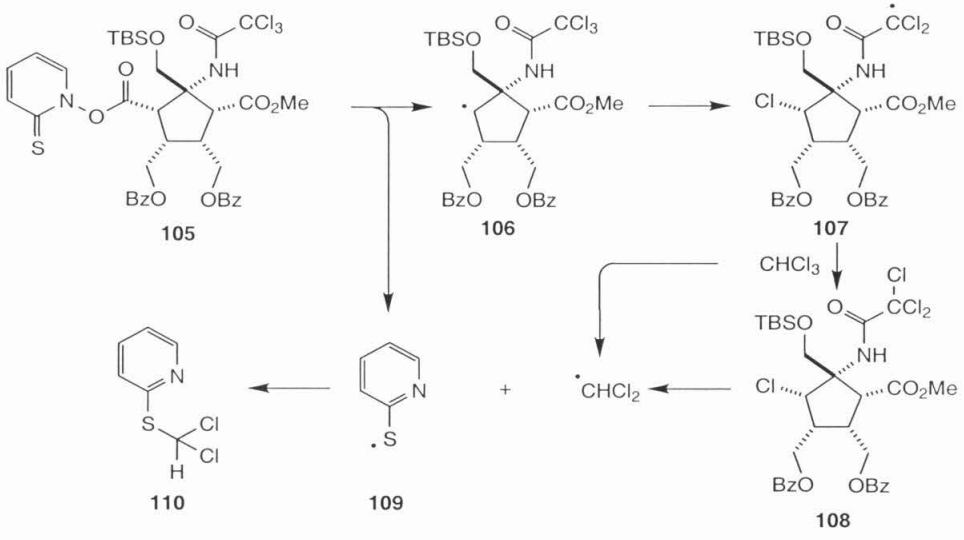


(5)

Barton had shown that, in the absence of an initiator, a thiohydroxamate ester (like **105**) would decarboxylate in CCl_4 to give a product with a new carbon chlorine bond. The thiopyridyl radical byproduct would be trapped by the resulting trichloromethine radical. We postulated that if the rearrangement of **105** according to this mechanism was allowed to occur in a chlorine donor solvent then the steric demands of the intermediate radical **106**, coupled with entropic considerations, would inhibit intermolecular chlorination long enough for intramolecular chlorine transfer to take

place (Scheme 21). Chlorination would then occur at the resulting dichloroacetamidyl radical position to give product **108**.

Scheme 21

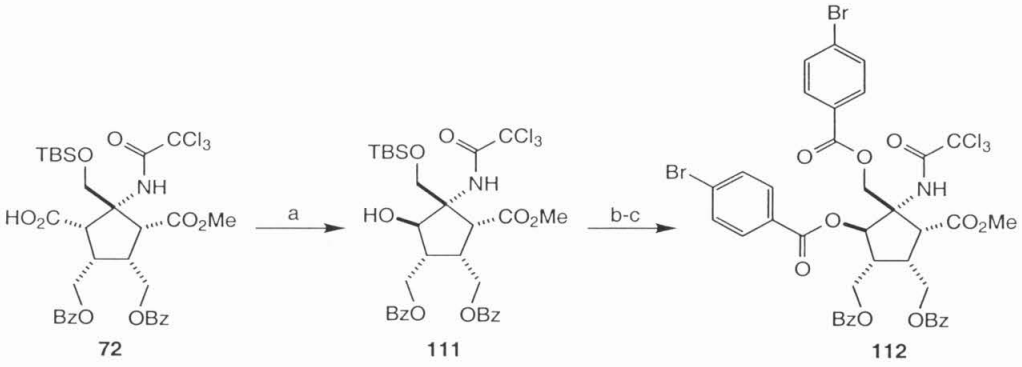


Thus, Barton ester **105** was formed in $CHCl_3$ (**72** was insoluble in CCl_4) and allowed to stir for 5 hours until consumption of starting material was indicated by TLC and the reaction had faded to colorless from the initially yellow solution. This reaction resulted in clean formation of a single product at higher R_f than starting material.

Initial examination of the ^{1}H-NMR spectrum of this product indicated that it had decarboxylated to give a substituent at the desired position but retained the trichloroacetamide moiety. The product was believed to be one of the desired chlorine transfer diastereomers. Low resolution mass spectral analysis gave no clear molecular ion peak but gave fragments displaying an isotope distribution pattern consistent with either 3 chlorines or 4, thus making mass spectral determination of chlorine content ambiguous. In hopes of obtaining a crystalline derivative for X-ray analysis, the p-

bromobenzoate derivative was synthesized and found to contain *two* bromo-benzoate esters (by ^{1}H-NMR)! Thus, structure **112** was assigned to the product and subsequent nOe analysis of **112** confirmed that the unexpected bromobenzoxy group was in the desired position for chlorination but opposite in stereochemistry (Scheme 22) based on reciprocal enhancements observed between the trichloroacetamide N-H and the benzoxy methine C-H.

Scheme 22



Conditions: a) 2-thiopyridine-*N*-oxide, EDC, DMAP, $CHCl_3$; b) HF-CH_3CN; c) $BrC_6H_4CO_2H$, EDC, DMAP.

Barton had documented the formation of hydroxyl and hydroperoxyl products of oxygen trapping in his report.[37] In those cases, the reaction was performed in an oxygen saturated toluene solution. Oxygen trapping in the presence of a chlorine donor was not reported. Combined, these data strongly indicate structure **111** for the product obtained from attempted intramolecular chlorine transfer, the result of an *inter*molecular oxygenation by dissolved oxygen in the solvent, without participation of the internal trichloroacetamide chlorine donor.

Reevaluating Intramolecular Chlorine Transfer

At this point, a reconsideration of the feasibility of intramolecular chlorine transfer was in order. It is noteworthy that only 1,2-chlorine migration is known and there are no examples of intramolecular homolytic chlorine transfer across larger rings (>3) in the literature. Furthermore, a reaction like the Hofmann-Loefler-Freitag[49] pyrrolidine synthesis would appear to offer precedent but, in fact, it proceeds through an intermolecular radical trapping event to give the formal product of 1,5-chlorine transfer.

Schiesser has studied the homolytic intramolecular chlorine transfer mechanism and, in a full paper on the subject published contemporaneously with our chlorine transfer experiments, detailed the outcome of a computational study of this mechanism.[50] It was concluded that the cyclic transition states **113-115** (6-8 member rings, Scheme 23) were 37-56 kcal/mol higher than the ground state and, thus, could not reasonably be part of a reaction pathway under "normal" or mild conditions. To rationalize this outcome it was argued that transfer of halogen must proceed through a concerted "divalent" transition state wherein the breaking and forming bonds are co-linear, analogous to the SN_2 mechanism. Deviation from co-linearity of the breaking and forming bonds enforced by an intramolecular geometry causes the activation barrier to increase substantially. Consistent with this explanation is the trend observed by Schiesser of decreased activation barrier with increased ring size in the transition states **113-115**.

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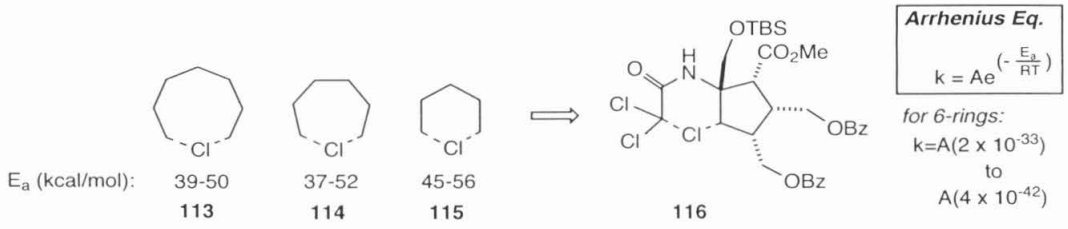
[49] For examples see: (a) Titouani, S. L.; Lavergne, J.-P.; Viallefont, P. *Tetrahedron* **1980**, *36*, 2961. (b) Kimura, M.; Ban, Y. *Synthesis* **1976**, 201. (c) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657.

[50] Schiesser, C. H.; Wild, L. M. *J. Org. Chem.* **1998**, *63*, 670.

Scheme 23



The Schiesser study is directly applicable to the attempted intramolecular chlorine transfer reactions described in this dissertation. Intramolecular chlorine transfer with **116** required the six member ring transition state (E_a=45-56 kcal/mol in Schiesser's study) and was further hampered by the 16-20 kcal/mol rotational barrier to get from the thermodynamically favored, but unreactive "cis-amide" to the reactive "trans-amide" conformation. By plugging Schiesser's values for E_a for the six member ring transition state (45-56 kcal/mol) into the Arrhenius equation at 25 °C, a reasonable reaction rate ($k > 8 \times 10^{-6}$ s^{-1}; $t_{1/2}$ = 1 day) would require $A > 4 \times 10^{27}$ s^{-1}!

Although intramolecular chlorine transfer was not realized, the outcome of attempted chlorine transfer demonstrated that substrate directed stereoselective radical mediated functionalization of the cyclopentane nucleus of **72** could be achieved. Taking this lead, our attention then shifted to a recently reported series of natural products, axinellamines A-D **2-5**,[2] possessing a similar core to that of palau'amine **1** but with opposite relative stereochemistry at the chlorine position and one other position on the ring.

IV. Enantioselective Synthesis of the Axinellamine Core

Introduction

Following the discovery that **72** did not participate in an intramolecular chlorine transfer, and the publication of Schiesser's report that such mechanisms have prohibitively high activation barriers,[50] our interest in accessing natural products with the highly functionalized chlorocyclopentyl core was renewed by the report, in 1998, by Quinn and co-workers of a new class of marine natural products, axinellamines A-D **2-5** (Figure 11).[2] The axinellamines contain a remarkably similar densely functionalized chlorocyclopentyl core to that of palau'amine,[1] however, the stereochemistry of the chlorine substituent is opposite to that in palau'amine (relative to the adjacent aminomethylene) suggesting an intermolecular chlorine transfer could install the requisite chlorine in an intermediate similar to **72**.

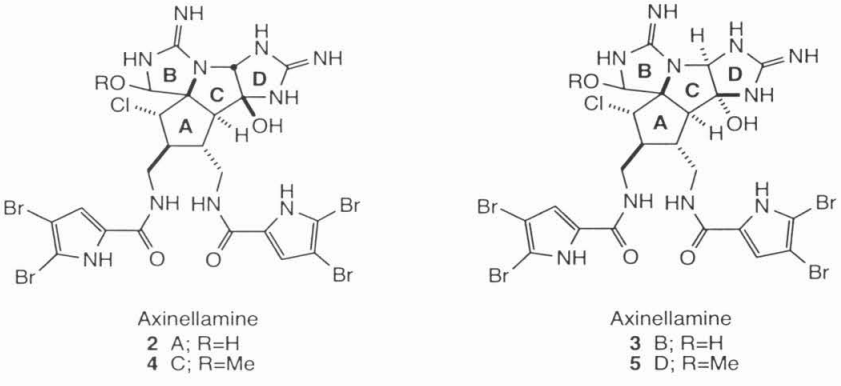


Figure 11. Axinellamines A-D.

The axinellamines were isolated from the Australian marine sponge *Axinella* sp. Axinellamines B-D showed bioactivity against *Helicobacter pylori* (1000μM), a bacterium associated with pepticular and gastric cancer, but axinellamine A **2** was not

reported to have bioactivity. Their structures were determined by spectral methods and were found to differ from each other in the identity of substituent -OR, (OR=OH in A and B, OR=OMe in C and D), and the stereochemistry of the C-D ring fusion.[2]

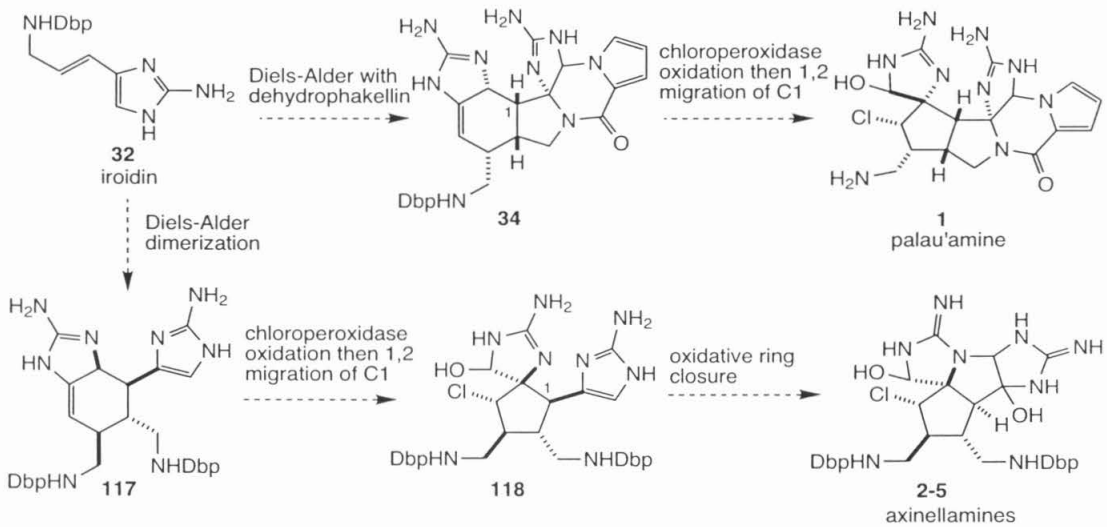
The complex tetracyclic framework of the axinellamines is reminiscent of the nitrogen rich hexacyclic structure of palau'amine **1**.[1] A comparative dissection shows that both possess (1) a pair of five-member cyclic guanidines, (2) a substituted pyrrolidine ring, (3) at least one acyl-pyrrole unit, (4) a chlorine substituent, and (5) a stereochemically dense, highly functionalized, cyclopentyl core onto which the aforementioned groups are appended. At first glance, the axinellamines appear to be quite different from palau'amine **1** in the arrangement and connectivity of the individual substructures they have in common. However, the similarity of the unusual chlorocyclopentyl cores strongly suggests a biogenetic connection between the two classes of natural products (Scheme 24).

One could propose rearrangements which produce axinellamine-like connectivity from the palau'amine connectivity, but it is important to note that the relative stereochemistry of the substituents in the axinellamines would prohibit their spontaneous rearrangement to or from the corresponding palau'amine derivatives. Furthermore, palau'amine **1** and the Styloguanidines **29-31** have been found together[1] but there have been no reports of either being isolated from the same source as the axinellamines, making a direct interconnection unlikely.

Scheuer's proposed biosynthesis of palau'amine **1** (Scheme 24, top row) provides insight into the possible origin of the axinellamine structure.[1] He proposed the Diels-Alder reaction of dehydrophakellin **33** with oroidin **32** to give the adduct **34**.

Chloroperoxidase mediated oxidation and concomitant 1,2 migration of C-1 then gives the palau'amine skeleton **1**. By analogy, the Diels-Alder cyclodimerization of oroidin **32** would give adduct **117** that, after chloroperoxidase oxidation and 1,2 migration of C-1, would give the axinellamine-like compound **118**. Oxidation of the amino-imidazole function followed by intramolecular nucleophilic attack by the guanidine would then give the axinellamines **2-5**. This biosynthetic scheme is only conjecture but nevertheless highlights the similarity of the axinellamines to the palau'amines and styloguanidines through their apparent origins in the oxidative rearrangement of oroidin Diels-Alder adducts.

Scheme 24

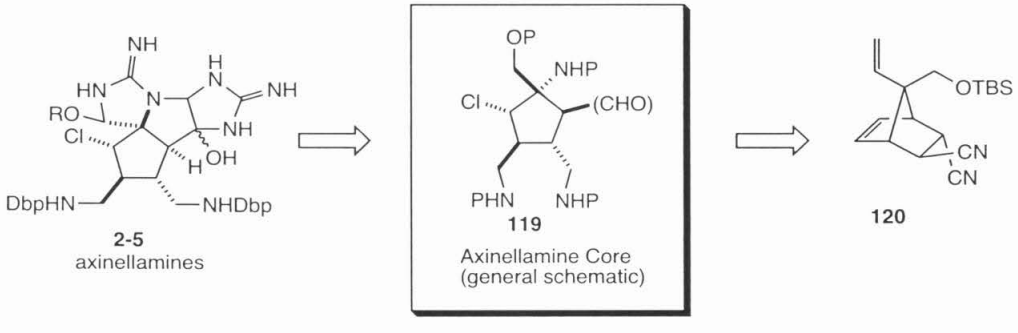


In the palau'amine studies (section III of this dissertation) the attempted intramolecular chlorine transfer (**72** → **73**) resulted in formation of a single isomer of **111** having the relative stereochemistry of the chlorine substituent of the axinellamine core. With the subsequent report of the axinellamines we could view this result as a "model" study and, thus, we turned our attention to the synthesis of a fully

functionalized axinellamine core having correct relative stereochemistry and functionalization at all positions. The complete synthesis of the axinellamine core based on that hypothesis is described below and constitutes the final body of work performed for this dissertation.

Our initial retrosynthetic strategy identified trans-dinitrile **120** as a suitable starting material from which the axinellamine core could be accessed (Scheme 25). From **120** we targeted a general core architecture **119** which embodies the main stereochemical requirement of a synthesis of **2-5** wherein the two nitriles would be surrogate functionality for the trans aminomethylene substituents of **119** and the bridging quaternary carbon of **120** would become the quaternary carbon of **119**. Ozonolysis of the endocyclic olefin of **120** would provide functional handles for elaboration of the remaining substituents of **119** including the chlorine substituent, which would be installed using Barton chemistry.[37]

Scheme 25



We looked to the post Nakamura fragmentation[29] intermediates of the palau'amine core synthesis for a starting point of the axinellamine synthesis. In this way it was thought that some of the strengths of the palau'amine route could be incorporated into a synthesis of the axinellamine core while some of the weaknesses could be

addressed in the context of the new synthesis. In particular, we hoped to reintroduce asymmetry that was lost in the Nakamura fragmentation (**87** → **88**),[29] and build in, at an earlier stage, the diamine functionality that had been delayed in the palau'amine synthesis. With these goals in mind, a new route was developed which began with anhydride **93** and took advantage of Bolm's recently reported methodology[51] for the enantioselective methanolysis of meso anhydrides to introduce asymmetry.

A number of key features make this synthetic plan attractive. It begins with an advanced intermediate from the palau'amine study and, therefore, benefits from the successful Nakamura reaction (**87** → **88**) worked out in that synthesis. The subsequent meso anhydride **93** maps well onto Bolm's asymmetric methanolysis[51] reaction and the resulting disposition of acid and ester would allow selective epimerization of the ester to give the trans substituted norbornene.[52] This trans relationship makes possible the required aminations at these two positions that was found to be prohibitively difficult in the analogous cis oriented substrate **67** (section III). Finally, the utilization of successful functional group manipulations worked out in the palau'amine study for late stage elaboration of the axinellamine core promised a higher probability of success in this route.

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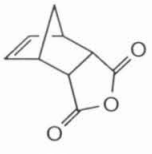
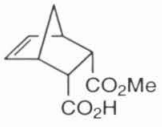
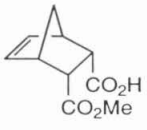
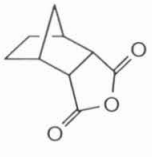
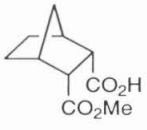
[51] Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett*, **1999**, 195.

[52] C-α-epimerization of a methyl ester vicinal to a carboxylic acid (cis → trans) has been accomplished with NaOMe: (a) Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132. (b) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. (c) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789. And with KO^{t}Bu: (d) Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. *Tetrahedron: Asymmetry* **1999**, *10*, 3403.

Results and Discussion

Anhydride **93** was synthesized in 8 steps and 52% overall yield from spiro[2.4]hepta-4,6-diene 1-methanol **7** according to the sequence reported in section III of this dissertation. Bolm had previously reported the quinine and quinidine promoted asymmetric methanolyses of norbornene-like anhydrides **121** and **122** in 83-86% yield and 94-98% ee giving us confidence that the methanolysis procedure would prove fruitful when applied to **93** as well (Table 4).[51]

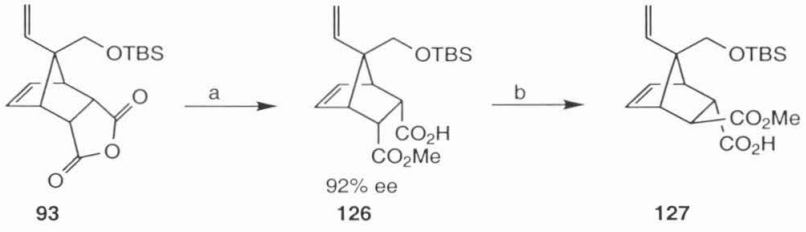
Table 4. Bolm's asymmetric methanolysis of meso anhydrides.

Entry	Anhydride	product	promoter/ yield (ee)
1.	 **121**	 **122**	quinidine/ 83% (98%)
2.		 **123**	quinine/ 85% (98%)
3.	 **125**	 **124**	quinine/ 86% (94%)

Conditions: MeOH (3 eq), promoter (1.1 eq), anhydride (1 eq), 1:1CCl_4/PhMe, -50 deg C, 48 h.

In the event, treatment of **93** with methanol in 1:1 toluene/CCl_4 in the presence of 1 eq. of quinine (Scheme 26) gave the expected acid/methyl ester **126** in quantitative yield and 92% ee.[53]

Scheme 26



93 **126** **127**

Conditions: a) quinine, MeOH, CCl_4, toluene; b) 5 eq LDA then H^+, 73% (from **93**)

The success of this reaction with **93** opened the door for separate asymmetric syntheses of both enantiomers of the axinellamine core because Bolm's study showed that the quinine and quinidine promoted methanolyses produced opposite enantiomers in equally high efficiency (Table 4). It was found that treatment of acid-ester **126** with 5 equiv LDA in ether at –78 °C followed by warming to 0 °C effected complete conversion to trans acid-ester **127** which was obtained in 73% yield after chromatography. Reactions performed at lower temperature (-78 °C) failed to completely consume starting material as did reactions using fewer equivalents of LDA. If allowed to warm to 23 °C, appreciably amounts of a colored product formed which may indicate methoxide elimination to form the corresponding ketene.[54] The product **127** was

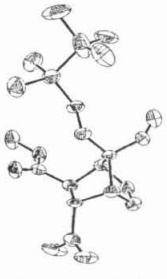


Figure 12. ORTEP of **127.**

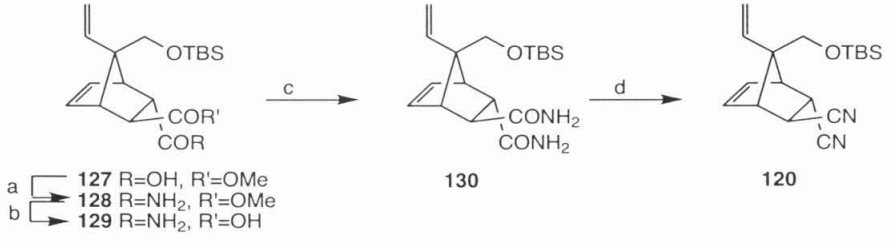
[53] The enantiomeric excess was determined by preparation of the amide derived from (R)-(+)-α-phenethylamine and integration of the methyl doublets in the ^1H NMR spectrum.

[54] Ester enolates undergo elimination to form ketenes at room temperature. See: (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Ireland, R. E.; Mueller R. H. *J Am. Chem. Soc.* **1972**, *94*, 5897.

dissolved in boiling hexanes and the solution was allowed to cool to obtain X-ray quality crystals. Single crystal X-ray diffraction analysis of **127** confirmed its constitutional structure as well as relative and absolute stereochemistry (Figure 12). The absolute configuration of **127** was (2*S*, 3*S*), indicating the formation of the (2*R*, 3*S*) acid ester in the Bolm methanolysis (**93** → **126**) and is consistent with Bolm's report of the stereochemical bias imparted by the quinine promoter.[51]

From trans acid-ester **127**, an iterative protocol was developed to access the desired dinitrile **120** (Scheme 27). First, treatment of **127** with EDC and HOBt in CH_2Cl_2 followed by quenching the initially formed HOBt ester with 25% ammonia in water gave ester-amide **128**.[46] Then, hydrolysis of the methyl ester of **128** with KOH in THF/H_2O and treatment of the resulting acid-amide again with EDC and HOBt in CH_2Cl_2 followed by 25% ammonia gave trans-diamide **130** in 83% yield (from **127**).

Scheme 27



Conditions: a) EDC, HOBt then 25% NH_3; b) KOH, THF/H_2O; c) EDC, HOBt then 25% NH_3, 83% (from **127**); d) TFAA, pyr. THF -78 °C, 93%.

Dinitrile **120** was finally realized in 93% yield from **130** by double dehydration with TFAA and pyridine in THF at –78 °C according Compagna's procedure.[13] Initial attempts to reduce diamide **130** to the corresponding diamine **132** with LAH in refluxing THF were unsuccessful, returning either unreacted starting material or complex mixtures of starting material and unidentified partial reduction products. The ease of synthesis of

120 from **130** and the known reduction of nitriles to amines with LAH or $NaBH_4$ according to Ganem's CoB_2 catalyzed method made the dinitrile an attractive recourse for access to diamine **132** (Scheme 28).[55]

Simple reductions of **120** at 0 °C or room temperature with LAH, resulted in slow reduction to the desired product **132** with concomitant formation of a product believed to be amino alcohol **134** as a side-product. Presumably, formation of **134** resulted from aluminum oxide contaminants in the LAH as it could not be suppressed by rigorous exclusion of water from all other components of the reaction. In hopes of circumventing the use of LAH, the Ganem procedure of nitrile reduction using $NaBH_4$ and in-situ formed CoB_2 ($NaBH_4$ + $CoCl_2$) was applied to **120**. While complete reduction to the desired diamine **132** probably occurred, the norbornene olefin proved unstable to the reducing conditions and only the saturated diamine **133** was observed (as evidenced by the lack of endocyclic olefinic C-H signals in the ^{1}H-NMR of the unpurified product). Furthermore, the microfine CoB_2 precipitate proved problematic to remove by filtration. The CoB_2 additive is known to be a proficient hydrogenation catalyst and H_2 is a byproduct of CoB_2 formation; therefore, it was reasoned that this procedure could be effective if the CoB_2 was formed and isolated in a separate step then added to the reduction. Ganem had previously reported the use of preformed CoB_2 in reductions of nitriles; however, in our hands the preformed CoB_2 catalyst also promoted hydrogenation of the olefin.[55] A more convenient variant of the catalyst was prepared by forming the CoB_2 in the presence of 300 wt% celite based on the anticipated weight

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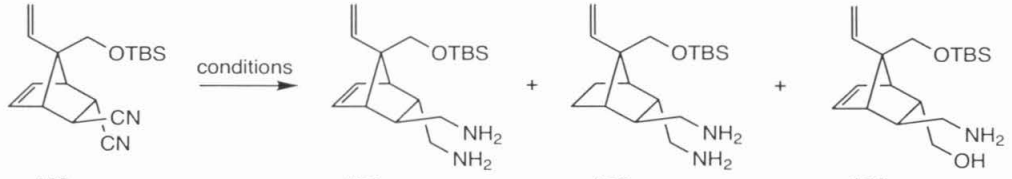
[55] For a review see: (a) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. See also: (b) Osby, J. O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67. (c) McManis, J. S.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 2041. (d) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* ***1982***, *104*, 6801.

of CoB_2 product to give a 25 wt% CoB_2 powder. This fluffy grey solid filtered easily and was tested with LAH as the reductant in hopes the more active hydride source could compensate for the less active celite adsorbed catalyst. To our delight, it was found that the LAH reduction of **120** using 10 wt% of 25% CoB_2 adsorbed on celite proceeded smoothly and rapidly (<5 min) to the desired diamine **132** at 0 °C in ether in 93% yield.

Scheme 28



120 132 133 134

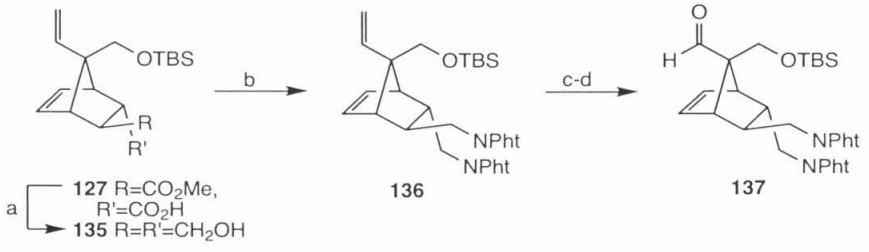
1. $NaBH_4/CoCl_2$	not observed	observed	not observed
2. $NaBH_4/CoB_2$	not observed	observed	not observed
3. LAH (no catalyst)	observed	not observed	observed
4. LAH/10 wt% of 25% CoB_2 on celite	93% < 5 min	not observed	not observed

The unpurified diamine product was not contaminated with either the amino-alcohol side product **134** or the saturated product **133** (by TLC) and was converted to its bis(trifluoroacetamide) or bis(^{t}butyloxycarbonyl) derivative for subsequent studies that are not reported here.

Despite the work invested in synthesizing dinitrile **120**, and optimizing its reduction to diamine **132**, the overall sequence (**127** → **132**) was needlessly circuitous and a more direct route to a protected version of **132** was investigated. To that end, trans-acid-ester **127** was subjected to exhaustive reduction with LAH in ether to give a

single diol **135** in 81% yield (Scheme 29). Mitsunobu coupling of diol **135** with two eq. of phthalimide using 2.5 eq each of DEAD and PPh_3 in THF gave bis(phthalimide) **136** in 88% yield after chromatography.[56] Despite the particularly laborious purification to remove 5 eq. of reagent byproducts, the two step overall sequence from **127** to protected diamine **136** was vastly superior to the previous 6 step sequence for the analogous transformation via dinitrile **120**.

Scheme 29



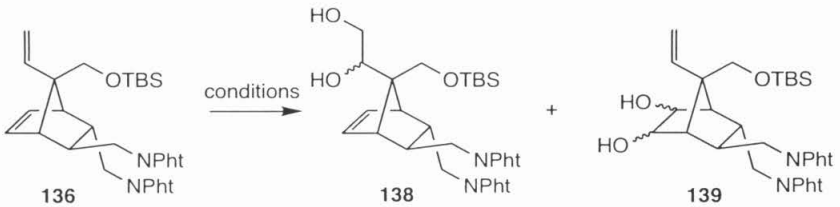
Conditions: a) LAH, 81%; b) phthalimide, DEAD, PPh_3, 88%; c) OsO_4, NMO, $(DHQD)_2Pyr$, 98%; d) $NaIO_4$, K_2CO_3, 92%.

With an efficient synthesis of diene-bisphthalimide **136** worked out, the next task was selective oxidative cleavage of the terminal olefin and Curtius rearrangement to install the third amino functionality. A similar selectivity problem had been overcome in the palau'amine core synthesis when diene **95** was selectively dihydroxylated at the less hindered (though electronically less reactive) terminal olefin. In the palau'amine study, the ligand, $(DHQD)_2Pyr$, was necessary to promote adequate reaction rate and did not play an apparent role in olefin selectivity (reactions performed without ligand produced little product at all). In contrast, the less hindered endocyclic olefin of **136** proved susceptible to dihydroxylation in the absence of a ligand (Scheme 30). In a comparative study, it was found that oxidation of **136** using 5 mol% OsO_4, and 300

[56] Slusarska, E.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, *2*, 402.

mol% NMO in THF/water gave, after 50% conversion, 30% of the desired diols **138** and 10% undesired diols **139**. When the same reaction was performed with 5 mol% $(DHQD)_2Pyr$, only the desired diols **138** were detected even after complete conversion of starting material.[43]

Scheme 30



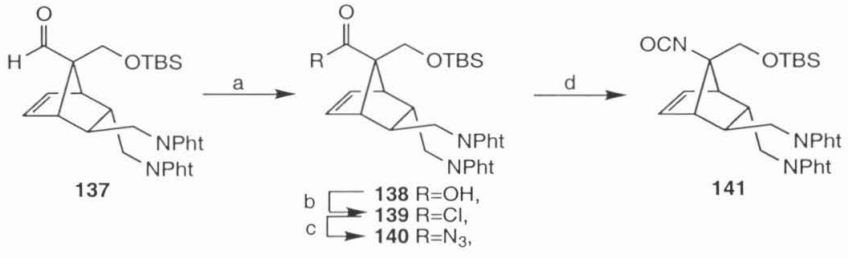
Yield @ 50% conversion without ligand	30	10
Yield @ 100% conversion with 5% $(DHQD)_2Pyr$	79	0

As in the palau'amine study, while olefin selectivity was complete (to the limit of NMR detection), stereoselection was poor, giving **138** as a 1:1 mixture of diastereomers. In practice, the optimum conditions were those used for the above study and gave 79% yield of the chromatographically pure diols **138**.

Diols **138** were subjected to $NaIO_4$ cleavage in 1:1 THF/water in the presence of 3 eq. K_2CO_3 to give a 92% yield of aldehyde **137** and complete the two-step LeMieux-Johnson protocol.[43] Oxidation of aldehyde **137** to carboxylic acid **140** using pH=4 buffered $NaClO_2$ in 5:1 ^{t}BuOH/DMSO gave a quantitative yield of a mixture of the

desired acid **140** plus 5-10% of the corresponding acid chloride (Scheme 31).[57] The unpurified mixture was then fully converted to the acid chloride using oxalyl chloride in CH_2Cl_2.[58] Following removal of solvent *in vacuo*, the acid chloride was dissolved in DMSO and treated with 1.2 eq NaN_3 to give, after aqueous workup, the corresponding acyl azide. Curtius rearrangement of the acyl azide in refluxing benzene was monitored by IR for disappearance of the azide stretch (ν 2132) and appearance of the isocyanate stretch (ν 2249).[59] Upon complete conversion, the reaction was cooled to room temperature and the benzene solution was directly chromatographed to give isocyanate **141** in 67% yield from **137**.

Scheme 31



Conditions: a) $NaClO_4$ pH=4, ^tBuOH, DMSO; b) $(COCl)_2$; c) NaN_3, DMSO; d) PhH, reflux, 67% (from **137**).

Conversion of the isocyanate **141** to the desired Cbz amine **142** using the method employed in the palau'amine study (BnOH solvent, 110 °C, DMAP) resulted in significant decomposition and the best yield obtained was 36%. In hopes of eliminating the need for excess BnOH, anionic additions were explored. It was found that lithium

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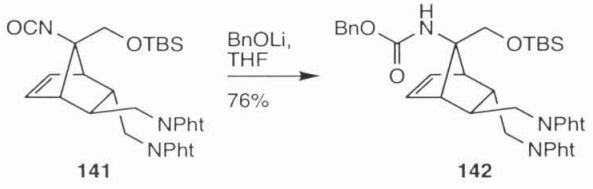
[57] (a) Lindgren, B. O.; Nilsson, T. *Acta, Che. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 4825.

[58] Devos, A.; Remion, J.; Frisque-Hebian, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc. Chem. Commun.* **1979**, 1180.

[59] Simon, W.; Seibl, J.; Clerc, T. *Spectral Data for Structural Determination of Organic Compounds*; 2nd ed.; Springer-Verlag: Berlin, **1989**.

benzyloxide readily added to the isocyanate in THF to give the desired Cbz amine, while the magnesium salt was moderately reactive and the sodium salt was slow and was accompanied by decomposition. In a preparative scale reaction, treatment of 1.2 eq BnOH with 1.1 eq BuLi followed by addition of the isocyanate at 0 °C resulted in immediate formation of the desired Cbz amine **142** obtained in 76% yield after work up and chromatography.[60]



141 **142** (6)

Ozonation of **142** in CH_2Cl_2 at –78 °C followed by reductive workup with PPh_3 gave a dialdehyde whose structure was initially assigned **143** but later was found to be **144** (Scheme 32). In-situ epimerization from the initially formed dialdehyde **143** to **144** was observed by monitoring the progress of the reduction by ^{1}H-NMR. After 3 h at 23 °C a 1:1 mixture of **143** and **144** was observed and after 16 h essentially only **144** was present. By TLC, a poorly defined streak from baseline was believed to correspond to **143**, while **144** was a well defined spot at higher R_f. As expected, over the course of the reduction, **143** disappeared completely from TLC. In practice, 3 eq. of K_2CO_3 were added to the reaction 30 min. after the PPh_3 was added to induce epimerization.[61] After 2 h only **144** was apparent by TLC. No apparent loss in yield resulted from the

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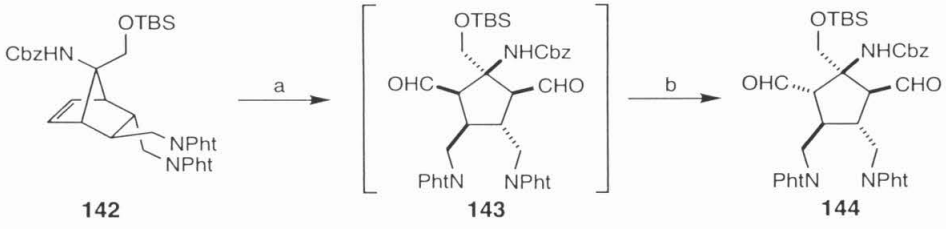
[60] BnOLi alcoholysis of acyl oxazolidinones: (a) Evans, D. A.; Lundy, K. M. *J. Am. Chem. Soc.* **1992**, *114*, 1495. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (c) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. BnOLi alcoholysis of hindered isocyanates: (d) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493. (e) Ichikawa, Y.; Osada, M.; Ohtani, I.; Isobe, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1449. (f) Lantzsch, R.; Arlt, D. *Synthesis* **1977**, 756.

[61] For epimerization of a similar dialdehyde see ref 8.

procedure and the yield of **144** was consistently above 85% after chromatographic purification. The structure of **144** was determined unambiguously by nOe difference analysis.

Scheme 32



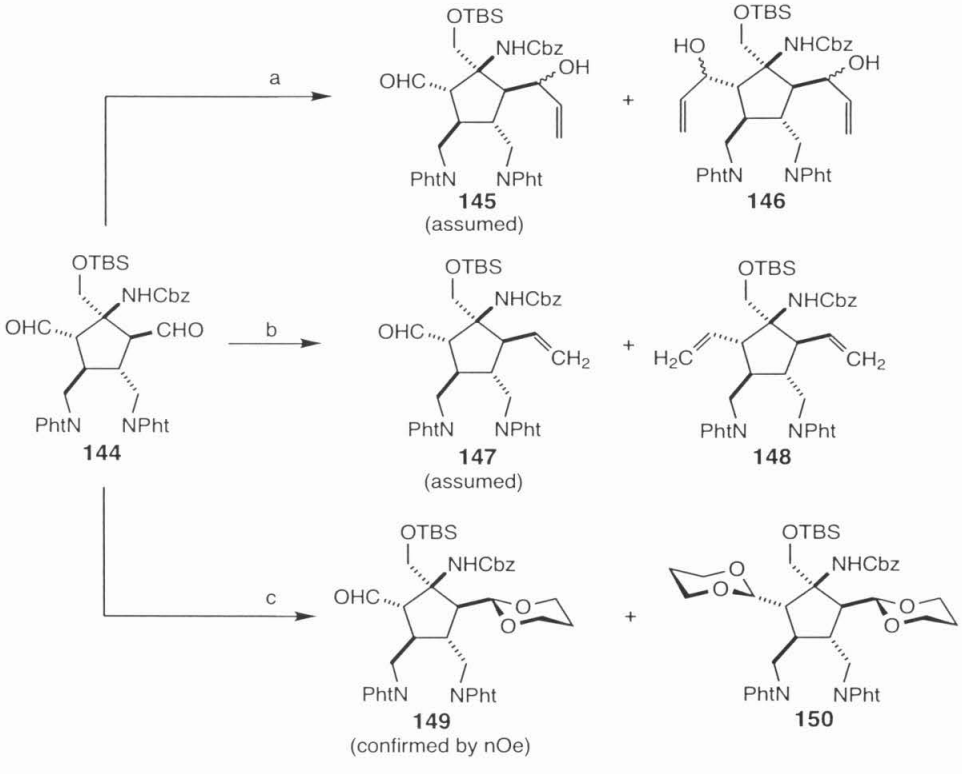
Conditions: a) O_3/O_2, 23 °C, then PPh_3; b) K_2CO_3 (3 eq), 88%.

Selective protection of the C-2 carboxaldehyde was required by the synthetic plan. The outcome of the ozonation step was somewhat discouraging because our strategy counted on the differing steric environments of the C-2 and C-5 carboxaldehydes in structure **143** to provide a bias for selective chemistry at the desired aldehyde. In models of **143**, C-5 was significantly more hindered than C-2 due to the N-H and amino methylene groups flanking it on the same face of the ring. On the other hand, C-2 is adjacent only to the N-H group on the same face leaving it more accessible to nucleophiles or reducing agents.

In the trans ozonation product **144,** there is much less steric bias between the C-2 and C-5 carboxaldehydes. Only the difference between the carbamate N-H and the silyloxymethylene would influence selective chemistry at these sites. Thus, we envisioned using the carbamate nitrogen to direct additions to the C-2 carboxaldehyde. Scheme 33 reports the outcome of some of the methods that were attempted. Addition of vinyl magnesium bromide produced the desired product of vinyl addition in 30-50% yield (based on ^{1}H-NMR of the mixture of **145** and **146**) but it was difficult to stop at

exclusively the mono-addition product **145** which was chromatographically inseperable from **146**. The use of additive $Mg(OTf)_2$ offered modest improvement; however, removal of Mg(II) from the product was problematic and the product of double addition **146** would begin to form at approximately 60% conversion.

Scheme 33

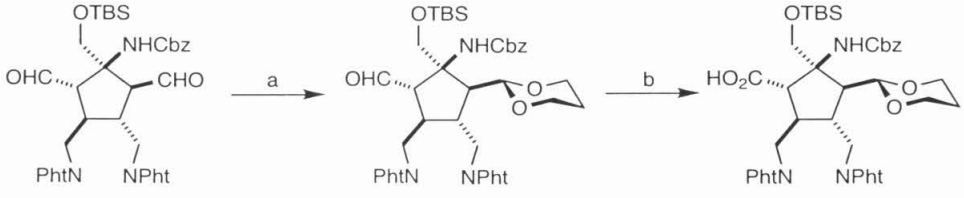


Unfortunately, the double addition product **146** was the same R_f as **145** and proved to be neither observable by TLC during the course of the reaction nor removable by chromatography after workup, but its presence could be determined and quantified in the NMR spectrum of the product mixture. Although mixtures of **145** and **146** could be cleanly oxidized to the corresponding α,β-unsaturated ketones using PCC in CH_2Cl_2 in the presence of 4Å sieves, that mixture remained inseparable as well. Wittig olefination of **144** with 2 eq of methylene triphenylphosphorane (methyl triphenylphosphonium

bromide + KO^{t}Bu in THF) at -78 °C was similarly non-selective returning a mixture of starting material, plus mono-, and bis- olefinated products **147** and **148**.[62]

Success was realized in the protic acid catalyzed acetalization of **144**. It was found that treatment of **144** in ether with 1,3-propane diol and PPTS resulted in selective formation of the desired mono-acetal **149** in 59% yield. Ethereal solvents proved superior to benzene or CH_2Cl_2 for the acetalization due to significant protolytic cleavage of the silyl ether and poorer aldehyde selectivity in the latter solvents. Substituting TsOH for PPTS only amplified the formation of the undesired products.

Scheme 34



144 **149** **151**

Conditions: a) 1,3-propanediol, Et_2O, PPTS, 23 °C, 59%; b) $KMnO_4$, pH=7, ^{t}BuOH.

Unambiguous determination of the structure of **149** was provided by extensive nOe analysis. First, reciprocal enhancements were observed between H-α and the carbamate N-H and aldehyde C-H protons (Figure 13). This established the stereochemical relationship between the single remaining carboxaldehyde and the quaternary carbon. Further confirmation of structure was evident in reciprocal enhancements observed between H-β and the carbamate N-H. It was, therefore, concluded that the carboxaldehyde is anti to the carbamate and the acetal is syn to the

[62] Maryonoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

carbamate in **149**. These key structural elements provided the functional group layout required for the axinellamine core synthesis.

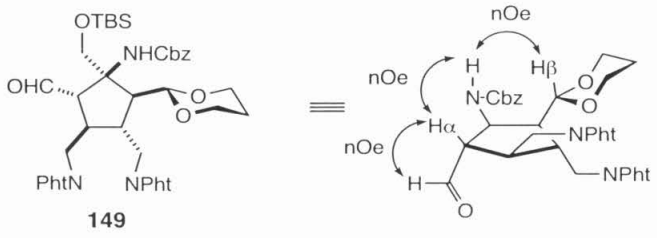
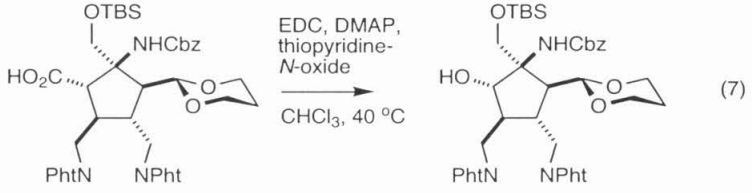


Figure 13. Evidence of stereochemistry of **149**.

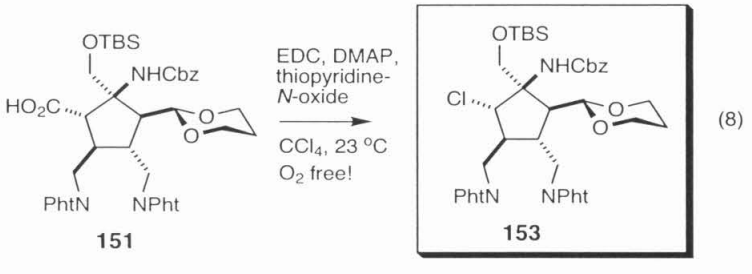
Oxidation of **149** to the corresponding carboxylic acid **151** proceeded smoothly using the Masamune conditions[31] at pH=7 and the product was carried on to the key chlorine installation step. Reaction of **151** with EDC (1.5 eq) and DMAP (0.1 eq) in the presence of thiopyridine-*N*-oxide (1.1 eq) in $CHCl_3$ resulted in formation of a single product in 50% yield, after chromatography, with spectroscopic characteristics (^{1}H-NMR, ^{13}C-NMR, IR) consistent with the desired chlorine transfer product.[37] Evidence confirming the stereochemical assignment was seen in nOe difference measurements which showed reciprocal enhancements between the carbamate N-H and the putative chloromethine C-H. Mass spectral analysis (MALDI), however, gave a mass ion for [M+Na] at 806.322 indicating the hydroxylated product **152** ([M+Na]=806.308) and not the chlorinated product had been formed (Equation 7). Furthermore, neither the mass ion nor any fragmentation products displayed evidence of chlorine content in their isotope distributions. Combustion analysis of the product also favored the hydroxylation, ruling out **152** as a product formed from **153** during ionization in the mass spectrometer. It was concluded that **152** formed when the radical intermediate formed upon decarboxylation of **152** was trapped by adventitious oxygen and the resulting hydroperoxide was reduced by sulfur species present in the reaction. This

conclusion was confirmed when formation of **152** was observed in a control reaction in which the Barton ester of **151** was allowed to react in benzene while open to the air. *No potential chlorine source was present in that reaction.* Data obtained in chlorine transfer attempts in the palau'amine synthesis, which had previously been ambiguous, was reinterpreted in light of this realization and were found to be wholly consistent with oxygen, rather than chlorine, transfer (see discussion at the end of section III).



(7)

Having confirmed the identity and stereochemistry of hydroxylated product **152**, chlorine transfer was next attempted using a better chlorine donor (CCl_4) and rigorously deoxygenated conditions. Therefore, prior to use, CCl_4 was distilled under dry N_2 (to remove any non-volatile oxygenated species) then it was sparged with dry Ar for 30 min while being subjected to sonication[63] and finally, the solution of acid **151** (1 eq), DMAP (0.1 eq), and thiopyridine-*N*-oxide (1.5 eq) in 1.5 mL of thusly prepared CCl_4 in a sealed tube was degassed with 4 cycles of freeze-pump-thaw under Ar and transferred to a glovebox.



(8)

[63] Ph.D. thesis of Dr. Emad El-Sayad. #3056; Département de Chimie Organique; Université de Gèneve.

The final reagent, EDC (1.5 equiv), which initiates the reaction, was then added under the oxygen free atmosphere of the glovebox, the tube was sealed and the reaction was stirred for 12 hours then directly subjected to silica gel chromatography to give a 76% yield of a new product and none of the previously observed hydroxylated side product. The new product was spectroscopically consistent with the desired chlorine transfer product **153** (as had been the hydroxylated product); however, strong evidence of the identity of new product was obtained in the high resolution mass spectrum which gave a mass ion for [M+Na] at 824.2727, compared with a calculated [M+Na]=824.2746 for **153**, and an isotope distribution pattern indicating one chlorine. The stereochemistry of addition was determined by reciprocal nOe's observed between the chloromethine C-H and the carbamate N-H indicating chlorine incorporation had occurred selectively from the less hindered face. Therefore, the new product was found to be the desired chlorine transfer product **153**, representing the enantioselective first synthesis of a fully functionalized core of the axinellamines A-D.

V. General Conclusion

Investigations into the potential of spiro[2.4]hepta-4,6-diene-1-methanol **7** as a general scaffold for the synthesis of functionalized cyclopentane substructures of synthetic utility resulted in the discovery of a new homoconjugate addition to an activated cyclopropane, the study of a highly functionalized cyclopentyl intermediate en route to palau'amine, and the enantioselective synthesis of the fully functionalized axinellamine core. We have demonstrated that a cyano derivative of **7** functions as a novel electrophile accepting soft carbanionic nucleophiles to give the products of ring opening homo-conjugate addition. It was shown that those products could be obtained in high stereochemical fidelity from the enantioenriched starting material and the diene products could be selectively reduced to synthetically interesting nitrile conjugated mono-olefins using mild hydrogenation conditions.

Next, **7** was implemented as a starting material in the synthesis of the elaborate natural product palau'amine **1**. Initial studies by Koch established a repertoire of functional manipulations that could be applied to Diels-Alder derivatives of **1** and served as the foundation for original work reported here. Further studies on palau'amine synthesis by the author expanded the scope of chemistry that could be done on norbornene **52**. The mode of radical fragmentation of the cyclopropane ring was highly dependent on the type of substitution on the ring system. This trend was observed in a series of examples. Two highly functionalized potential precursors to the palau'amine core were accessed from **52** and the feasibility of intramolecular chlorine transfer was investigated with these; however, intramolecular chlorine transfer was not achieved but

the possibility of an intramolecular chlorine transfer approach to the palau'amine core was not ruled out.

Finally, studies of **7** culminated with the successful first synthesis of the densely functionalized core of axinellamines A-D **2-5**. The synthesis featured an advanced stage desymmetrization of a meso anhydride using the chemistry of Bolm. This approach allowed the advancement of the synthesis with achiral intermediates accessible in large quantity before asymmetry was introduced. Subsequent steps included installation of the trans aminomethylene groups in an efficient manner and, only at a late stage, was the cyclopentane revealed through an ozonation that lead to an unexpected trans dialdehyde product, presaging the stereochemical preference for substituents on the densely functionalized ring system. The final step was a stereoselective intermolecular chlorine transfer using chlorine donor solvent CCl_4 under strictly O_2 free conditions. The identity and relative stereochemistry of the core **153** was proven by NMR and mass spectral methods. Efforts in this laboratory to convert **153** to the completed natural products **2-5** are ongoing.

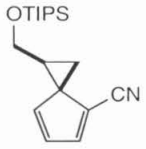
VI. Experimental Procedures

General Procedures. All reactions were performed under an atmosphere of dry nitrogen using oven dried or flame dried glassware. Reaction solvents were purchased from Aldrich or Fluka and were purified as follows: Tetrahydrofuran (THF) was distilled from benzophenone ketyl or passed over activated alumina; dichloromethane (CH_2Cl_2) was distilled from CaH or passed over activated alumina; diethyl ether (Et_2O) was distilled from benzophenone ketyl or passed over activated alumina; acetonitrile (CH_3CN) was passed over activated alumina; toluene (PhMe) was passed over activated alumina; benzene (PhH) was distilled from sodium pellets; dimethylformamide (DMF) was stored over 4Å molecular sieves prior to use; dimethylsulfoxide (DMSO) was stored over 4Å molecular sieves prior to use; methanol (MeOH) was distilled from magnesium methoxide. Carbon tetrachloride (CCl_4) was percolated through silica gel, distilled under dry N_2, then sparged with Ar for 30 min with sonication before use. Ethyl acetate, hexanes, pentane and dichloromethane used for work up and chromatography were obtained as technical grade and flash distilled prior to use or were purchased as reagent grade or higher from Aldrich or Fluka. All reagents were purchased from Aldrich or Fluka as reagent grade or better and used without further purification with the following exceptions: Tributyltinhydride was distilled at reduced pressure (<1 torr); triethylamine (TEA), diisopropylamine, pyridine, and ethyldiisopropylamine (Hünig's base) were distilled from KOH; benzyl alcohol was stored over 4Å molecular sieves prior to use; propane-1,3-diol was distilled at reduced pressure (<1 torr) from K_2CO_3; *meta*-chloroperbenzoic acid (*m*-CPBA) was washed with pH=7.4 buffer then crystallized twice

from dichloromethane; triphenylphosphone was crystallized from 95% EtOH. Chromatographic purification of products was performed on Baker 7024-R silica gel, EM Science Geduran silica gel 60, or Fluka Silica Gel 60 using a forced flow of EtOAc/hexanes eluant (unless noted otherwise) at 0.1-0.15 bar. Thin layer chromatography was performed using Merck Silica Gel 60 F_{254} TLC plates and visualized by fluorescence quenching under UV light. In addition, all TLC plates were stained using either ceric ammonium molybdate (CAM), ethanolic anisaldehyde, or aqueous potassium permanganate stain. NMR spectra were recorded on a General Electric QE Plus or Varian Mercury 300 operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively, and are referenced to the internal solvent signals. Data for ^{1}H-NMR spectra are reported as follows: chemical shift relative to tetramethylsilane (δ in ppm), multiplicity (s, singlet; d, doublet; dd, doublet of doublets; m, multiplet), integration, coupling constant (J in Hz). Measurements of nuclear Overhauser enhancement (nOe) were performed at 500 MHz by the Laboratorium für Organische Chemie NMR service at ETH in Zürich. IR spectra were recorded on a Perkin Elmer Spectrum RXI FT-IR spectrometer or paragon 1000 FTIR spectrometer using NaCl salt plates and are reported in terms of frequency of absorption (ν, cm^{-1}). Optical rotations were measured on a Jasco DIP-1000 digital polarimeter operating at the sodium D line. Gas chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatograph with a flame ionization detector and a 30 m J&W Cyclodex-B capillary column. High-resolution mass spectra were obtained from the UC Irvine Mass Spectral facility or the Laboratorium für Organische Chemie mass spectrometry lab at ETH in Zürich. Combustion analyses were performed by the Mikroelementaranalysches Laboratorium at the ETH in Zürich. X-ray

crystallography was performed by Professor Volker Gramlich of the Laboratory of Crystallography at ETH in Zürich.

The term "*in vacuo*" refers to rotary flash distillative removal of bulk solvent at < 40 °C under reduced pressure (25-100 torr) followed by further evaporation of the residue at high vacuum (< 1 torr) to remove trace solvent. Unless otherwise noted, reactions are presumed to be at equilibrium temperature with the external environment and are reported in terms of the composition of the external bath as follows: "-78 °C" indicates acetone/dry ice suspension; "-10 °C" indicates ice/salt melt; "0 °C" indicates water/ice melt; "23 °C" indicates ambient air temperature. Temperatures greater than 23 °C were measured in the external heating bath.



24

***O*-triisopropylsilylspiro[2.4]hepta-4,6-diene-1-methanol-4-nitrile 24.** To a solution of **19** (8.4g, 30 mmol) in 210 mL THF cooled to -78 °C was added chlorosulfonyl isocyanate (2.9 mL, 32 mmol) dropwise over 30 min. The mixture was stirred an additional 30 min then poured into stirring water (1.5 L), EtOAc (1 L), and TEA (15.5 mL, 111 mmol). The resulting suspension was adjusted to pH=6 by adding 1N HCl or TEA as indicated by pH paper. The mixture was stirred for 56 h. The organic layer was then separated, washed 1 x 200 mL sat. NaCl and dried over sodium sulfate. Solvent was removed *in vacuo* to give intermediate amide **23** as a viscous orange oil (9.37g, 97% mass balance; 10:1 mixture of diastereomers). The unpurified material was then taken up in 200 mL THF and cooled to -78 °C, and pyridine (23 mL, 0.28 mol) was added

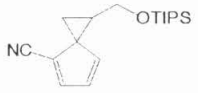
followed by freshly distilled TFAA (4.1 mL, 29 mmol) dropwise over 20 min. The resulting orange reaction was quenched immediately with 200 mL water and extracted 2 x 300 mL pentane. The combined extracts were washed 1 x 200 mL water, 2 x 200 mL 1N HCl, 1 x 200 mL pH=7 phosphate buffer (1.25 M), 1 x 200 mL saturated aqueous NaCl, then dried over Na_2SO_4. Solvent was removed *in vacuo* to give a brown oil that was purified by chromatography on silica gel (20:1 hexanes/EtOAc) to give **24** as an oil (4.09g, 46%, 2 steps).

^{1}H-NMR (C_6D_6, 300 MHz)δ 6.68 (dd, 1H, *J*=2.6, 1.5), 6.49 (dd, 1H, *J*=5.2, 1.5), 6.14 (dd, 1H, *J*=5.2, 2.6), 3.55 (dd, 1H, *J*=11.2, 4.1), 3.42 (dd, 1H, *J*=11.2, 5.6), 2.36 (dddd, 1H, *J*=9.0, 8.1, 5.6, 4.1), 1.72 (dd, 1H, *J*=12.0, 9.0), 1.68 (dd, 1H, *J*=12.0, 8.1), 1.07-0.88 (m, 21H).

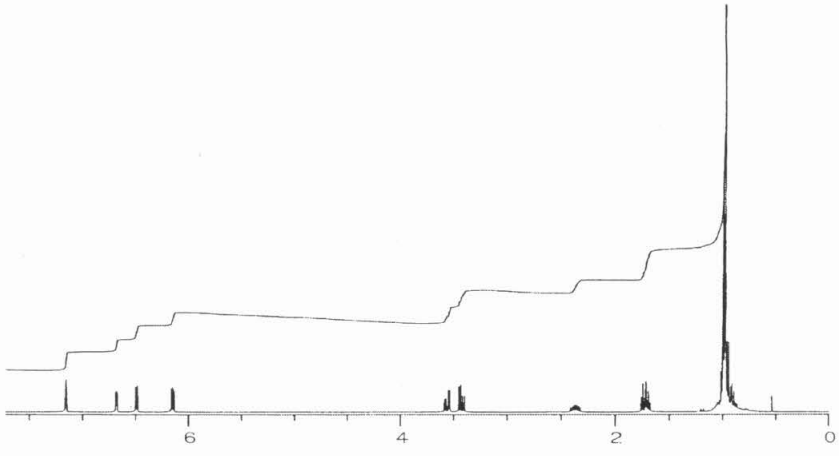
^{13}C-NMR ($CDCl_3$, 75 MHz)δ 142.84, 142.16, 129.18, 119.07, 115.56, 62.58, 44.48, 32.51, 18.93, 18.07, 11.98.

IR (thin film) ν 2945, 2867, 2210, 1729, 1467, 1384, 1259, 1138, 1110, 1013, 882, 783.

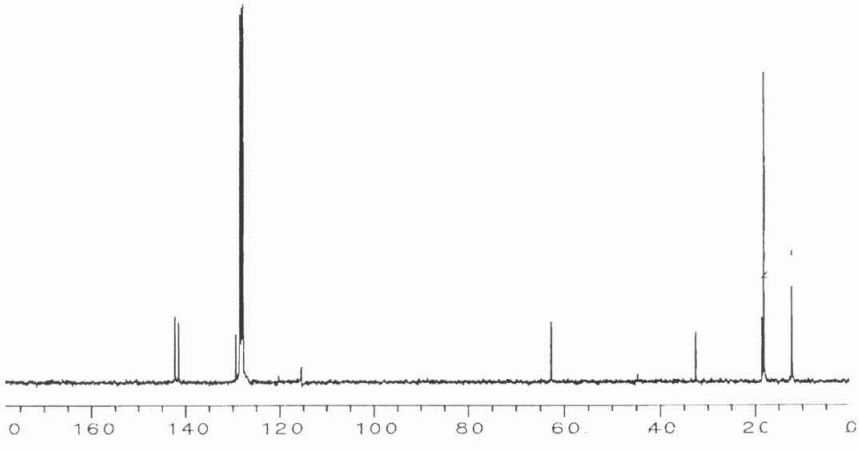
HRMS(CI) calc'd for $C_{18}H_{29}NOSi$: $[M]^+$ 303.2018; found 303.2010.



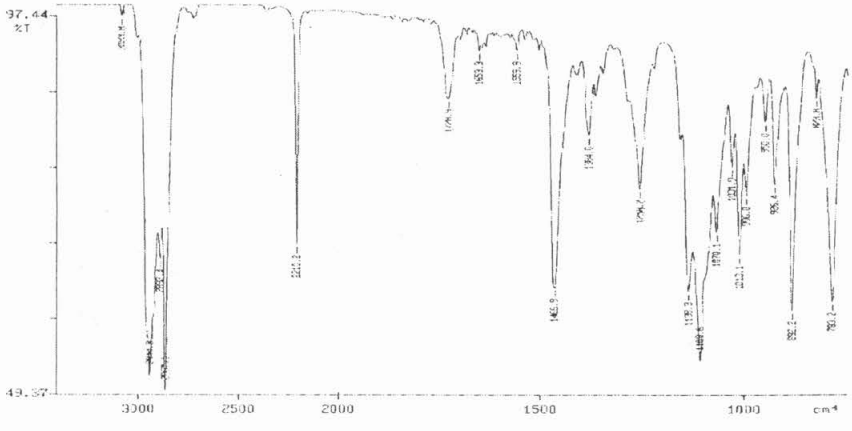
^{1}H-NMR
300 MHz
C_6D_6



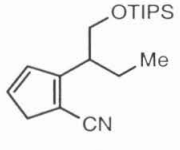
^{13}C-NMR
75 MHz
C_6D_6



FTIR
thin film



General procedure for cuprate additions To a solution of alkyl, alkenyl, or aryl magnesium bromide or lithium (3.66 mmol) in THF (12 ml) cooled to 0 °C was added CuI (1.83 mmol, 348 mg). The resulting dark suspension was stirred for 30 min then cooled to -78 °C and **24** (0.608 mmol, 0.194 ml of 100 mg/ml sol in THF) was added dropwise. The reaction was stirred for 1.5 h then warmed to 0 °C and quenched with saturated aqueous NH_4Cl (15 ml). The mixture was diluted with water (10 ml) and extracted with pentane (3 x 30 ml). The combined extracts were dried over anhydrous $MgSO_4$. Solvent removal *in vacuo* afforded an oil that was purified by chromatography on silica gel (hexanes: EtOAc 20: 1).



25a

(+)-25a: R = Methyl Obtained as a colorless oil (76%).

TLC: $R_f = 0.47$ (20:1 hexanes/EtOAc).

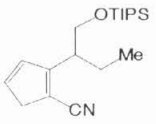
Optical rotation $[\alpha]_{Na}$ +60.2° (c = 1.37, $CHCl_3$).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.29 (dd, 1H, J = 5.3, 1.0), 5.95 (d br., 1H, J = 5.3), 3.72-3.60 (m, 2H,), 3.05-2.93 (m, 1H), 2.60 (s br., 2H), 1.67-1.33 (m, 2H), 1.08-0.92 (m, 21H), 0.76 (dd, 3H, J = 7.5, 7.5).

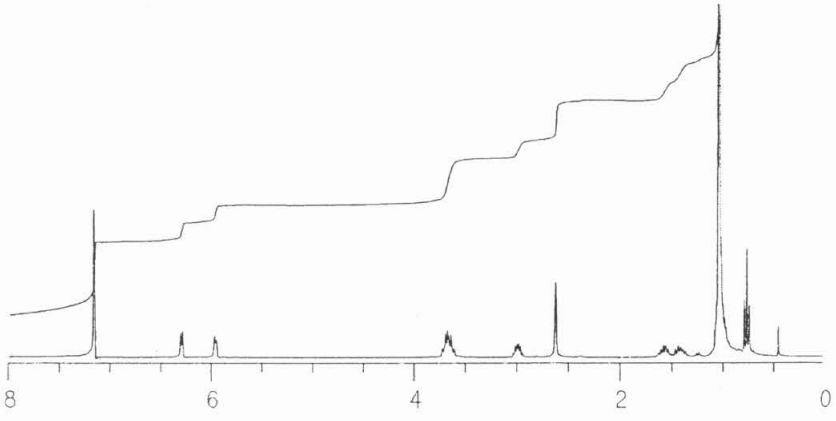
^{13}C NMR (C_6D_6, 75 MHz): 165.4, 138.3, 132.9, 65.8, 45.0, 43.5, 29.7, 23.2, 17.9, 11.9.

IR (thin film): 2943, 2867, 2210, 1463, 1382, 1368, 1248, 1119, 1067, 1010, 996, 882, 786.

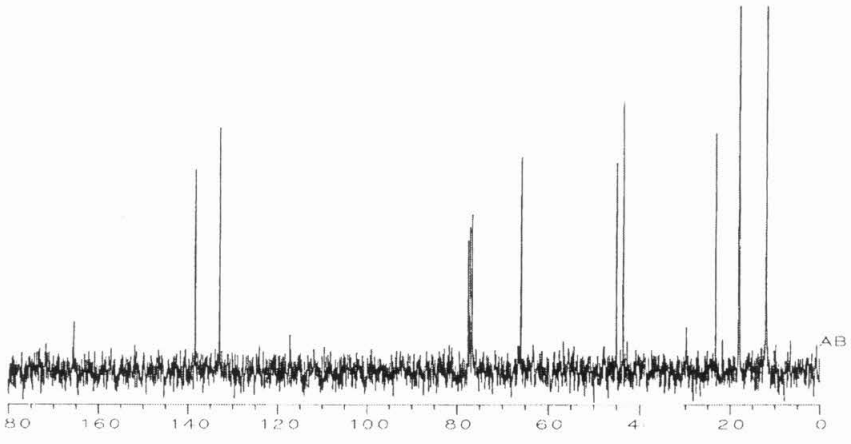
HRMS (FAB^+): calculated for $C_{19}H_{33}ONSi$: $(M+H)^+$ 320.2409, found 320.2412.



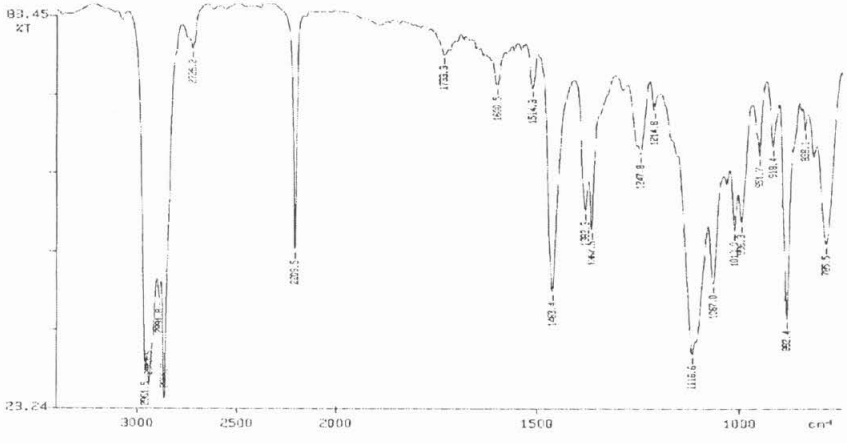
^{1}H-NMR
300 MHz
C_6D_6

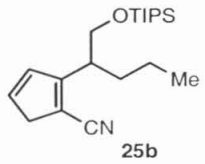


^{13}C-NMR
75 MHz
C_6D_6



FTIR
thin film





25b

25b: R = Ethyl Obtained as a colorless oil (83%).

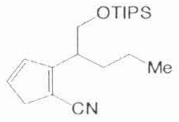
TLC: R_f = 0.49 (20:1 hexanes/EtOAc).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.30 (ddd, 1H, *J* = 5.3, 1.4, 1.3), 5.94 (dd br., 1H, *J* = 5.4, 0.5), 3.77 (dd, 1H, *J* = 9.6, J = 5.1), 3.60 (dd, 1H, *J* = 9.6, 4.2), 3.17-3.05 (m, 1H), 2.56 (s br., 2H), 1.50-1.36 (m, 2H), 1.20-1.07 (m, 2H), 1.10-0.91 (m, 21H), 0.83 (t, 3H, *J* = 7.1).

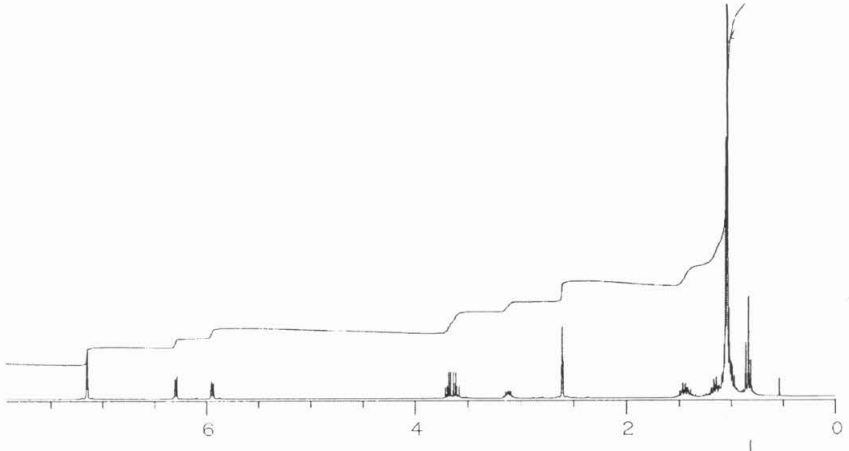
^{13}C NMR ($CDCl_3$, 75 MHz): 165.7, 138.4, 132.9, 117.2, 109.2, 66.2, 43.5, 42.9, 32.2, 20.6, 17.9, 14.0, 11.8.

IR (thin film): 2944, 2867, 2727, 2209, 1601, 1514, 1464, 1382, 1368, 1249, 1120, 1013, 997, 954, 919, 883, 792.

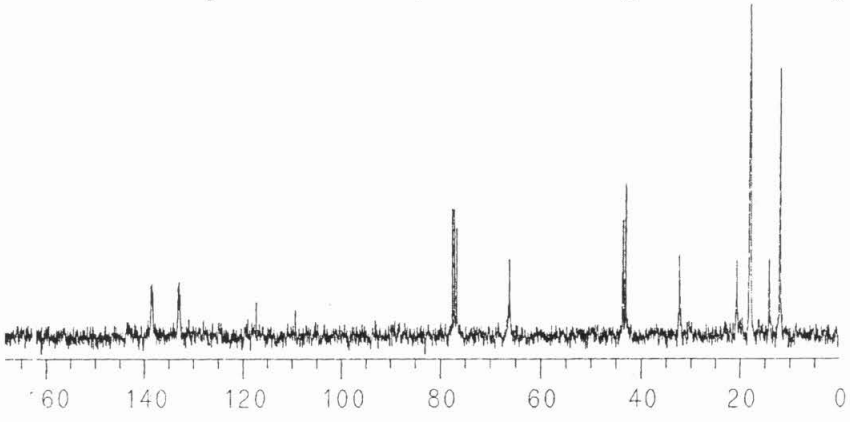
HRMS (FAB^+): calculated for $C_{20}H_{35}ONSi$: $(M+H)^+$ 334.2566, found 334.2561.



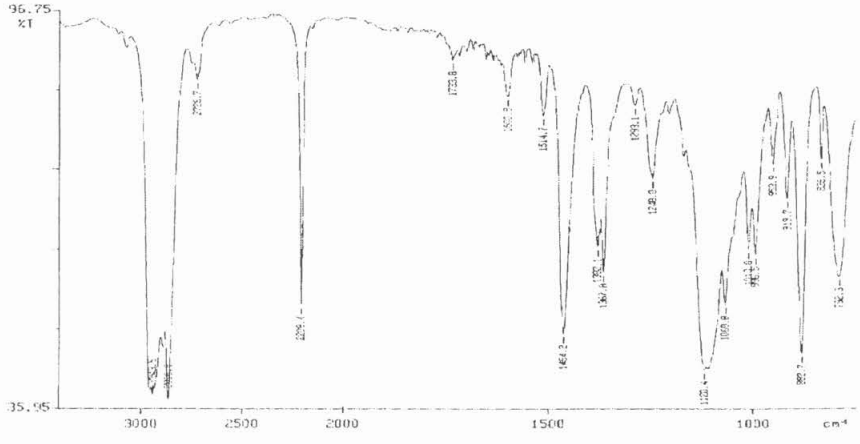
^{1}H-NMR
300 MHz
C_6D_6

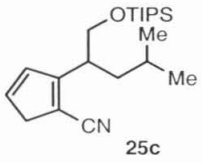


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





25c

25c: R = *i*-Propyl Obtained as a colorless oil (83%).

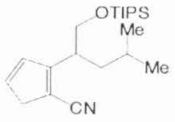
TLC: $R_f = 0.50$ (20:1 hexanes/EtOAc).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.30 (ddd, 1H, $J = 5.4, 1.4, 1.3$), 5.94 (dd br., 1H, $J = 5.4$, $J = 0.8$), 3.70 (dd, 1H, $J = 9.6, 5.2$), 3.61 (dd, 1H, $J = 9.6, 6.5$), 3.32-3.28 (m, 1H), 2.60 (d br., 2H, $J = 0.8$), 1.52-1.30 (m, 3H), 1.10-1.02 (m, 21H), 0.93 (d, 3H, $J = 6.2$,), 0.83 (d, 3H, $J = 6.2$).

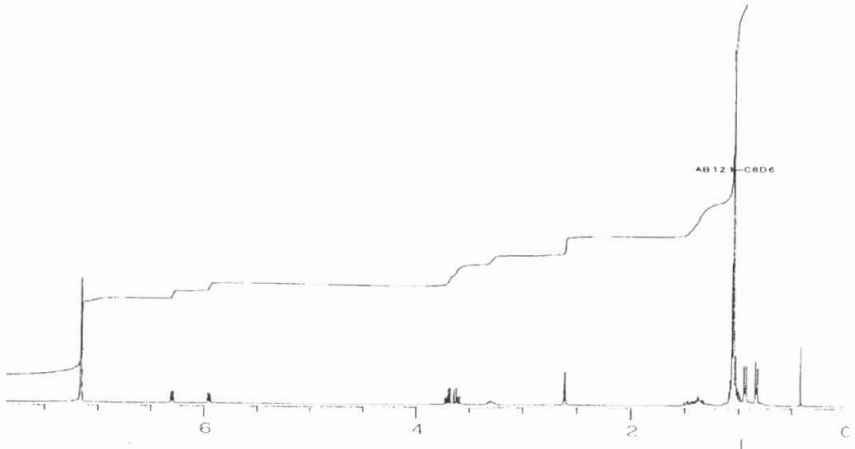
^{13}C NMR ($CDCl_3$, 75 MHz): 165.5, 138.4, 132.8, 117.1, 109.2, 66.6, 43.5, 41.1, 38.9, 25.7, 23.5, 21.9, 17.9, 11.8.

IR (thin film): 3078, 2957, 2867, 2209, 1602, 1515, 1465, 1368, 1250, 1112, 997, 953,919, 883, 784.

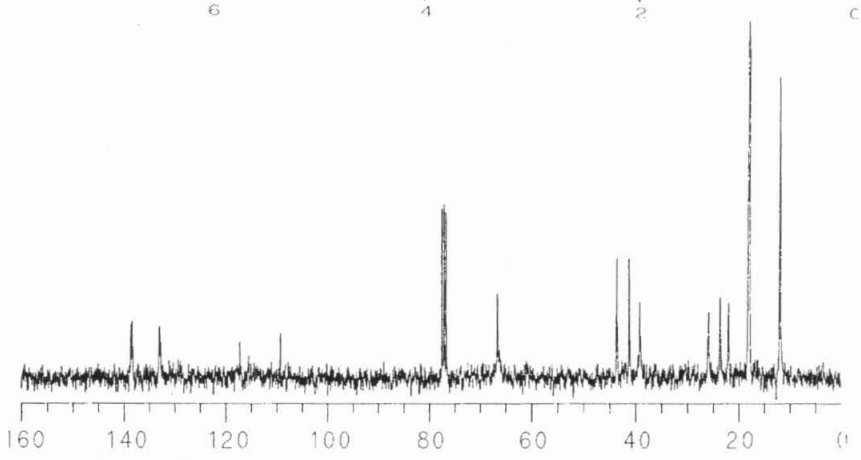
HRMS (FAB^+): calculated for $C_{20}H_{35}NOSi$: $(M+H)^+$ 334.2566, found 334.2561.



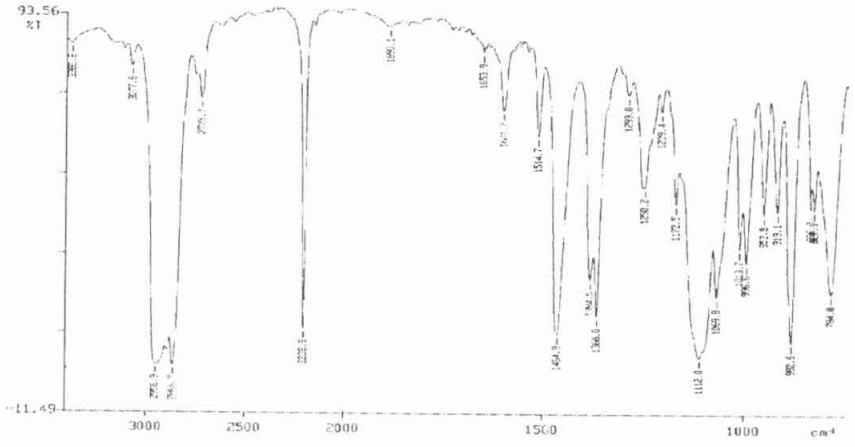
^{1}H-NMR
300 MHz
C_6D_6

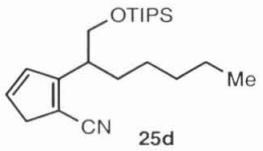


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





25d

25d: R = n-Butyl Obtained as a colorless oil (90%).

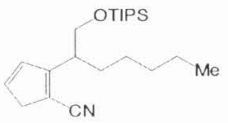
TLC: $R_f = 0.49$ (20:1 hexanes/EtOAc).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.32 (ddd, 1H, J = 5.4, 1.4, 1.3), 5.96 (d br., 1H, J = 5.4), 3.71 (dd, 1H, J = 9.7, 5.2), 3.64 (dd, 1H, J = 9.7, 6.3), 3.18-3.02 (m, 1H), 2.62 (s br., 2H), 1.63-1.38 (m, 2H), 1.50-1.15 (m, 6H), 1.11-0.98 (m, 21H), 0.85 (t, 3H, J = 6.7).

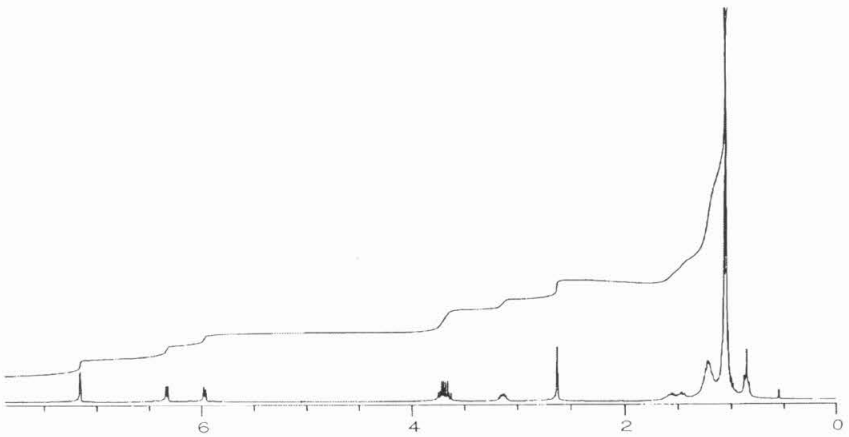
^{13}C NMR (C_6D_6, 75 MHz): 164.5, 138.1, 132.6, 116.8, 110.6, 66.5, 43.4, 32.1, 30.3, 27.3, 22.8, 18.1, 14.2, 12.3.

IR (thin film): 2942, 2866, 2209, 1464, 1368, 1249, 1111, 1070, 1014, 997, 953, 919, 883, 795, 727.

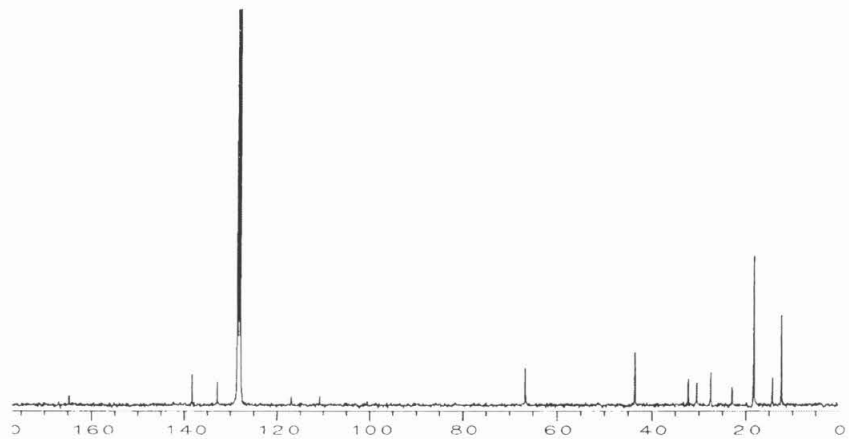
HRMS (FAB^+): calculated for $C_{22}H_{39}ONSi$: $(M+H)^+$ 362.2879, found 362.2877.



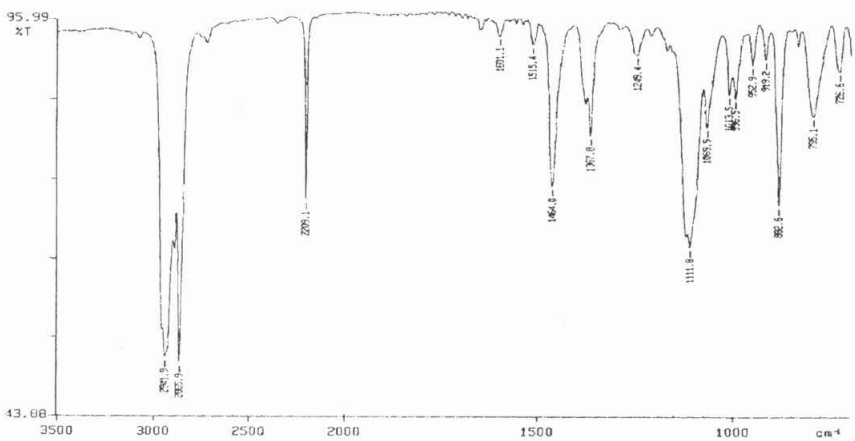
^{1}H-NMR
300 MHz
C_6D_6

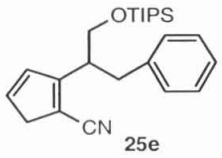


^{13}C-NMR
75 MHz
C_6D_6



FTIR
thin film





25e

25e: R = Phenyl Obtained as a colorless oil (97%).

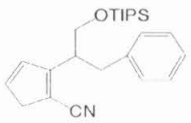
TLC: R_f = 0.51 (20:1 hexanes/EtOAc).

^{1}H NMR (C_6D_6, 300 MHz): δ 7.14-6.99 (m, 5H), 6.33 (ddd, 1H, *J* = 5.4, 1.3, 1.3), 5.89 (dd, br. 1H, *J* = 5.4, 1.2), 3.72 (dd, 1H, *J* = 9.8, 5.1), 3.66 (dd, 1H, *J* = 9.8, 5.7), 3.50-3.38 (m, 1H), 2.96 (dd, 1H, *J* = 13.7, 6.8), 2.70 (dd, 1H, *J* = 13.7, 8.7), 2.54 (ddd, 1H, *J* = 24.5, 1.3, 1.2), 2.42 (ddd, 1H, *J* = 24.5, 1.3, 1.2), 1.10-0.92 (m, 21H).

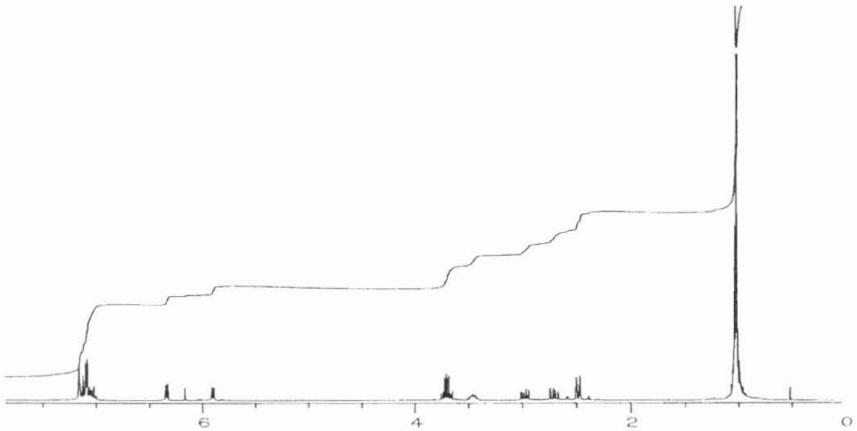
^{13}C NMR (C_6D_6, 75 MHz): 163.6, 139.3, 137.9, 133.0, 129.2, 128.6, 127.2, 116.6, 110.8, 65.6, 45.1, 43.3, 36.6, 18.1, 12.2.

IR (thin film): 2949, 2892, 2209, 1944, 1804, 1734, 1604, 1497, 1464, 1367, 1249, 1112, 1069, 1013, 883, 788, 750.

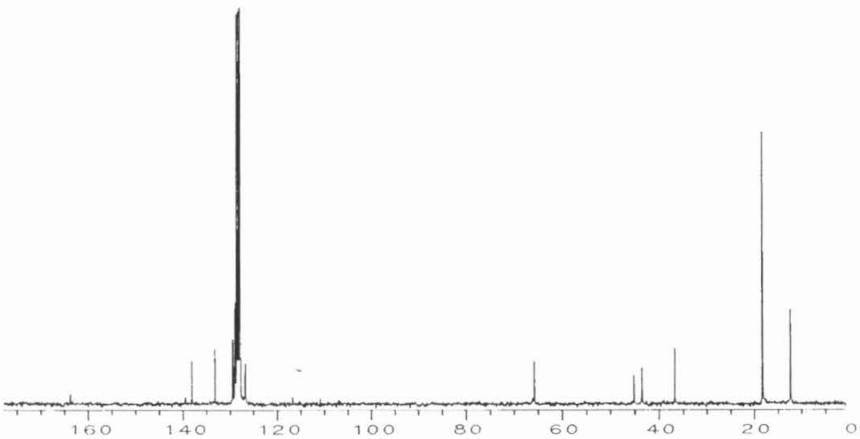
HRMS (FAB^+): calculated for $C_{24}H_{35}ONSi$: $(M+H)^+$ 382.2566, found 382.2567.



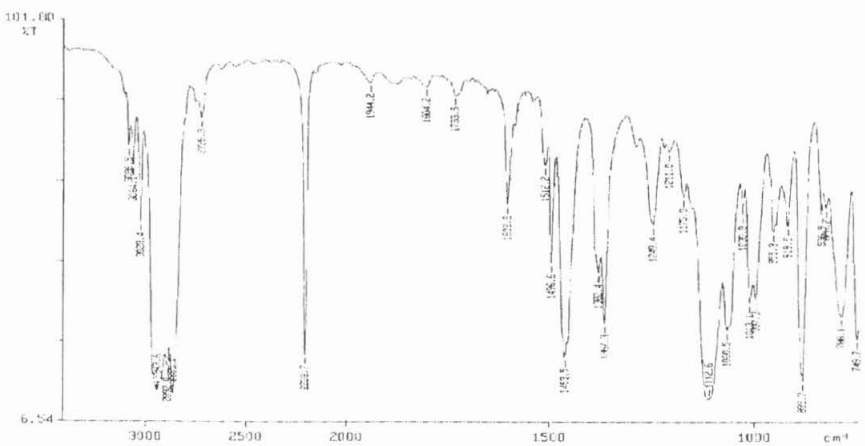
^{1}H-NMR
300 MHz
C_6D_6

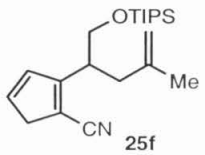


^{13}C-NMR
75 MHz
C_6D_6



FTIR
thin film





25f

25f: R = *i* - Propenyl Obtained as a colorless oil (82%).

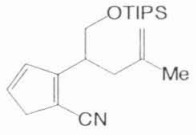
TLC: R_f = 0.47 (20:1 hexanes/EtOAc).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.30 (ddd, 1H, *J* = 5.4, 1.2, 1.1), 5.93 (d br., 1H, *J* = 5.4), 4.72 (d br., 1H, *J* = 9.0), 3.69 (dd, 1H, *J* = 9.6, 5.2), 3.64 (dd, 1H, *J* = 9.6, 6.1), 3.40-3.35 (m, 1H), 2.58 (s br., 2H,), 2.35 (dd, 1H, *J* = 14.0, 5.7), 2.20 (dd, 1H, *J* = 14.0, 9.6), 1.66 (s, 3H), 1.10-0.90 (m, 21H).

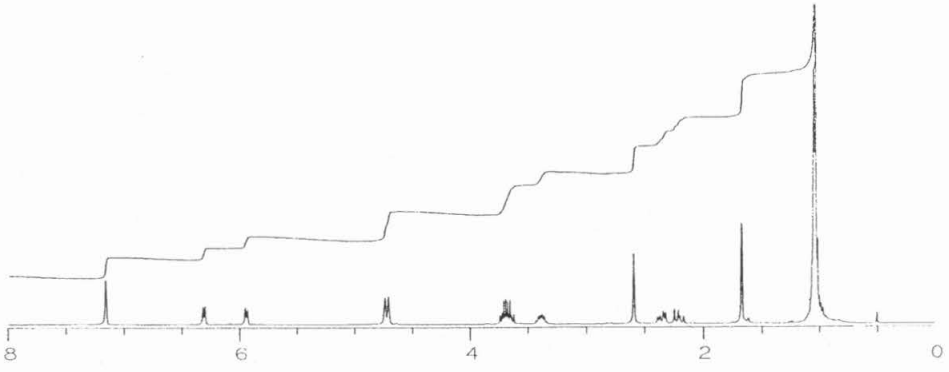
^{13}C NMR (C_6D_6, 75 MHz): 163.9, 142.9, 137.8, 132.8, 112.7, 66.3, 43.4, 41.4, 38.7, 22.1, 18.1, 12.2.

IR (thin film): 3075, 2943, 2866, 2208, 1649, 1463, 1368, 1115, 892, 790.

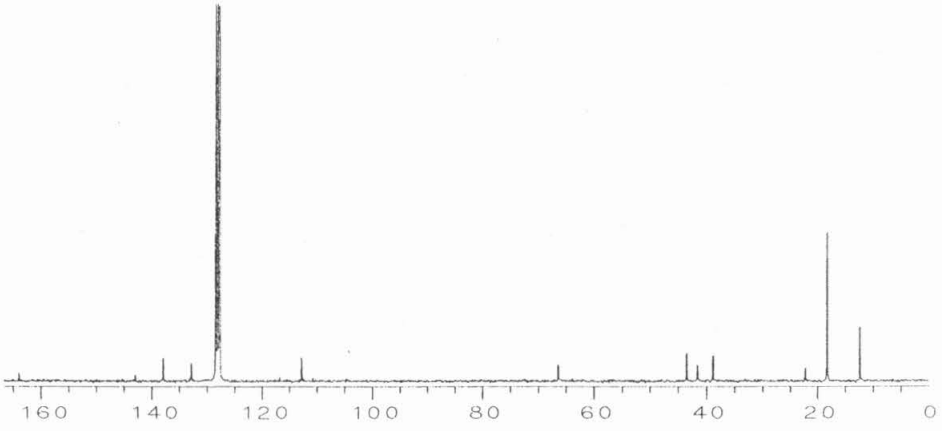
HRMS (FAB^+): calculated for $C_{21}H_{35}ONSi$: $(M+H)^+$ 346.2566, found 346.2555.



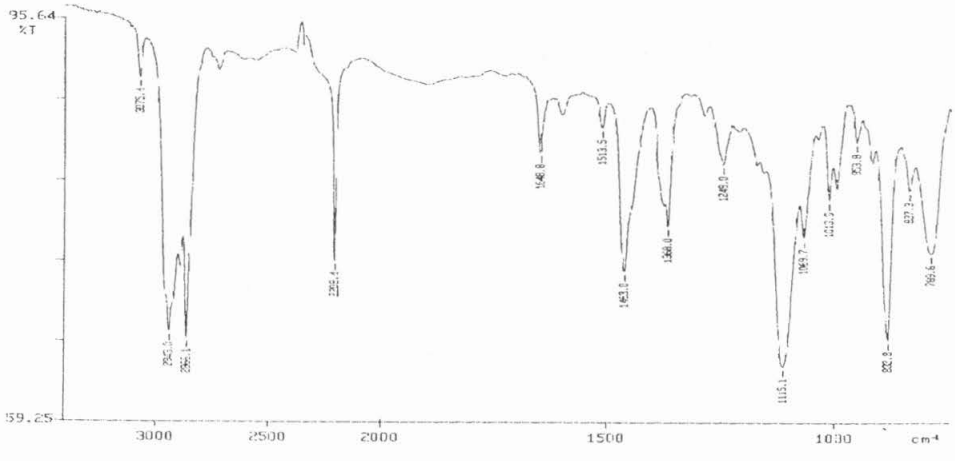
^{1}H-NMR
300 MHz
C_6D_6



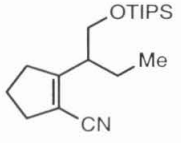
^{13}C-NMR
75 MHz
C_6D_6



FTIR
thin film



General procedure for selective hydrogenation. To a solution of cyclopentadiene-nitrile **25a-e** (0.136 mmol) in 11.4 ml of 25:1 v/v cyclohexane/EtOAc was added 10% w/w Pd/C (5.4 mg) and the mixture was stirred under 1 atm of H_2 at 23 °C until consumption of the starting material (15-24 h) was observed by TLC. The reaction was then filtered through celite and the solvent removed *in vacuo*. The residue was purified by chromatography on silica gel (hexanes: EtOAc 20: 1).



26a

(+)- 26a: R = Methyl Obtained as a colorless oil (93%).

TLC: $R_f = 0.49$ (20:1 hexanes/EtOAc).

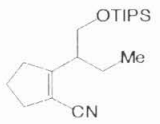
Optical rotation $[\_]_{Na}$ +41.3° (c = 1.19, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72 (dd, 1H, J = 9.6, 5.5), 3.66 (dd, 1H, J = 9.6, 7.5), 2.90-2.78 (m, 1H), 2.61-2.31 (2m, 4H), 1.98-1.86 (m, 2H), 1.64-1.28 (2m, 2H), 1.05-0.96 (m, 21H), 0.86 (t, 3H, J = 7.4).

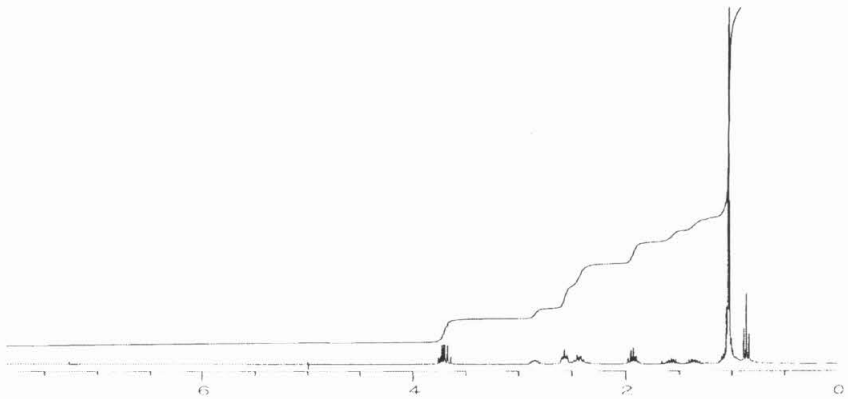
^{13}C NMR ($CDCl_3$, 75 MHz): 166.2, 117.0, 109.7, 65.3, 46.0, 34.0, 32.6, 22.6, 22.3, 18.0, 11.9.

IR (thin film): 2944, 2866, 2215, 1636, 1464, 1383, 1248, 1113, 1068, 1014, 996, 918, 882, 784, 682, 656.

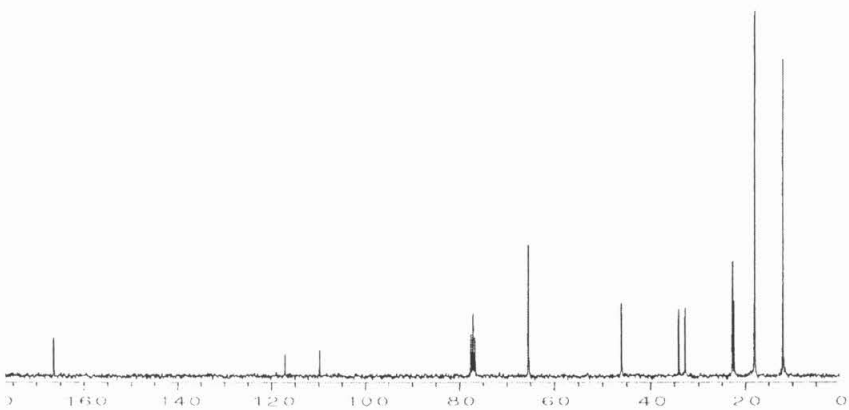
HRMS (FAB^+): calculated for $C_{19}H_{35}ONSi$: $(M+H)^+$ 322.2566, found 322.2555.



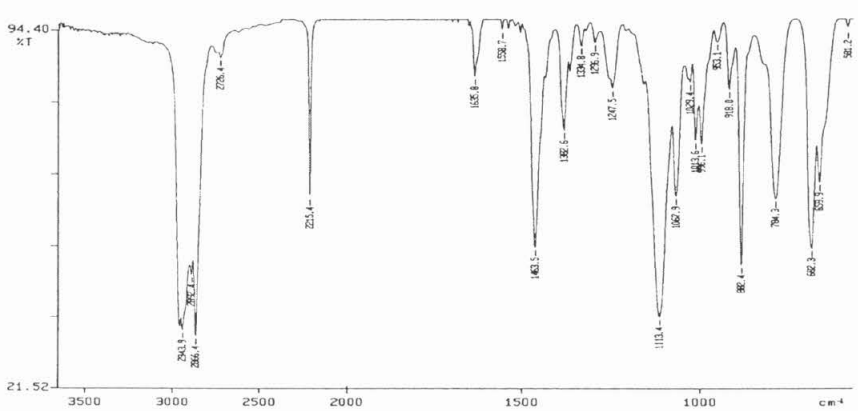
^{1}H-NMR
300 MHz
$CDCl_3$

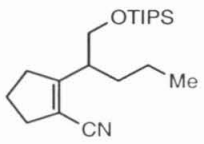


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





26b

26b: R = Ethyl Obtained as a colorless oil (85%).

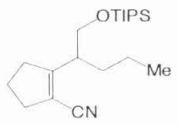
TLC: $R_f = 0.51$ (20:1 hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72 (dd, 1H, J = 9.6, 5.5), 3.66 (dd, 1H, J = 9.6, 7.6), 3.02-2.90 (m, 1H), 2.62-2.32 (2m, 4H), 2.00-1.85 (m, 2H), 1.54-1.20 (m, 4H), 1.06-0.98 (m, 21H), 0.91 (t, 3H, J = 7.1).

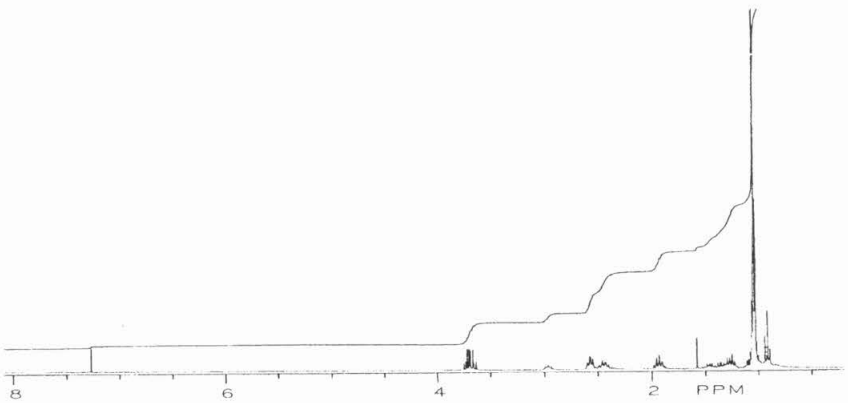
^{13}C NMR ($CDCl_3$, 75 MHz): 166.4, 117.0, 109.4, 65.6, 44.0, 34.0, 32.7, 31.4, 22.6, 20.6, 18.0, 14.1, 12.0.

IR (thin film): 2934, 2066, 2215, 1632, 1464, 1383, 1249, 1114, 1070, 1014, 996, 918, 882, 790, 682.

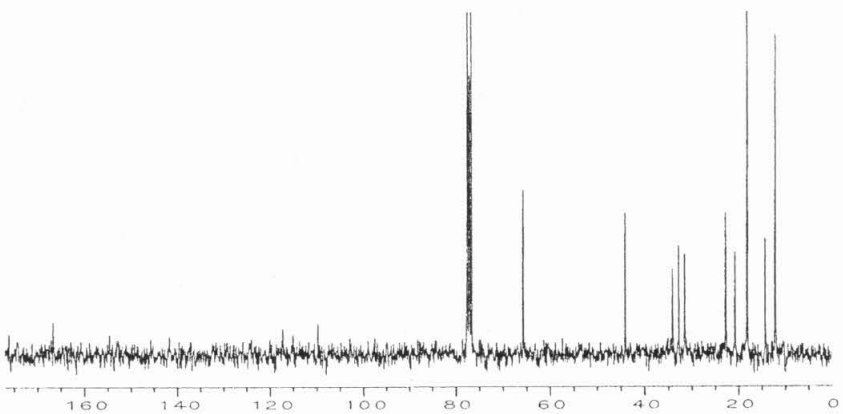
HRMS (FAB^+): calculated for $C_{20}H_{37}ONSi$: $(M+H)^+$ 336.2722, found 336.2722.



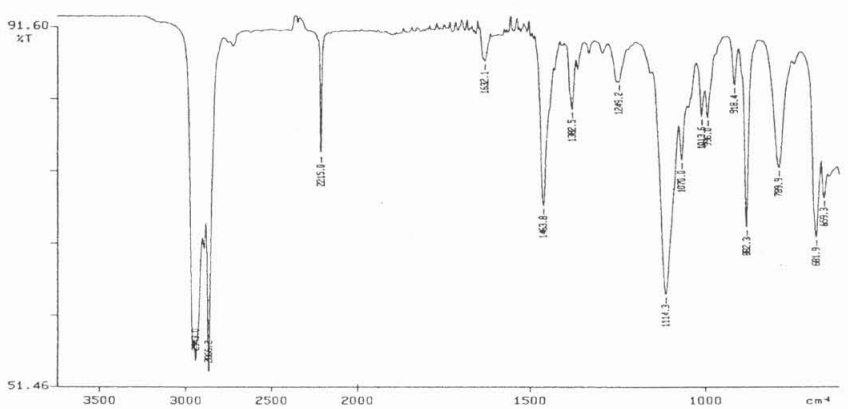
^{1}H-NMR
300 MHz
$CDCl_3$

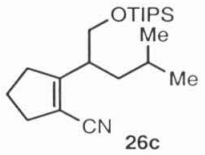


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





26c

26c: R = *i* - Propyl Obtained as a colorless oil (86%).

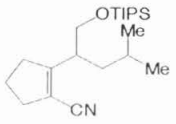
TLC: $R_f = 0.50$ (20:1 hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 300 MHz): 3.70 (dd, 1H, J = 9.6, 5.5), 3.63 (dd, 1H, J = 9.6, 7.6), 3.12-3.00 (m, 1H), 2.62-2.32 (2m, 4H), 2.02-1.85 (m, 2H), 1.48-1.27 (m, 3H), 1.06-0.98 (m, 21H), 0.92 (d, 3H, J = 6.5), 0.90 (d, 3H, J = 6.6).

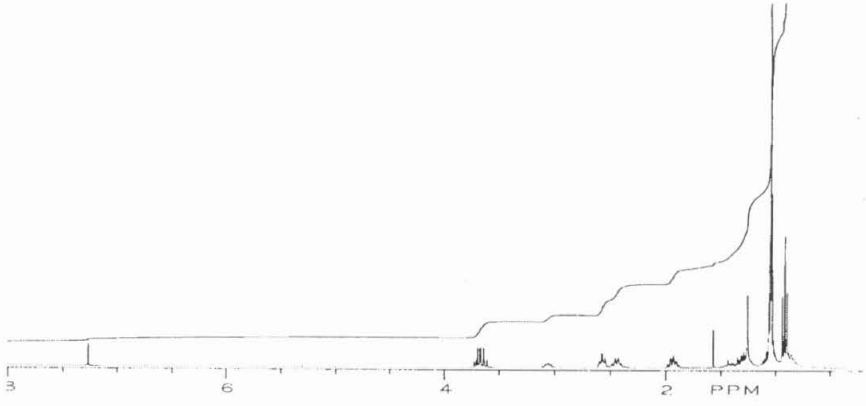
^{13}C NMR ($CDCl_3$, 75 MHz): 166.6, 117.1, 109.5, 65.9, 42.2, 38.4, 34.0, 32.7, 29.7, 25.9, 23.5, 22.1, 18.0, 12.0.

IR (thin film): 2926, 2867, 2216, 1633, 1464, 1385, 1368, 1260, 1110, 1070, 1014, 919, 882, 784, 683, 660.

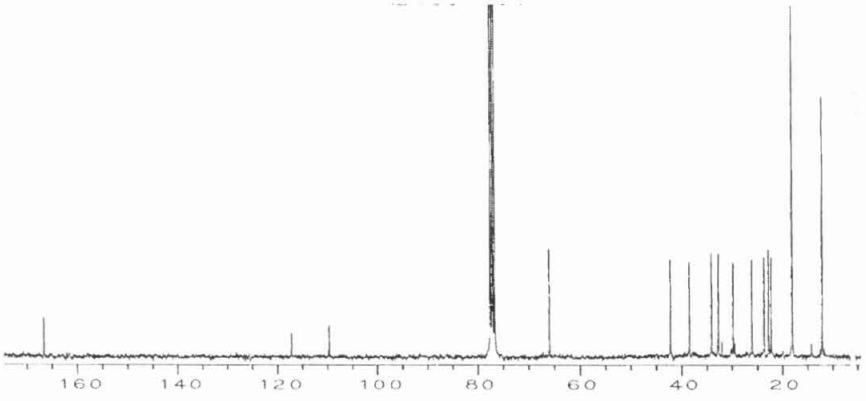
HRMS (FAB^+): calculated for $C_{21}H_{39}ONSi$: $(M+H)^+$ 350.2879, found 350.2864.



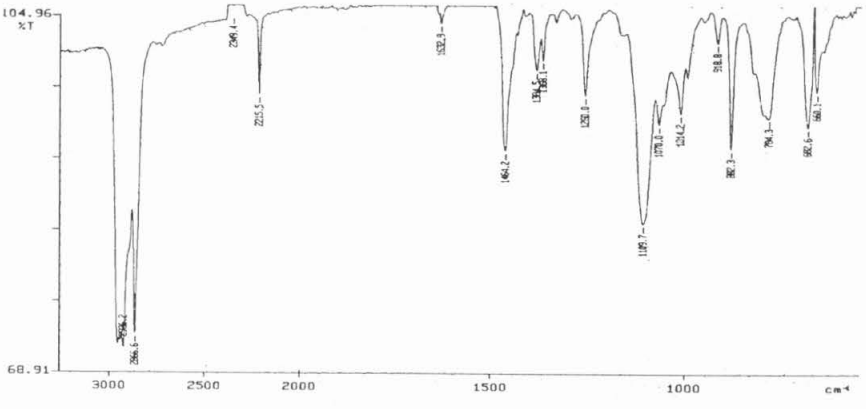
^{1}H-NMR
300 MHz
$CDCl_3$

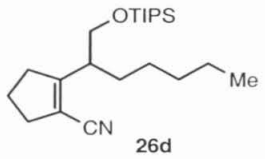


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





26d

26d: R = Butyl Obtained as a colorless oil (96%).

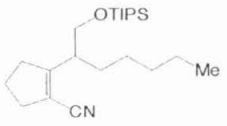
TLC: $R_f = 0.52$ (20:1 hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 300 MHz): 3.72 (dd, 1H, J = 9.6, 5.5), 3.66 (dd, 1H, J = 9.6, 7.6), 3.00-2.87 (m, 1H), 2.61-2.31 (m, 4H), 2.00-1.86 (m, 2H), 1.32-1.18 (m, 8H), 1.05-1.01 (m, 21H), 0.88 (t, 3H, J = 7.1).

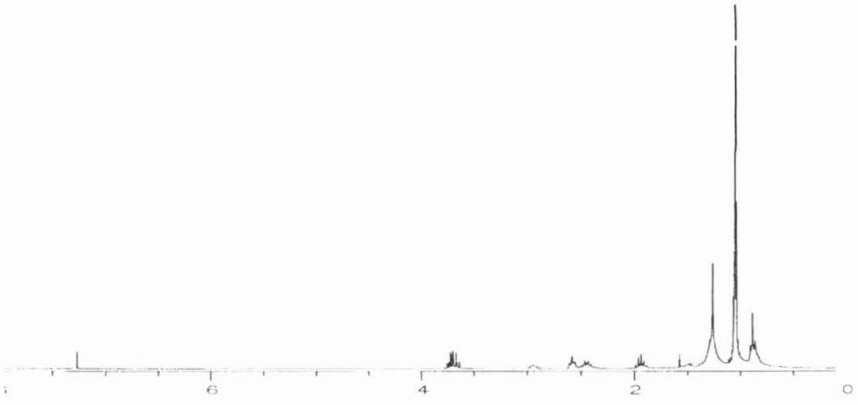
^{13}C NMR ($CDCl_3$, 75 MHz): 166.6, 117.1, 109.5, 65.6, 44.2, 34.0, 32.7, 31.8, 29.7, 29.2, 27.0, 22.5, 18.0, 14.0, 12.0.

IR (thin film): 2942, 2866, 2215, 1632, 1464, 1382, 1249, 1115, 1069, 1013, 996, 918, 882, 792, 682, 660.

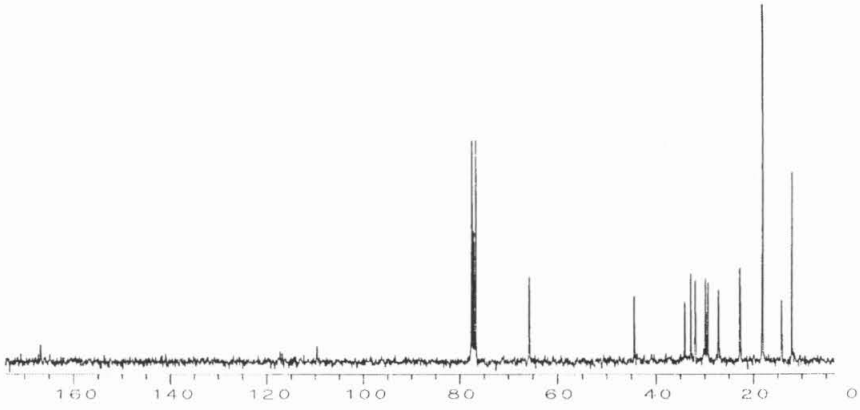
HRMS (FAB^+): calculated for $C_{22}H_{41}ONSi$: $(M+H)^+$ 364.3035, found 364.3029.



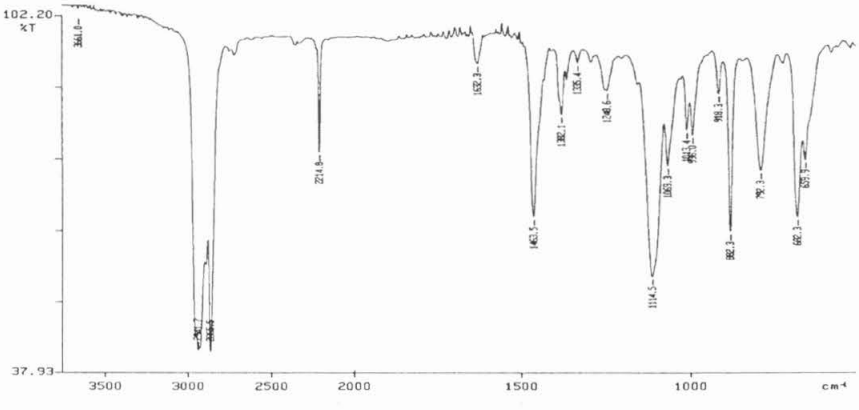
^{1}H-NMR
300 MHz
$CDCl_3$

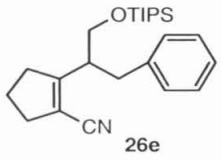


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





26e

26e: R = Phenyl Obtained as a colorless oil (86%).

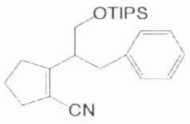
TLC: $R_f = 0.54$ (20:1 hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.31-7.13 (m, 5H), 3.77 (dd, 1H, J = 11.7, 5.8), 3.74 (dd, 1H, J = 11.7, 6.4), 3.31-3.20 (m, 1H), 2.93 (dd, 1H, J = 13.7, 6.5), 2.69 (dd, 1H, J = 13.7, 8.9), 2.53-2.39 (m, 4H), 1.99-1.78 (m, 2H), 1.09-0.94 (m, 21H).

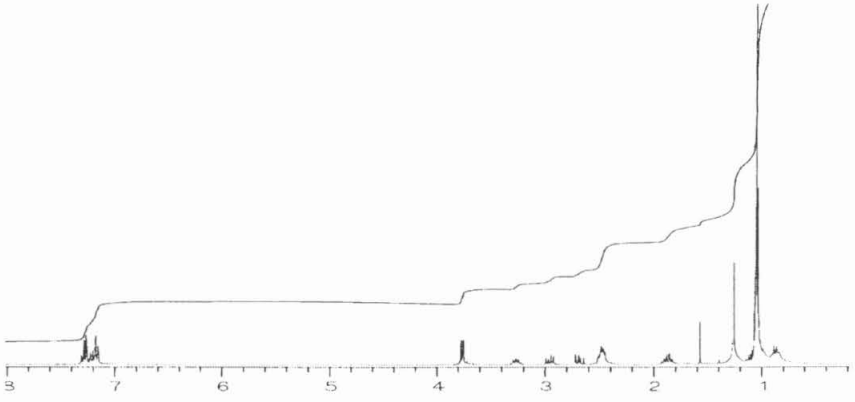
^{13}C NMR ($CDCl_3$, 75 MHz): 165.4, 139.0, 128.7, 128.4, 126.2, 116.8, 109.8, 65.0, 45.6, 35.7, 34.0, 33.6, 29.7, 18.0, 12.0.

IR (thin film): 2926, 2866, 2215, 1496, 1463, 1382, 1257, 1112, 1068, 996, 882, 784, 748, 684, 662.

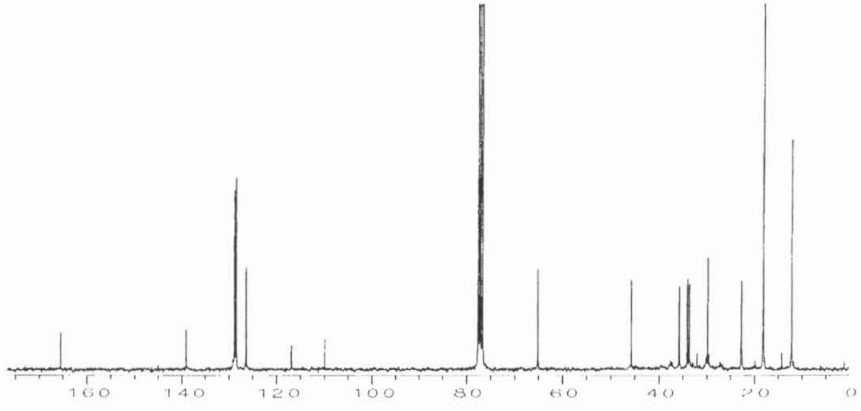
HRMS (FAB^+): calculated for $C_{24}H_{37}ONSi$: $(M+H)^+$ 384.2722, found 384.2711.



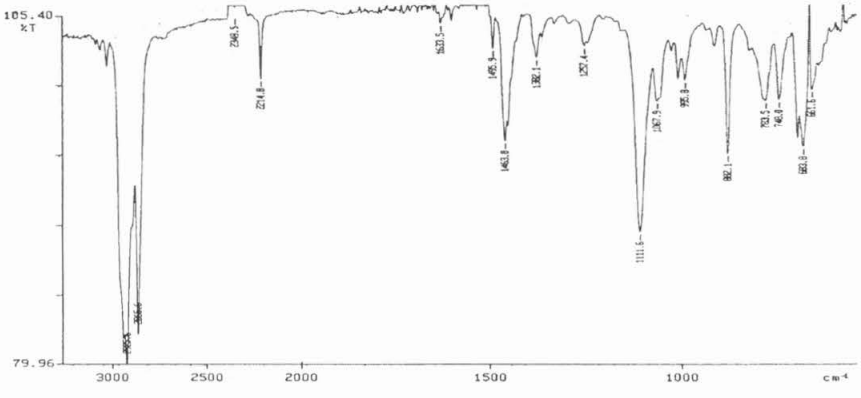
^{1}H-NMR
300 MHz
$CDCl_3$

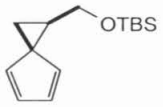


^{13}C-NMR
75 MHz
$CDCl_3$



FTIR
thin film





51. A solution of alcohol **7** (59.7 g, 0.49 mol) and Et_3N (82 mL, 0.59 mol) in 500 ml DMF was cooled to 0 °C and TBSC1 (81.0 g, 0.54 mol) in 300 mL DMF was added over a period of 15 min. A white precipitate was formed rapidly. The reaction was allowed to warm to 23 °C and was stirred for an additional 30 min. The mixture was then poured into 2 L of ice water and extracted with 3 x 300 mL pentane. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the desired product as a colorless oil in quantitative yield.

TLC R_f = 0.82 (4:1 hexanes/EtOAc).

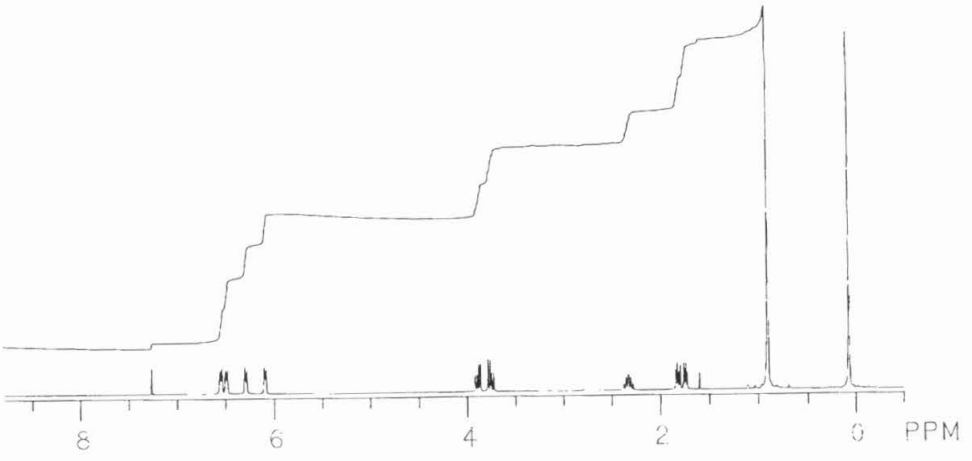
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.54 (d, 1H, *J*=5.2), 6.49 (d, 1H, *J*=5.0), 6.29 (d, 1H, *J*=5.2), 6.09 (d, 1H, *J*=5.0), 3.89 (dd, 1H, *J*=11.0, 5.4), 3.75 (dd, 1H, *J*=11.0, 6.8), 2.30-2.35 (m, 1H), 1.81 (dd, 1H, *J*=8.6, 4.1), 1.74 (dd, 1H, *J*=7.3, 4.1), 0.89 (s, 9H) 0.06 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 139.3, 134.9, 130.2, 128.4, 64.2, 41.8, 29.5, 25.9, 18.3, 17.4, -5.2.

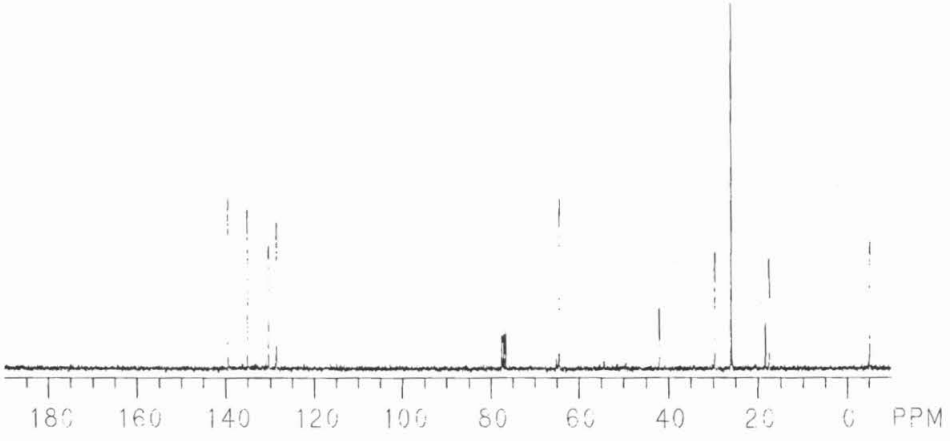
IR (thin film)ν 2956, 2930, 2858, 1472, 1256, llll, 1089, 1006.

HRMS(CI) calc'd for $C_{14}H_{24}OSi$, 236.1596 found 236.1590.

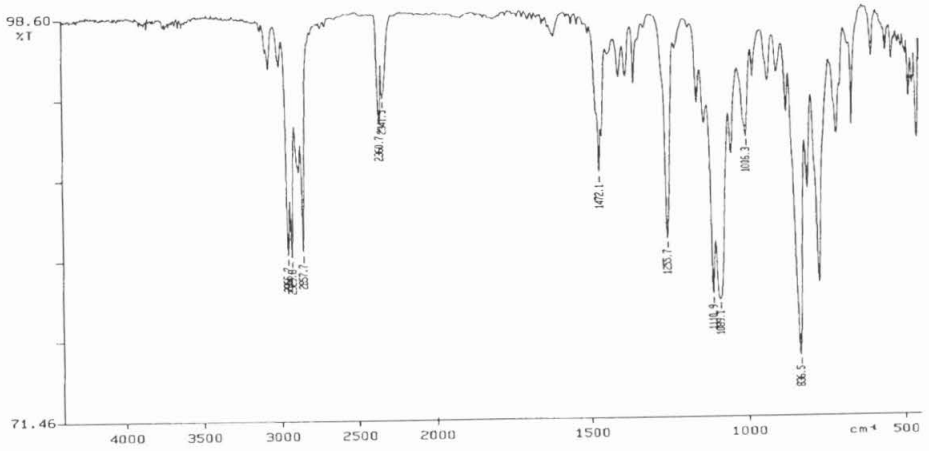
^{1}H NMR
300 MHz
$CDCl_3$

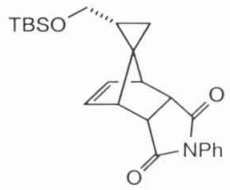


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





52. To a solution of **51** (116g, 0.491 mol) in 500 ml dichloromethane was added a solution of N-phenylmaleimide (83g, 0.48 mol) in 500 ml dichloromethane at 0 °C over a period of 30 min. The resulting yellow mixture was then filtered and concentrated *in vacuo*. The residue was recrystallized twice from 800 ml cyclohexane to afford 70g of white powder. The mother liquor was concentrated *in vacuo* and the residue dissolved in 500 ml of chlorobenzene. After stirring at reflux for 24 hours the solvent was removed *in vacuo* and the residue was recrystallized from cyclohexane again. This cycle was repeated three times to yield an additional 72g of microcrystalline solid for a combined yield of 142g of **52** (74%).

MP 156-157 °C.

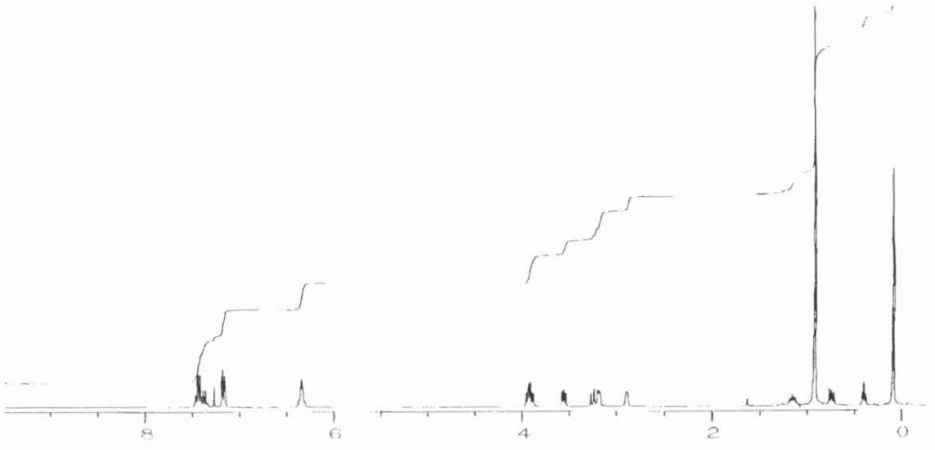
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 0 7.36-7.46 (m, 3H), 7.14 (d, 2H, J =7.2), 6.32 (s, 2H), 3.59 (dd, 1H, J=10.8, 6.7), 3.56 (s, 2H), 3.45 (dd, 1H, J=10.8, 7.0), 3.14 (s, 1H), 2.89 (s, 1H), 1.26-1.29 (m, 1H), 0.88 (s, 9H), 0.69 (dd, 1H, J =8.7, 5.5), 0.43 (t, 1H, J=5.5), 0.04 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ176.6, 134.8, 133.8, 131.8, 129.0, 128.5, 126.6, 64.0, 52.2, 51.0, 46.7, 46.0, 45.6, 25.9, 21.7, 18.3, 11.8, -5.27, -5.32.

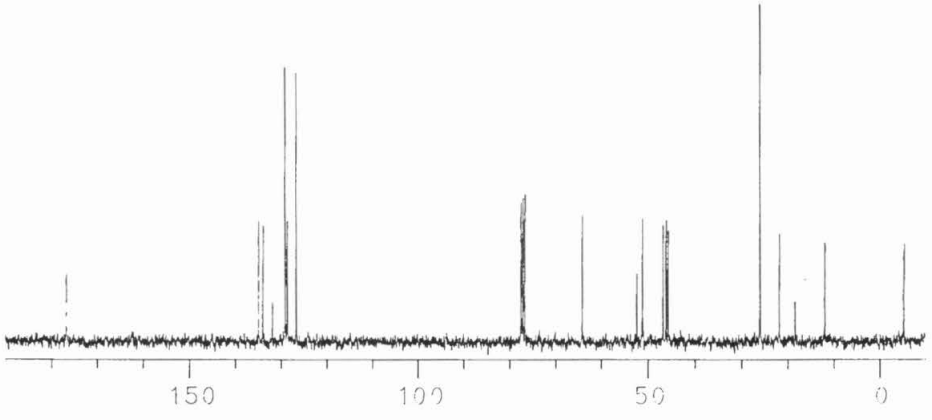
IR (thin film)ν 2954, 2929, 2857, 1710, 1494, 1472, 1379, 1255, 1182, 1082.

MS (CI) calcd for $C_{24}H_{31}NO_3Si$ 409.2073 found 409.2144.

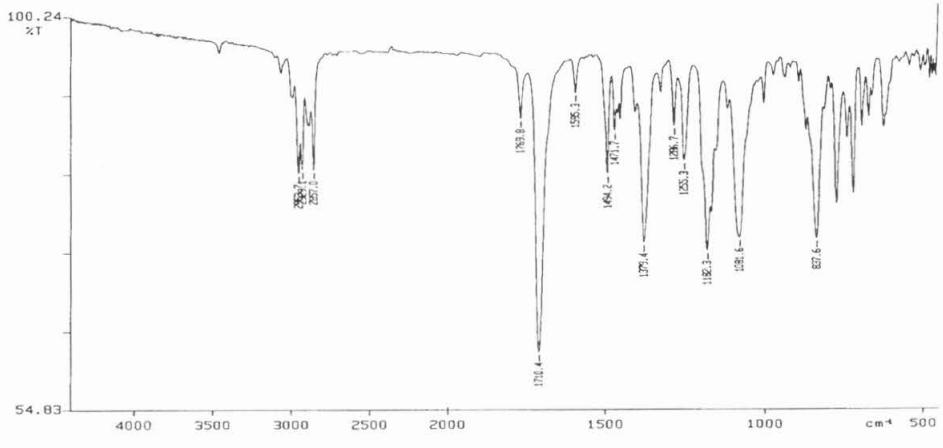
^{1}H NMR
300 MHz
$CDCl_3$

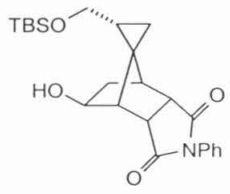


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





54. A mixture of olefin **52** (40.2 g, 98.8 mmol) and $RhCl(PPh_3)_3$ (2.7 g, 2.9 mmol) was dissolved in 900 mL of THF and cooled to 0 °C. Under N_2, freshly prepared catecholborane (15 mL, 141 mmol) was added dropwise. The resulting yellow solution was stirred for 9 h at 20 °C, then cooled to 0 °C. After the addition of 200 mL each of EtOH:THF (1:1), aqueous phosphate buffer (pH 7.0, 0.05 M) and H_2O_2 (30%) the mixture was stirred at 0 °C for 30 min, and then at 20 °C for 10 h. The reaction mixture was partitioned between 300 mL Et_2O and 300 mL H_2O. The aqueous layer was saturated with NaC1 and then extracted 2 x 200 mL ether. The combined organic layers were washed 5 x 100 mL 1 N NaOH, dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified colorless solid was taken on to the next step. Analytical samples were obtained by silica gel chromatography (9:2 pentane/EtOAc) or recrystallization from EtOH.

TLC $R_f = 0.37$ (2:1 hexanes/EtOAc).

MP 149-151 °C (recrystallized from EtOH).

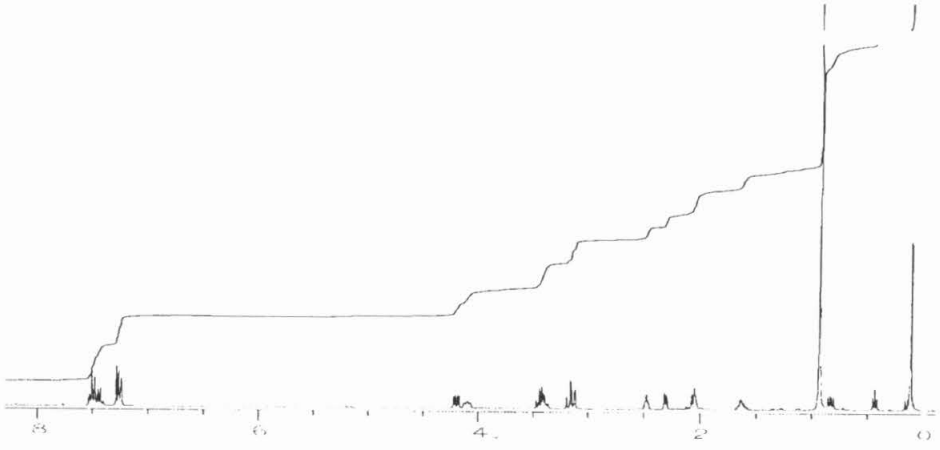
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.40-7.52 (m, 3H), 7.25 (dd, 2H, *J*=7.4, 1.5), 4.19 (dd, 1H, *J*=10.2, 4.2), 4.06-4.13 (m, 1H), 3.36-3.47 (m, 2H), 3.11-3.19 (m, 2H), 2.47 (t, 1H, *J*=4.1), 2.30 (d, 1H, J=5.3), 2.04-2.07 (m, 2H), 1.61-1.65 (m, 1H), 0.92 (s, 9H), 0.82 (dd, 1H, *J*=9.1, 5.5), 0.42 (t, 1H, *J*=5.5), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.7, 176.3 , 131.7 , 129.2, 128.8, 126.6 , 71.7, 65.0 , 51.9, 47.4, 44.9, 40.9, 40.0 , 38.0 , 25.8 , 22.3 , 18.2, 5.9 , -5.51, -5.54.

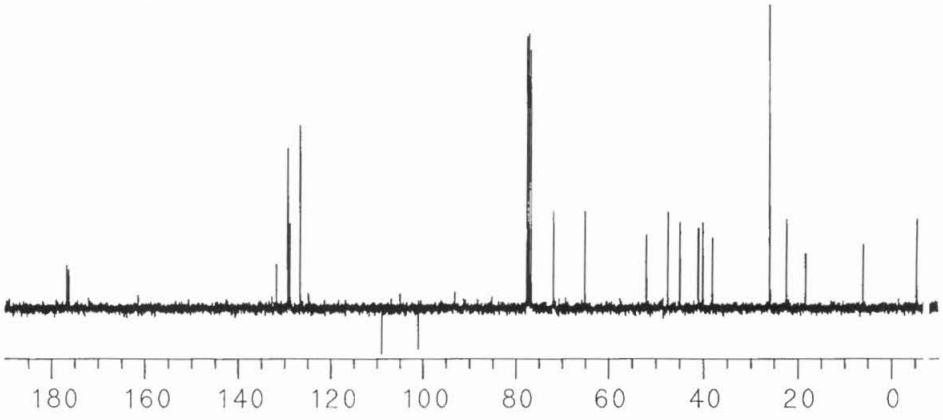
IR (thin film)ν 3471, 2955, 2858, 1713, 1503, 1471, 1373, 1257, 1178, 1084, 1059.

HRMS(CI) calc'd for $C_{24}H_{34}NO_4Si$ $(M+H)^+$, 428.2257 found 428.2249.

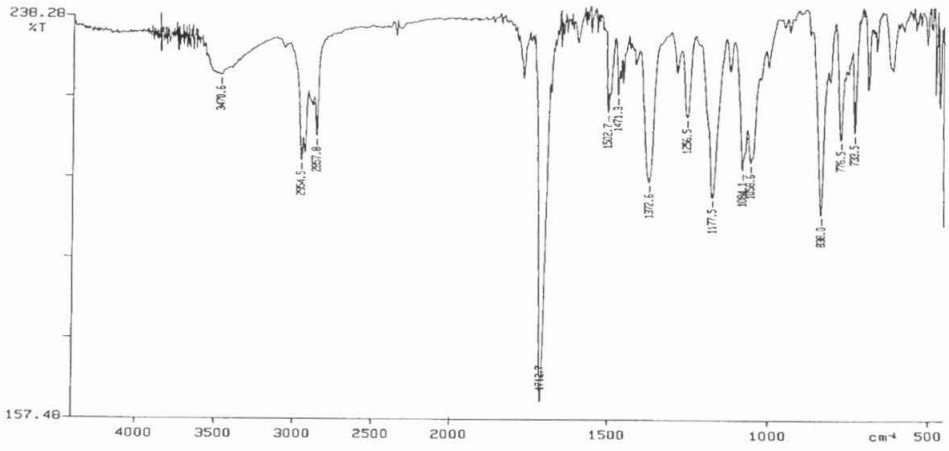
^{1}H NMR
300 MHz
$CDCl_3$

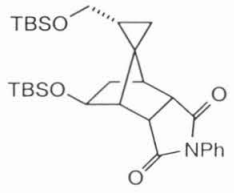


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





55. A solution of **54** (42 g, 98 mmol) and 2,6-lutidine (22 mL, 190 mmol) in 500 mL of CH_2C1_2 was treated with TBSOTf (27 mL, 120 mmol) at 0 °C. After 30 min the reaction mixture was poured onto 2 L of ice water and extracted 3 x 500 mL pentane. The organic layers were combined and washed 1 x 500 mL 1 N HC1, 1 x 500 mL saturated aqueous $NaHCO_3$, 1 x 500 mL brine, then dried over $MgSO_4$ and concentrated *in vacuo* to a colorless solid. The unpurified product was taken on to the next step. An analytical sample was obtained by recrystallization from cyclohexane.

TLC R_f=0.68 (2: 1 hexanes/EtOAc).

MP 141 °C (recrystallized from cyclohexane).

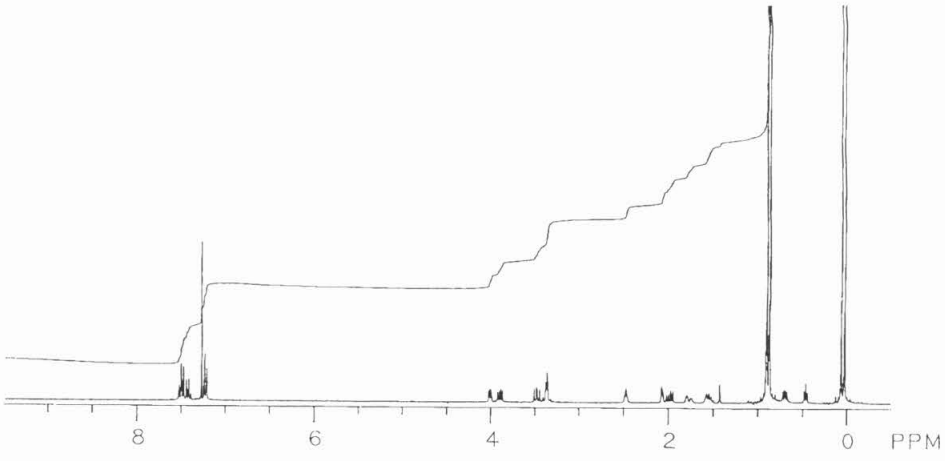
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.40-7.54 (m, 3H), 7.24 (dd, 2H, *J*=7.1, 1.5), 4.02 (dd, 1H, *J*=6.9, 2.7), 3.91 (dd, 1H, *J*=10.8, 5.5), 3.49 (dd, 1H, *J*=10.8, 7.7) 3.37-3.39 (m, 2H), 2.49 (t, 1H, *J*=4.3), 2.08 (d, 1H, *J*=4.5), 2.00 (dd, 1H, *J*=13.9, 6.9), 1.79 (dm, 1H, *J*=13.9), 1.54-1.59 (m, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.71 (dd, 1H, *J*=8.4, 5.0), 0.48 (t, 1H, *J*=5.0), 0.08 (s, 6H), 0.04 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.9, 176.8, 131.7, 129.3, 128.7, 126.4, 70.7, 63.9, 52.9, 47.2, 45.2, 41.1, 39.8, 39.3, 26.0, 25.7, 22.5, 18.4, 17.9, 7.7, -4.8, -5.0, -5.2, -5.3.

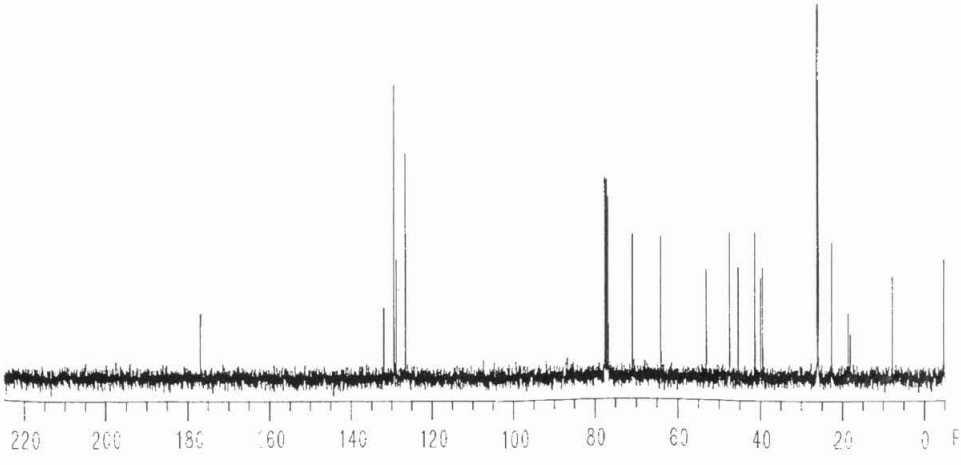
IR (thin film)ν 2955, 2930, 2887, 2858, 1715, 1501, 1472, 1370, 1255, 1176, 1094, 1002.

HRMS(CI) calc'd for $C_{30}H_{47}NO_4Si_2$ $(M+H)^+$ 542.3122 found 542.3111.

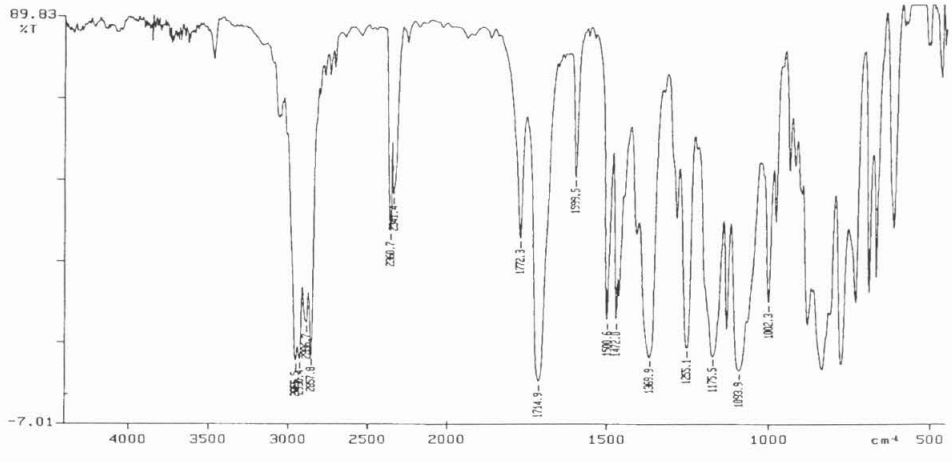
^{1}H NMR
300 MHz
$CDCl_3$

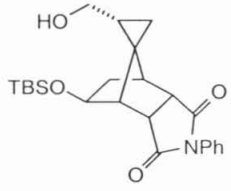


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





56. The bis-silyl ether (53 g, 98 mmol) prepared as described above was dissolved in 200 mL of CH_2C1_2. Methanol (1000 mL) was added, followed by the slow addition of dichloroacetic acid (81 mL, 980 mmol). After stirring at 23 °C for 2 h the reaction mixture was concentrated *in vacuo* to a total volume of 150-200 mL. Then ice water was added (1000 mL) and the mixture was extracted 3 x 500 mL ether. The organic layers were combined then washed 1 x 500 mL saturated aqueous $NaHCO_3$, 1 x 500 mL brine, then dried over Na_2SO_4 and concentrated *in vacuo* to give **56**. The unpurified primary alcohol was taken on without purification. An analytical sample was obtained by recrystallization from EtOH.

TLC $R_f = 0.27$ (1:1 hexanes/EtOAc).

MP 158-161 °C (recrystallized from EtOH).

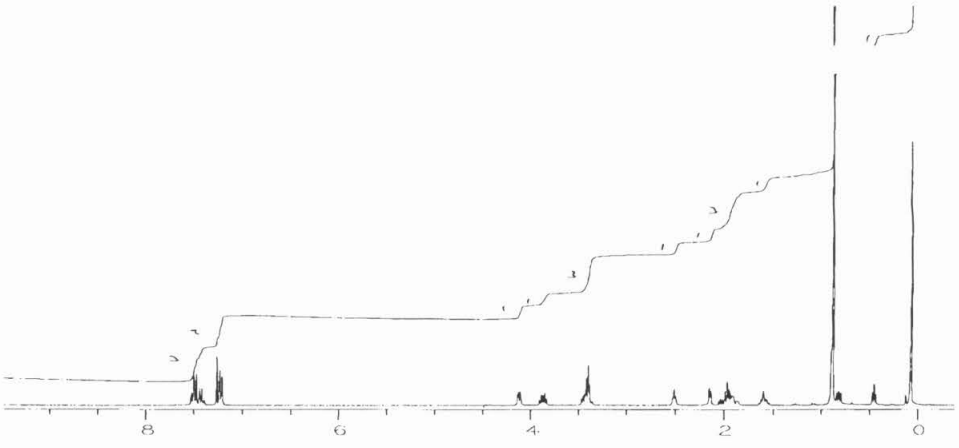
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.41-7.52 (m, 3H), 7.22 (d, 2H, *J*=7.2), 4.11 (dd, 1H, *J*=6.2, 2.1), 3.83-3.89 (m, 1H), 3.38-3.46 (m, 3H), 2.50 (t, 1H, *J*=4.5), 2.13 (d, 1H, *J*=4.5), 1.90-2.03 (m, 3H), 1.55-1.61 (m, 1H), 0.88 (s, 9H), 0.81 (dd, 1H, *J*=8.9, 5.4), 0.44 (t, 1H, *J*=5.4), 0.07 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.5, 176.4, 131.6, 129.3, 128.7, 126.4, 71.6, 64.1, 52.2, 47.3, 44.8, 41.1, 40.3, 38.6, 25.7, 22.9, 17.9, 7.0, -4.9, -5.2.

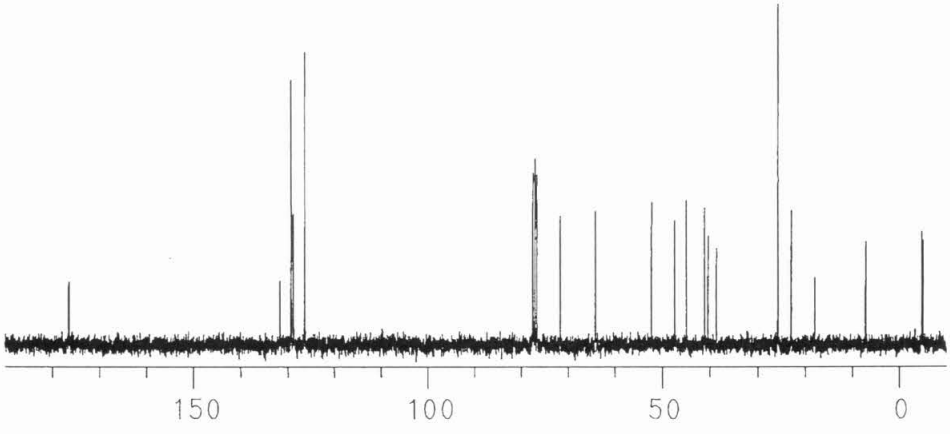
IR (thin film)ν 3467, 2954, 2930, 2885, 2857, 1772, 1713, 1599, 1500, 1472, 1374, 1255, 1178, 1132, 1096, 1051, 1002.

HRMS(CI) calc'd for $C_{24}H_{34}NO_4Si$ $(M+H)^+$, 428.2257 found 428.2247.

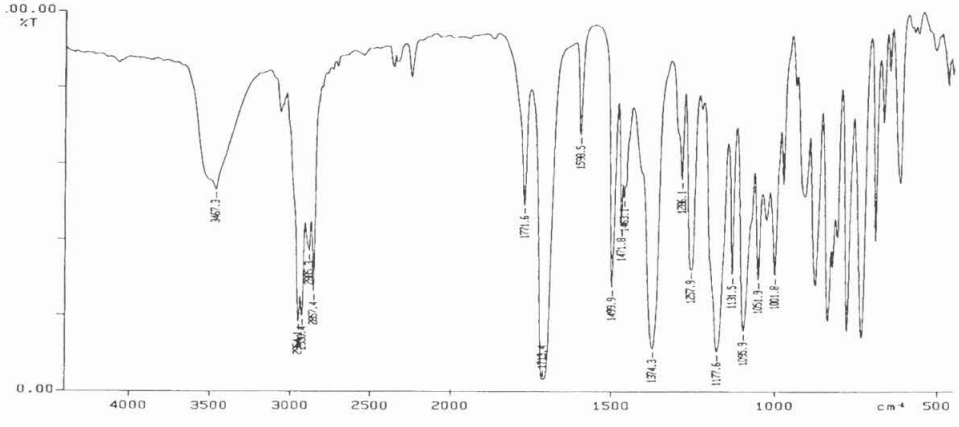
^{1}H NMR
300 MHz
$CDCl_3$

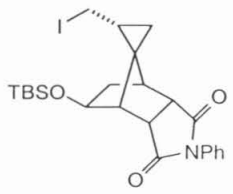


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





57. To a solution of **56** (42 g, 98 mmol) in 1000 mL acetonitrile/ether (1:4) were added triphenylphosphine (31 g, 118 mmol), imidazole (8.0 g, 118 mmol), and I_2 (30g, 120 mmol) at 0 °C. The resulting yellow, turbid reaction mixture was quenched by the addition of 1000 mL of a 10% aqueous solution of $Na_2S_2O_3$ after 30 min. The resulting two layers were separated and the organic phase was washed with 1 L of 15% aqueous $CuSO_4$, 1 L of water and 500 mL of brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5:1 hexanes/EtOAc) to give 38.5 g (73%, 4 steps) of **57** as a colorless solid.

TLC $R_f = 0.59$ (2:1 hexanes/EtOAc).

MP 144 °C (recrystallized from cyclohexane).

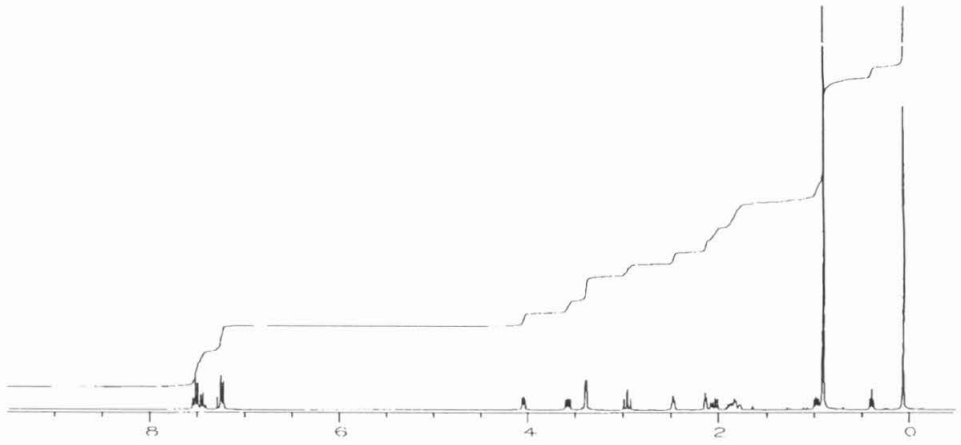
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.41-7.52 (m, 3H), 7.21 (dd, 2H, *J*=7.6, 1.4), 4.01 (dd, 1H, *J*=6.8, 2.3), 3.55 (dd, lH, *J*=10.0, 5.3), 3.353.36 (m, 2H), 2.92 (t, 1H, *J*=10.0), 2.45 (t, 1H, *J*=3.6), 2.10 (d, 1H, *J*=3.6), 2.02 (dd, 1H, *J*=14.1, 6.9), 1.79-1.85 (m, 2H), 0.95 (dd, 1H, *J*=8.5, 5.5), 0.88 (s, 9H), 0.37 (t, 1H, *J*=5.5), 0.03 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.4, 176.3, 131.6 , 129.3, 128.8, 126.4 , 70.4 , 52.2, 46.8, 44.8, 40.7, 47.2, 39.4 , 25.7 , 25.0 , 17.8 , 13.4 , 7.6, -4.9, -5.0.

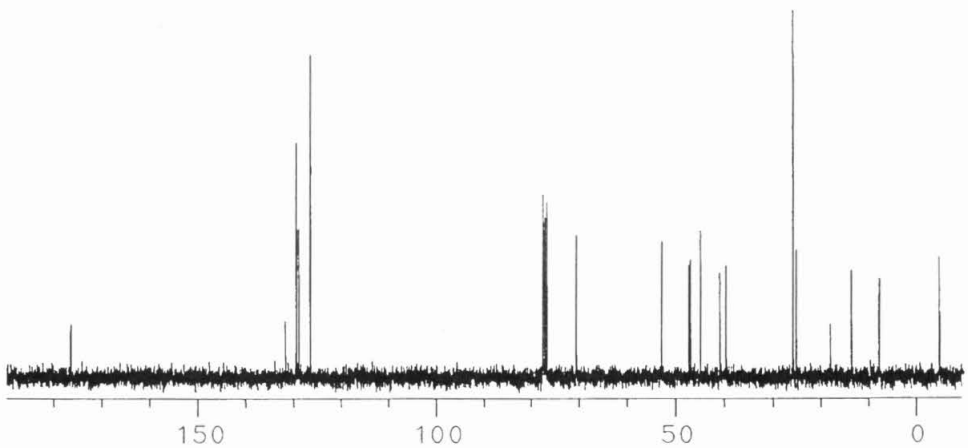
IR (thin film)ν 2954, 2930, 2896, 2856, 1772, 1714, 1598, 1500, 1472, 1373, 1253, 1178, 1132, 1093, 1001, 1002.

HRMS(CI) calc'd for $C_{24}H_{33}INO_3Si$ $(M+H)^+$, 538.1274 found 538.1268.

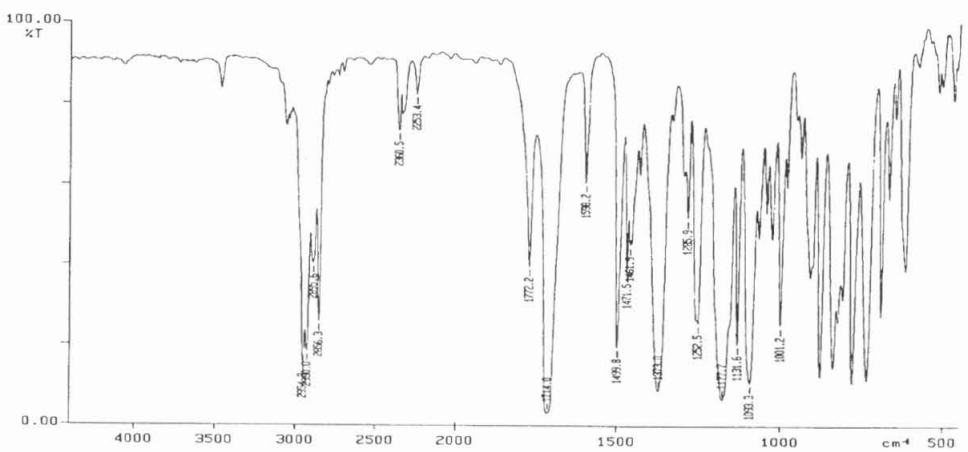
^{1}H NMR
300 MHz
$CDCl_3$

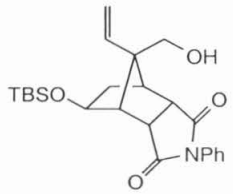


^{13}C NMR
75 MHz
$CDCl_3$

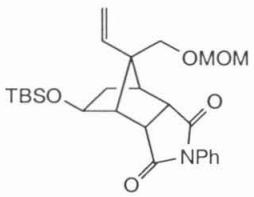


FTIR
thin film





60. Iodide **57** (1.05 g, 1.95 mmol) was dissolved in 10 mL of toluene and cooled to -10 °C. Dry air was bubbled through the solution. While bubbling was continued, Bu_3SnH (1.3 mL, 4.8 mmol) was added dropwise. The mixture was allowed to warm to 23 °C over a period of 3 h. Triphenylphosphine (511 mg, 1.95 mmol) was added and the resulting mixture was stirred for an additional 30 min, then concentrated *in vacuo*. The residue was redissolved in CH_2C1_2, washed with 100 mL water and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (1:1 hexanes/EtOAc) to afford 0.578g (69%) of **60** as a colorless solid containing ca. 10-20% of a chromatographically inseparable isomer. This mixture was taken on without further purification. **TLC** $R_f = 0.13$ (2:1 hexanes/EtOAc).



61. A solution of alcohol **60** (570 mg, 1.33 mmol) and diisopropylethylamine (1.16 mL, 6.67 mmol) in 10 mL CH_2C1_2 was treated with chloromethylmethylether (0.40 mL, 5.33 mmol) at 23 °C. After 3 h the mixture was poured onto saturated aqueous NH_4C1 and extracted 3 x 50 mL CH_2C1_2. The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (3:1 hexanes/EtOAc), to give 0.400g (67%) of **61** as a colorless solid.

TLC $R_f = 0.58$ (1:1 hexanes/EtOAc).

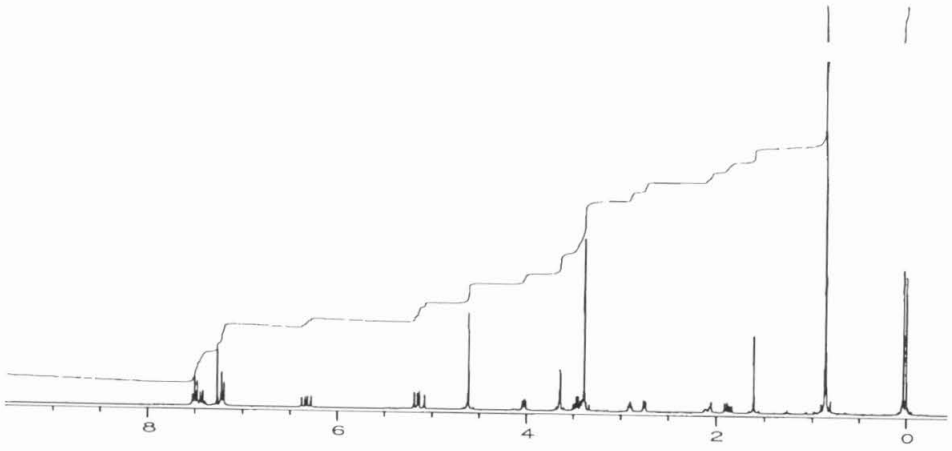
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.41-7.52 (m, 3H), 7.20 (dd, 2H, *J*=7.1, 1.5), 6.32 (dd, 1H, *J*=17.9, 11.1), 5.16 (dd, 1H), 4.02 (dd, IH, *J*=7.4, 3.4), 3.63 (s, 6r, 2H), 3.47 (dd, 1H, *J*=9.2, 5.5), 3.36-3.42 (m, 1H), 3.38 (s, 3H), 2.89 (t, 1H, *J*=3.8), 2.74 (d, 1H, J=5.4), 2.04-2.14 (m, 1H), 1.87 (dd, 1H, *J*=14.4, 7.4), 0.85 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.8, 140.4, 131.6, 129.3, 128.7, 126.4, 114.1, 96.9, 71.4, 69.9, 61.8, 55.5, 51.6, 46.3, 45.2, 43.5, 37.4, 25.7, 17.8,-4.9,-5.0.

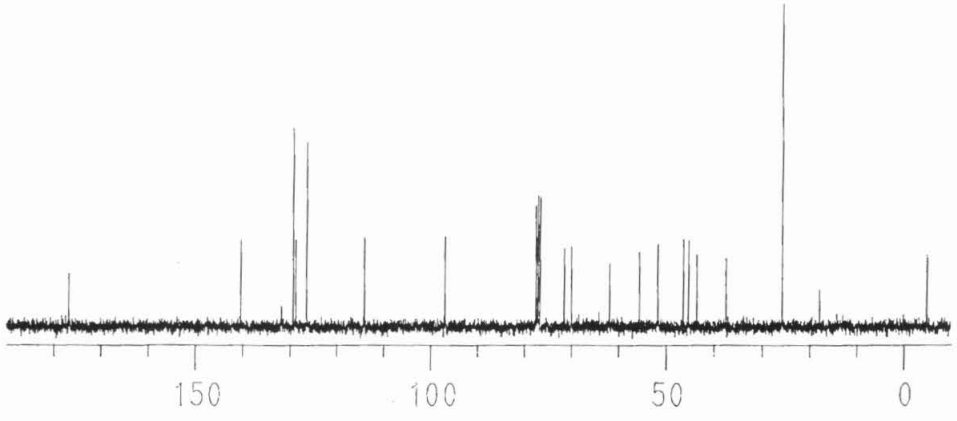
IR (thin film)ν 2953, 2886, 2858, 1775, 1715, 1600, 1497, 1472, 1372, 1254, 1180, 1106, 1045, 998.

HRMS(CI) calc'd for $C_{26}H_{38}NO_5Si$ $(M+H)^+$, 472.2519 found 472.2528.

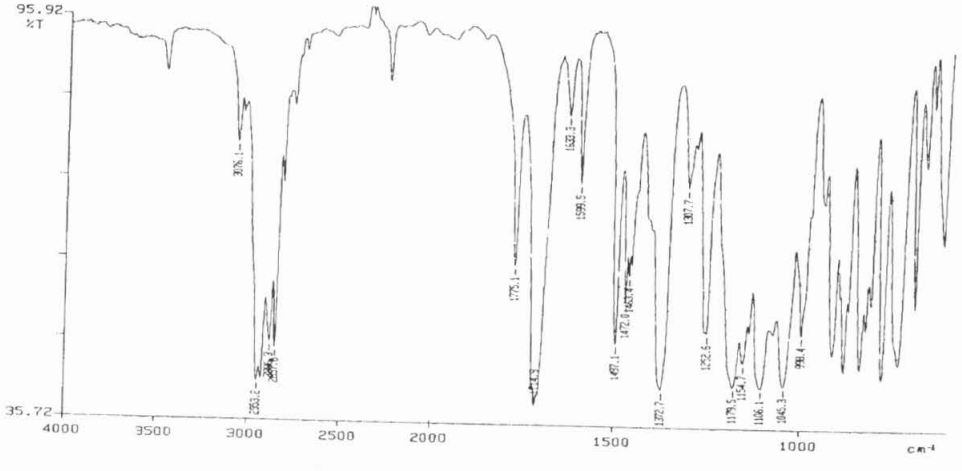
^{1}H NMR
300 MHz
$CDCl_3$

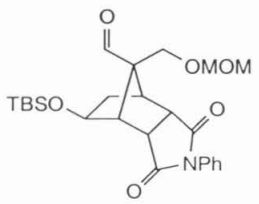


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





62. Into a solution of olefin **61** (334 mg, 0.71 mmol) in 10 mL CH_2Cl_2/MeOH (9:1) was passed a dilute stream of ozone in oxygen at -78 °C until the reaction became blue. The reaction was purged with N_2 until the blue color disappeared, then triphenylphosphine (205 mg, 0.78 mmol) was added and the reaction was warmed to 23 °C and stirred for 3 h. After the solvent was removed *in vacuo*, the resulting oil was purified by chromatography on silica gel (2:1 hexanes/EtOAc) to give 0.302g (90%) of aldehyde **62** as a colorless solid.

TLC R_f = 0.25 (2:1 hexanes/EtOAc).

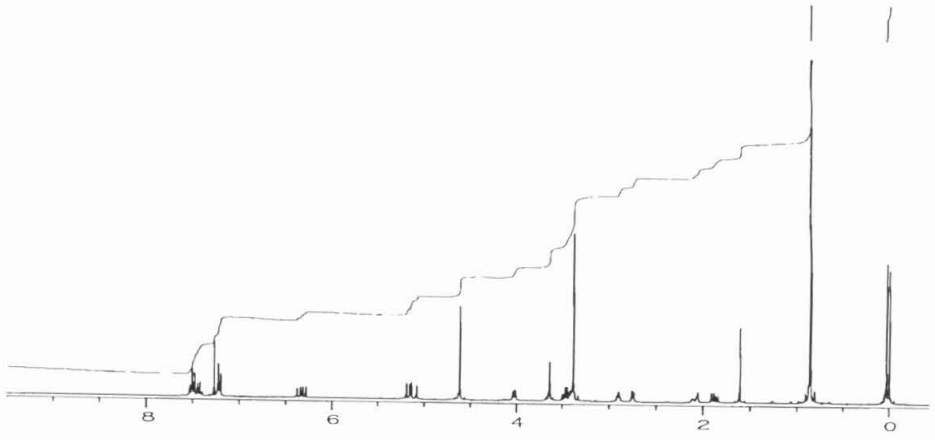
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 9.83 (s, 1H), 7.42-7.52 (m, 3H), 7.20 (dd, 2H, *J*=7.2, 1.4), 4.58 (s, 2H), 4.06 (dd, 1H, *J*=6.3, 3.0), 3.91 (d, 1H, *J*=10.4), 3.68 (d, 1H, *J*=10.4), 3.36-3.45 (m, 2H), 3.36 (s, 3H), 3.18 (m, 1H), 3.02 (d, 1H, *J*=5.4), 1.92-1.95 (m, 2H), 0.84 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 199.8, 176.0, 175.7, 131.5, 129.4, 129.0, 126.4, 96.6, 70.9, 69.9, 64.6, 55.7, 50.6, 45.2, 44.1, 40.7, 36.9, 25.6, 17.9,-5.0, -5.1.

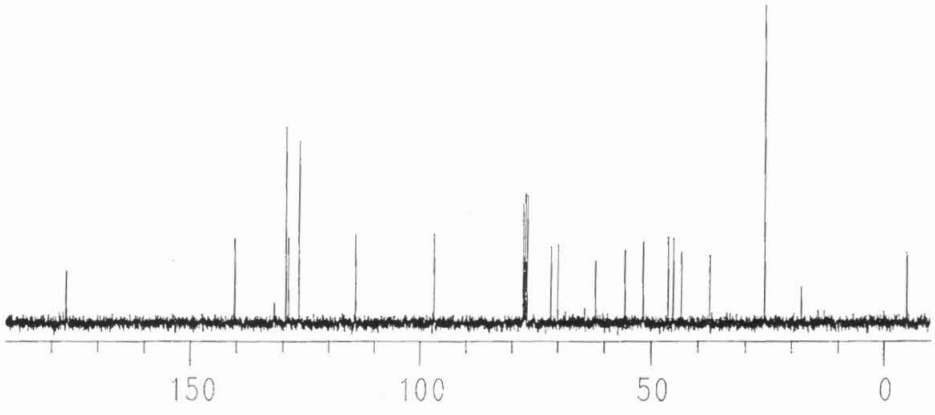
IR (thin film) ν 2953, 2887, 2858, 1776, 1715, 1598, 1498, 1472, 1376, 1254, 1180, 1106, 1042.

HRMS(FAB) calc'd for $C_{25}H_{35}NO_6Si$ $(M+H)^+$: 474.2312; found 474.2298.

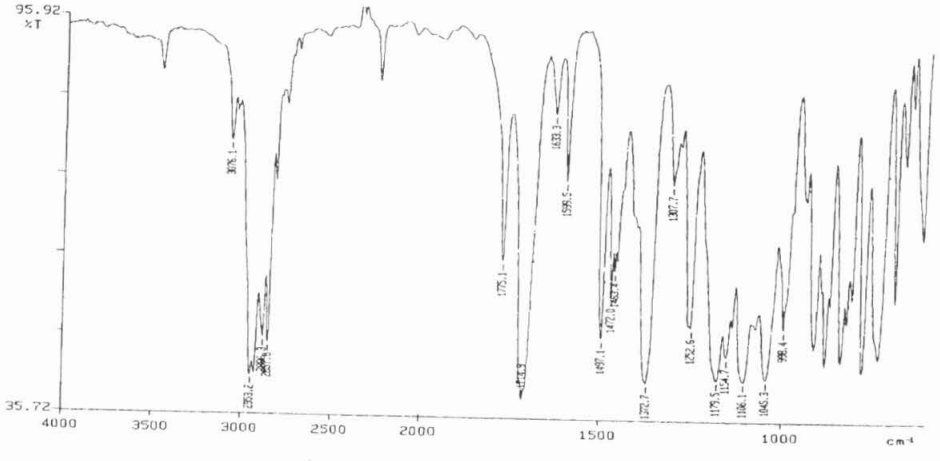
^{1}H NMR
300 MHz
$CDCl_3$

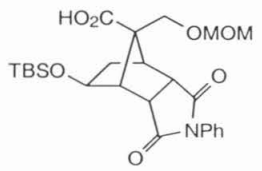


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





63. Aldehyde **62** (355 mg, 0.75 mmol) was dissolved in 9.0 mL ^{t}BuOH. An aqueous phosphate buffer solution (3.0 mL, pH 7.0, 1.25 M) and 4.5 mL of 1.0 M aqueous KMnO4 were added. After stirring for 30 min at 23 °C the reaction mixture was treated with saturated aqueous Na_2SO_3 solution until the purple color discharged and the reaction was heterogeneous brown. Then the mixture was filtered through celite and the filter cake was washed with 50 mL EtOAc. The two layers were separated and the organic phase was washed 3 x 50 mL 0.5 M KH_2PO_4. The combined aqueous layers were extracted 3 x 25 mL EtOAc. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 0.346 mg (94%) of **63** as a colorless foam that was spectroscopically pure.

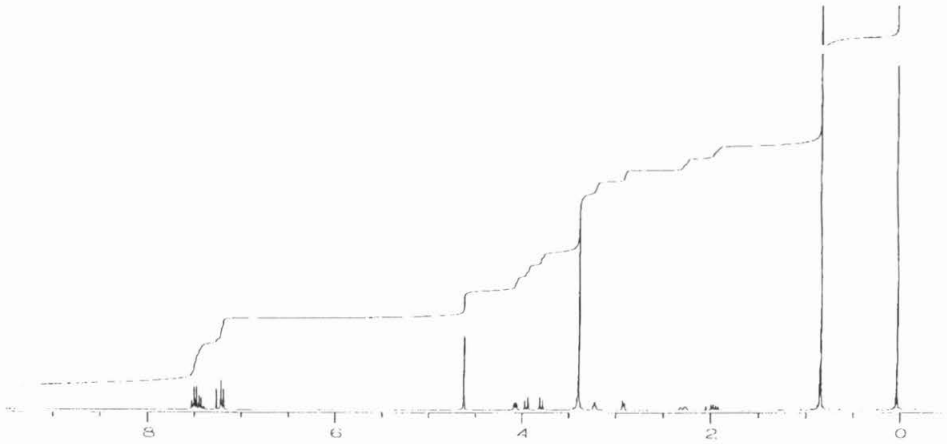
TLC R_f = 0.25 (1:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.39-7.52 (m, 3H), 7.18-7.21 (m, 2H), 4.62 (s, 2H), 4.07 (dd, 1H, J=7.2, 2.6), 3.95 (d, 1H, J=10.1), 3.79 (d, 1H, J=10.1), 3.36-3.44 (m, 2H), 3.39 (s, 3H), 3.22 (t, 1H, J=4.2), 3.91 (d, 1H, J=4.7), 2.29 (dm, 1H, J=14.8), 1.95 (dd, 1H, J=14.8, 7.2), 0.84 (s, 9H), 0.03 (s, 6H).

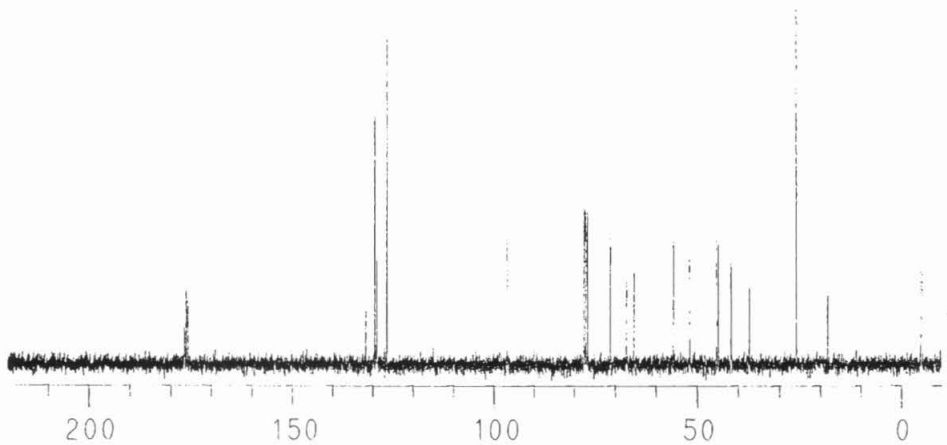
^{13}C-NMR ($CDCl_3$, 75 MHz)δ 176.5, 176.1, 175.7, 131.6, 129.3, 128.9, 126.4, 96.6, 71.0, 67.1, 65.3, 55.7, 51.7, 45.1, 44.7, 41.6, 37.2, 25.8, 18.0,-5.0,-5.2.

IR (thin film)ν 2953, 2857, 1714, 1498, 1472, 1378, 1252, 1184, 1103, 1038.

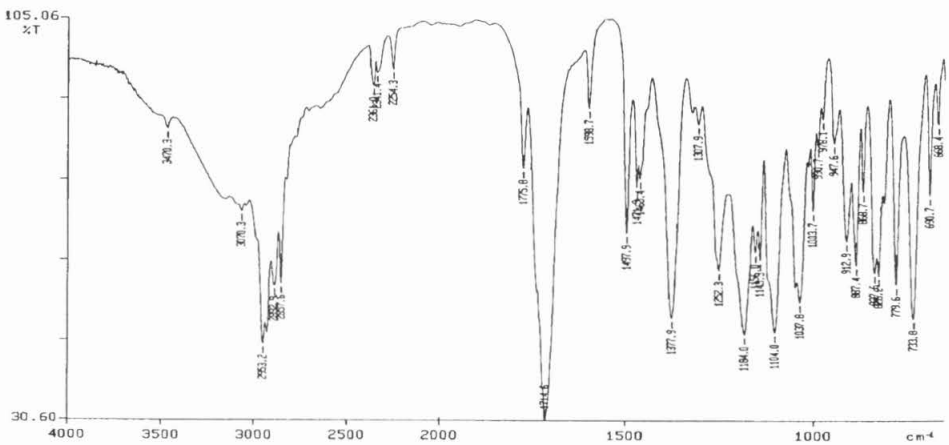
^{1}H NMR
300 MHz
$CDCl_3$

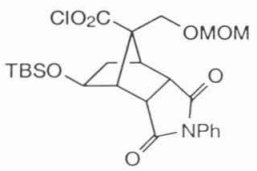


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film

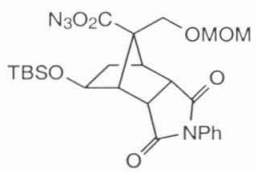




Acid chloride of **63**. To a solution of **63** (346 mg, 0.71 mmol) in 15 mL CH_2Cl_2 at 0 °C was added freshly distilled thionylchloride (260 μL, 3.53 mmol) followed by 1 drop of DMF. The reaction mixture was warmed to 23 °C and stirred for 1 h. The solvent was removed *in vacuo* and the residue was redissolved in 10 mL dry benzene and concentrated again to remove the excess of $SOCl_2$. The unpurified acid cloride (356 mg, 0.70 mmol) was taken on to the next step.

TLC R_f = 0.67 (1:1 hexanes/EtOAc).

IR (thin film) 2953, 2858, 1798, 1715, 1498, 1472, 1378, 1254, 1182, 1104, 1042.

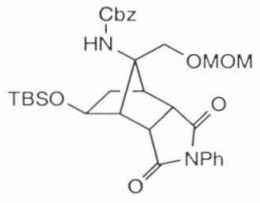


Acylazide of **63**. Sodium azide (55 mg, 0.85 mmol) in 5 mL DMSO was added to a solution of the acid chloride (356 mg, 0.70 mmol) prepared as described above in 10 mL DMSO at 23 °C. After 9 h the resulting clear, orange solution was poured onto ice water and extracted 3 x 10 mL ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid.

TLC R_f = 0.28 (2:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.39-7.52 (m, 3H), 7.17-7.20 (m, 2H), 4.62 (s, 2H), 4.04 (dd, 1H, *J*=7.2, 2.5), 3.94 (d, 1H, *J*=10.3), 3.72 (d, 1H, *J*=10.3), 3.35-3.40 (m, 2H), 3.38 (s, 3H), 3.27 (t, 1H, *J*=3.3), 2.85 (d, 1H, *J*=2.8), 2.27 (d, 1H, *J*=14.9), 1.94 (dd, 1H, *J*=14.9, 7.2), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) .

IR (thin film)ν 2953, 2931, 2858, 2138, 1777, 1714, 1498, 1462, 1377, 1260, ll91, 1102.



64. The acylazide of **63** obtained as described above was dissolved in 20 mL of dry benzene and stirred at reflux temperature and the reaction was monitored by IR. After 30 min the conversion was complete and the solvent was removed *in vacuo* to give a solid residue. The isocyanate **64** thus obtained was used without purification.

IR (thin film) ν 2953, 2858, 2259, 1778, 1714, 1498, 1472, 1376, 1259, 1184, 1099.

65. To the unpurified isocyanate **64** was added 10 mL of benzyl alcohol. The mixture was stirred at 110 °C for 4 h then the solvent was removed by vacuum distillation (<1 torr) and the residue was purified by chromatography on silica gel (2:1 hexanes/EtOAc) to afford 251 mg (58% from aldehyde **62**) of **65** as a colorless solid.

TLC R_f = 0.29 (2:1 hexanes/EtOAc).

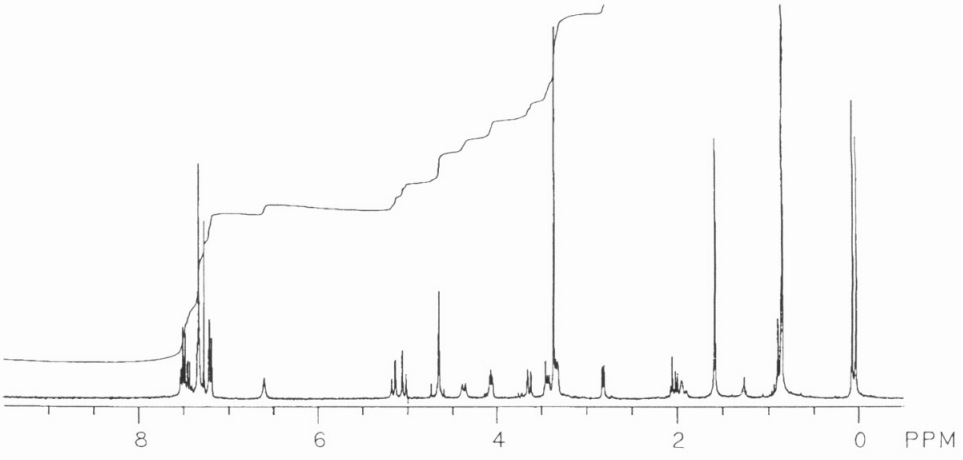
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.33-7.52 (m, 3H), 7.32 (s, 5H), 7.18-7.21 (m, 2H), 6.60 (s, 1H), 5.15 (d, 1H, *J*=12.5), 5.03 (d, 1H, *J*=12.5), 4.64 (s, 2H), 4.36 (d, 1H, *J*=10.8), 4.05 (dd, 1H, *J*=7.2, 3.5), 3.63 (d, 1H, *J*=10.8), 3.36-3.43 (m, 2H), 3.35 (s, 3H), 3.32 (t, 1H, *J*=3.4), 2.81 (d, 1H, *J*=5.6), 1.94-2.04 (m, 2H), 0.85 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 175.9, 154.8, 136.5, 131.5, 129.2, 128.8, 128.2, 127.8, 127.6, 126.2, 126.0, 96.8, 72.5, 71.0, 66.1, 64.7, 55.4, 49.9, 45.5, 43.0, 42.9, 37.1, 25.5, 17.6, -5.1, -5.2.

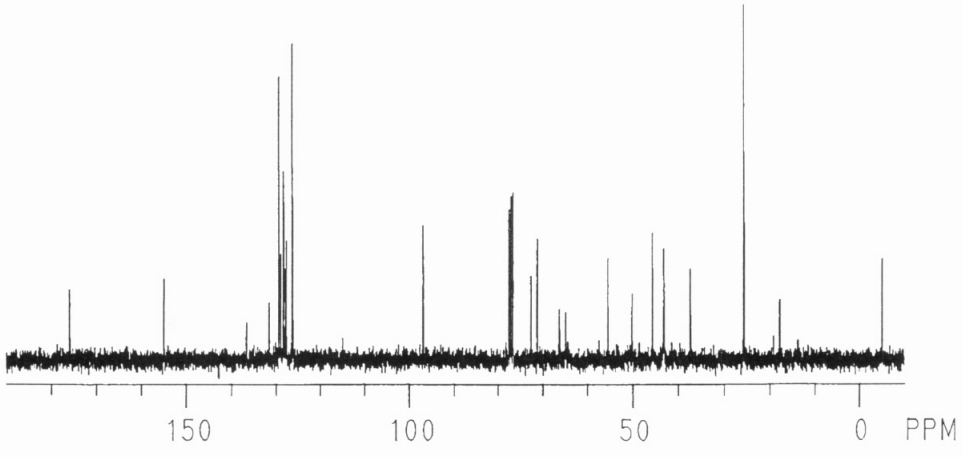
IR (thin film)ν 3390, 29S4, 2858, 1777, 1715, 1504, 1456, 1375, 1256, 1219, 1179, 1068, 1042.

HRMS(CI) calc'd for $C_{32}H_{42}N_2O_7Si$ $(M+H)^+$: 595.2840; found 595.2849.

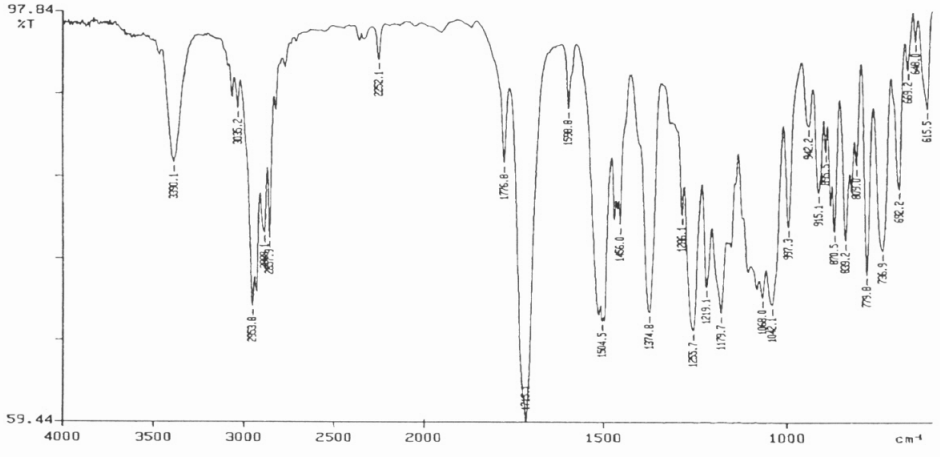
^{1}H NMR
300 MHz
$CDCl_3$

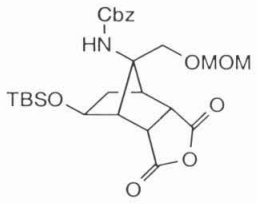


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





66. Imide **65** (146 mg, 0.25 mmol) was dissolved in 6.3 mL dioxane at 20 °C and an aqueous 2 N LiOH solution (0.63 mL, 1.25 mmol) was added. The resulting mixture was stirred for 1 h at 23 °C then the solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with 50 mL of 1 N $NaHSO_4$ and dried over Na_2SO_4. Solvent was removed *in vacuo* to give a 1:1 mixture of regioisomeric acids (146 mg, 95%) which was used without further purification.

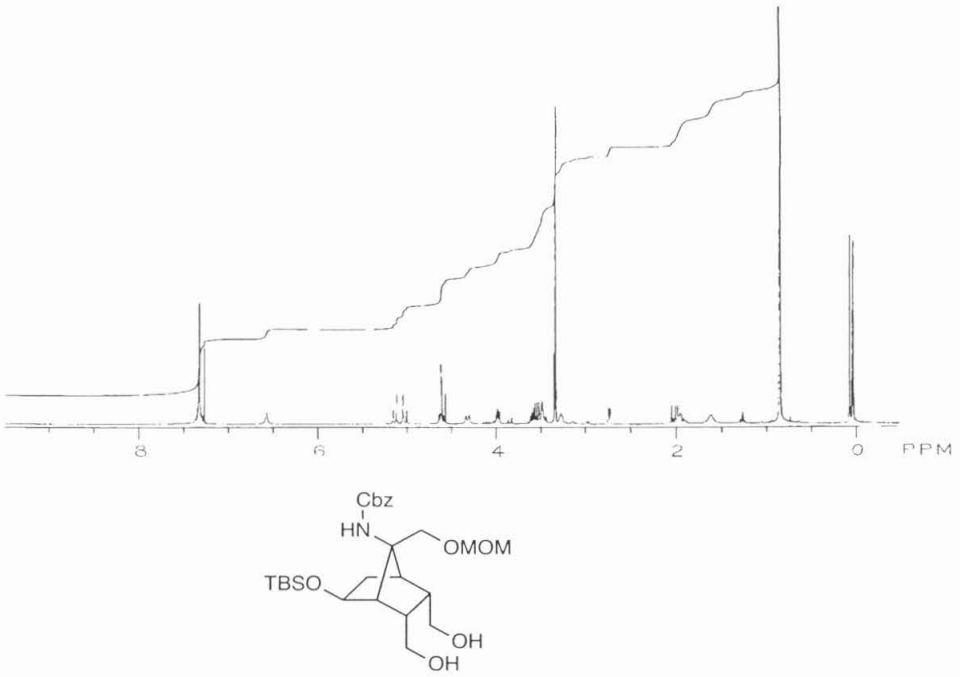
TLC $R_f = 0.31$ and 0.14 (1:1 hexanes/EtOAc).

The mixture of isomeric acids (106 mg, 0.17 mmol) prepared as described above was dissolved in 5 mL of toluene and heated to reflux for 1 h. The reaction mixture was allowed to cool to 23 °C, then poured onto 50 mL of 1 N HCl and extracted 3 x 25 mL pentane. The combined organic extracts were washed with 50 mL saturated aqueous $NaHCO_3$, 50 mL brine then dried over Na_2SO_4. Solvent removal *in vacuo* gave 0.073g (83%) of anhydride **66** as a colorless oil (73 mg, 83%).

TLC $R_f = 0.44$ (2:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.31 (s, 5H), 6.57 (s, 1H, 5.13 (d, 1H, *J*=12.4), 5.02 (d, 1H, *J*=12.4), 4.61 (s, 2H), 4.31 (d, 1H, *J*=10.8), 3.97 (dd, 1H, *J*=7.0, 3.9), 3.47-3.61 (m, 3H), 3.33 (s, 3H), 3.26 (t, 1H, *J*=1.4), 2.73 (d, 1H, *J*=5.0), 1.93-2.04 (m, 2H), 0.84 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

^{1}H NMR
300 MHz
$CDCl_3$



67. To a solution of anhydride **66** (0.073g, 0.140 mmol) in 5 ml of THF was added a 1.0 M solution of $LiAlH_4$ (280 μL, 0.28 mmol) at-78 °C. After 1 h the reaction was quenched by the dropwise addition of 10% aqueous H_2SO_4 and extracted 3 x 5 mL ether. The combined organic layers were washed with 10 mL saturated aqueous $NaHCO_3$, 10 mL brine then dried over Na_2SO_4. Concentration *in vacuo* afforded a mixture of regioisomeric lactones. To the unpurified mixture was added 5 mL of THF and the solution was cooled to 0 °C. A 2 M $LiBH_4$ solution in THF (140 μL, 280 mmol) was then added dropwise and the clear, colorless reaction mixture was stirred at 23 °C for 4 h, then cooled to 0 °C, quenched with 1 N HCl and extracted with 10 mL CH_2Cl_2. The organic layer was washed with 5 mL saturated aqueous $NaHCO_3$, 5 mL brine then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by

chromatography on silica gel (1:5, hexanes/EtOAc) to afford 40 mg (56% from imide **65**) of diol **67**.

TLC $R_f = 0.24$ (1:2 hexanes/EtOAc).

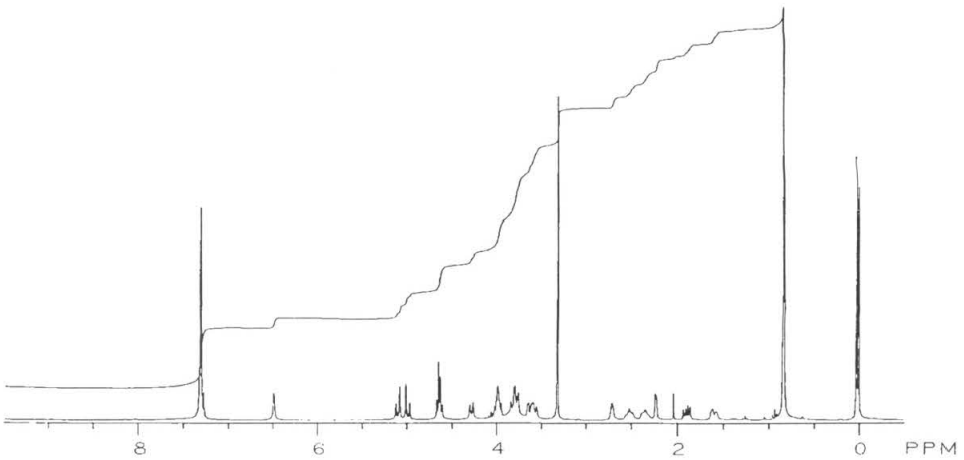
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.30 (s, 5H), 6.48 (s, 1H), 5.10 (d, 1H, *J*=12~6), 4.98 (d, 1H, *J*=12.6), 4.60-4.66 (m, 2H), 4.27 (d, 1H, *J*=10.7), 3.55-4.12 (m, 8H), 3.32 (s, 3H), 2.71 (s, 1H), 2.48-2.52 (m, 1H), 2.25-2.34 (m, 1H), 2.22 (d, 1H, *J*=3.2), 1.89 (dd, lH, *J*=14.0, 7.5), 1.60 (dm, 1H, *J*=14.0), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 155.3, 136.8, 128.2, 127.7, 127.8, 96.8, 69.4, 68.9, 65.9, 64.8, 61.6, 60.1, 55.2, 52.2, 44.1, 39.8, 38.7, 35.2, 25.6, 17.7,-4.9,-5.1.

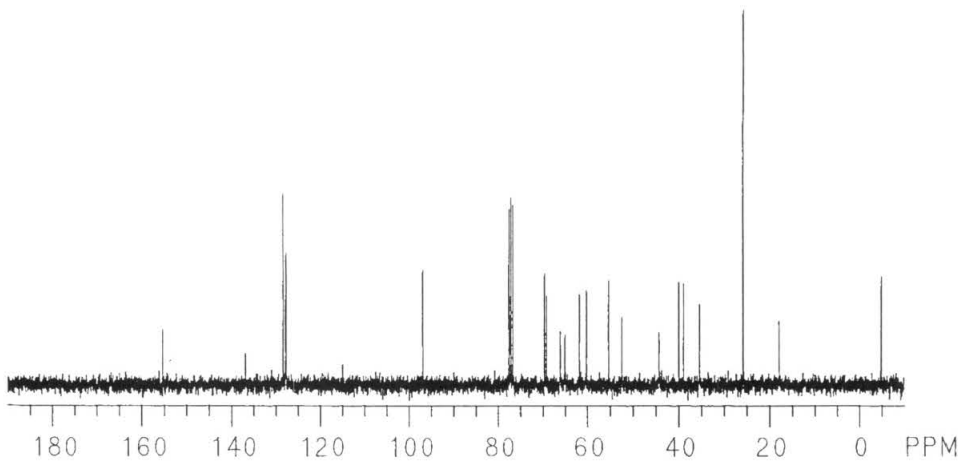
IR (thin film) ν 3392, 2954, 2886, 2858, 1715, 1515, 1471, 1258, 1108, 1043.

HRMS(FAB) calc'd for $C_{26}H_{43}N_7Si$ $(M+H)^+$: 510.2887; found 510.2885.

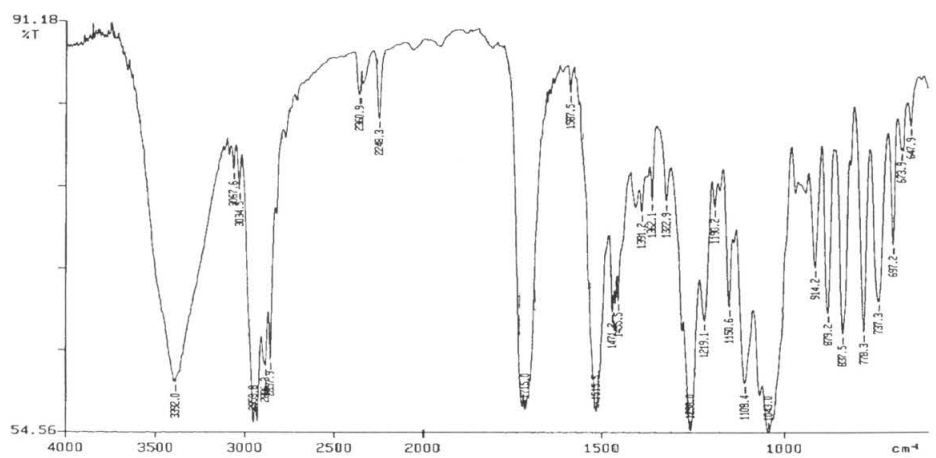
^{1}H NMR
300 MHz
$CDCl_3$

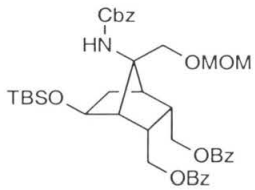


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





68. Benzoylchloride (48 μL, 0.41 mmol) was added dropwise to a solution of diol **67** (0.070g, 0.14 mmol) in 2.0 mL CH_2C1_2 and 0.2 mL pyridine at 0 °C. The mixture was warmed to 23 °C and stirred for l h, then poured onto 10 mL ice cold 1 N HC1 and extracted 3 x 10 mL ether. The combined organic layers were washed with 10 mL saturated aqueous $NaHCO_3$, 10 mL brine then dried over Na_2SO_4. Concentration *in vacuo* afforded a colorless oil, which was purified by chromatography on silica gel (4:1, hexanes/EtOAc) to give 91 mg (91%) of **68** as a white solid.

TLC R_f = 0.25 (4:1 hexanes/EtOAc).

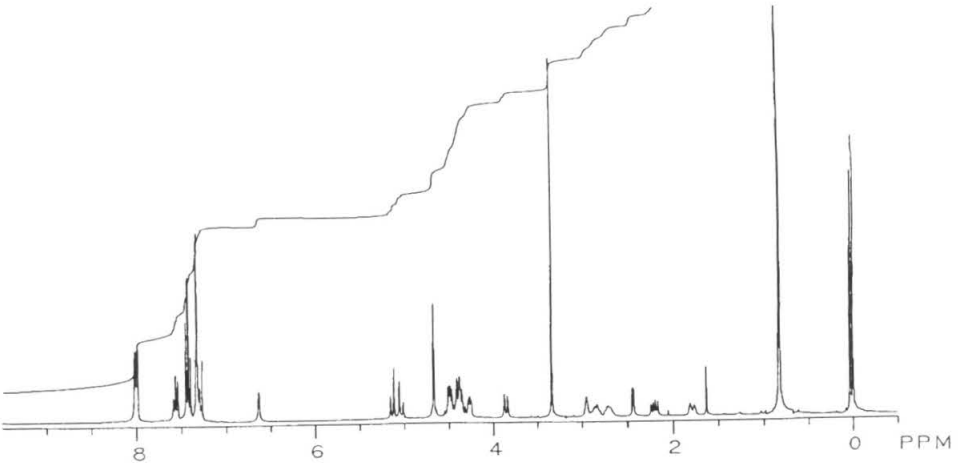
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.97-8.01 (m, 4H), 7.53-7.59 (m, 2H), 5.13 (d, 1H, *J*=12.4), 5.03 (d, 1H, *J*=12.4), 4.66 (s, 2H), 4.24-4.51 (m, 6H), 3.85 (d, 1H, *J*=10.6), 3.33 (s, 3H), 2.94 (t, 1H, *J*=1.4), 2.68-2.86 (m, 2H), 2.43 (d, 1H, *J*=2.8), 2.20 (dd, 1H, *J*=14.3, 7.5), 1.78 (d, 1H, *J*=14.3), 0.82 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 166.2, 166.0, 155.2, 136.8, 133.1, 129.63, 129.61, 129.56, 129.48, 128.3, 128.2, 127.7, 127.6, 96.7, 69.2, 69.1, 65.9, 64.7, 62.6, 61.1, 55.3, 50.7, 43.6, 35.9, 34.4, 35.1, 25.6, 17.7, -5.0, -5.1.

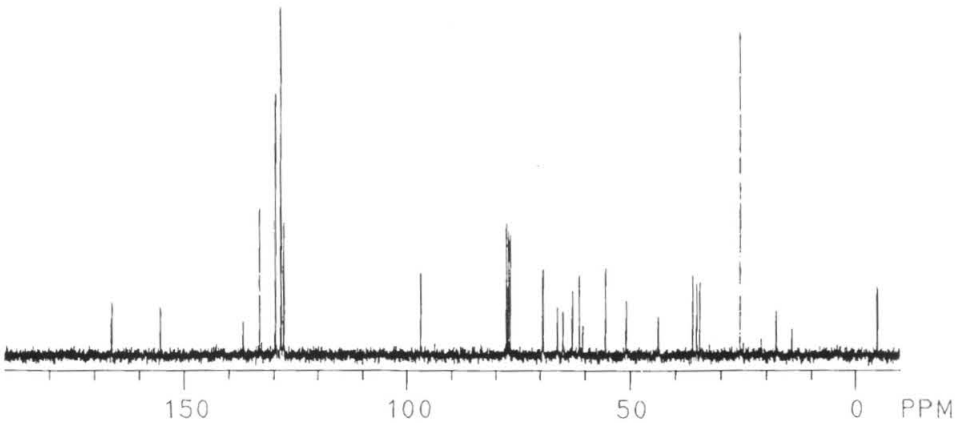
IR (thin film)ν 3392, 3066, 2955, 2857, 1716, 1514, 1453, 1270s, 1110, 1070, 1043.

HRMS(EI) calc'd for $C_{32}H_{42}N_2O_7Si$ $(M+H)^+$: 718.3411; found 718.3418.

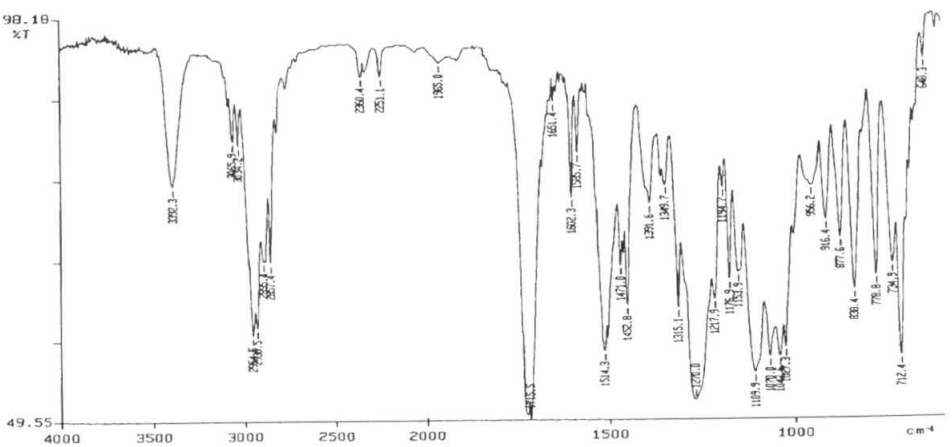
^{1}H NMR
300 MHz
$CDCl_3$

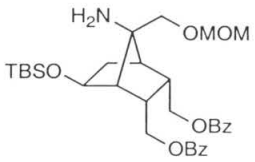


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





Amine (intermediate between **68** and **69**). A solution of carbamate **68** (0.0347g, 48 μmol) in 5 mL absolute ethanol containing 7 mg Pearlman's catalyst was stirred under 1 atm H_2 for 4 h. The mixture was then filtered through celite and the filter cake was washed with 5 mL EtOAc. The filtrate was concentrated *in vacuo* to afford 28 mg (100%) of the unpurified amine which was taken on to the next step.

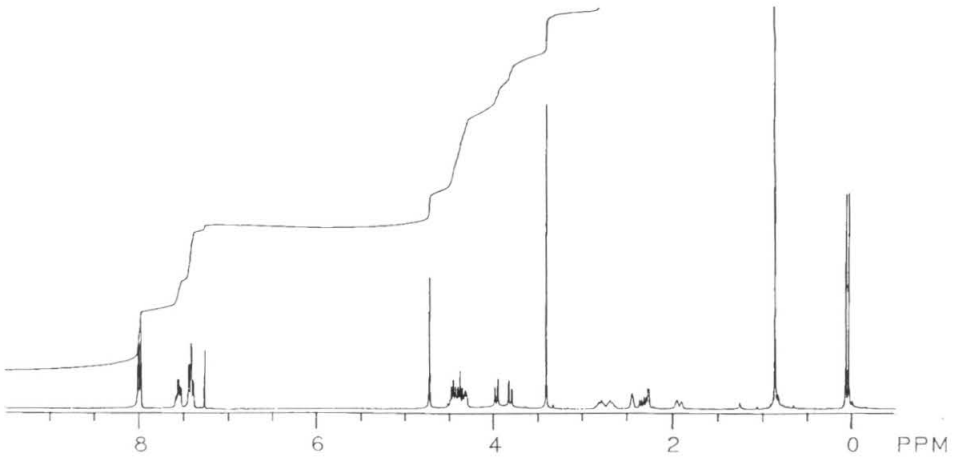
TLC R_f = 0.23 (2:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.97-8.01 (m, 4H), 7.52-7.59 (m, 2H), 7.38-7.44 (m, 4H), 4.72 (s, 2H), 4.29-4.41 (m, 5H), 3.96 (d, 1H, *J*=10.1), 3.80 (d, 1H, *J*=10.1), 3.7-4.3 (s, 2H), 3.40 (s, 3H), 2.66-2.81 (m, 2H), 2.43 (s, 1H), 2.32 (dd, 1H, *J*=14.7, 7.5), 2.26 (d, 1H, *J*=3.3), 1.92 (d, 1H, *J*=14.7), 0.85 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

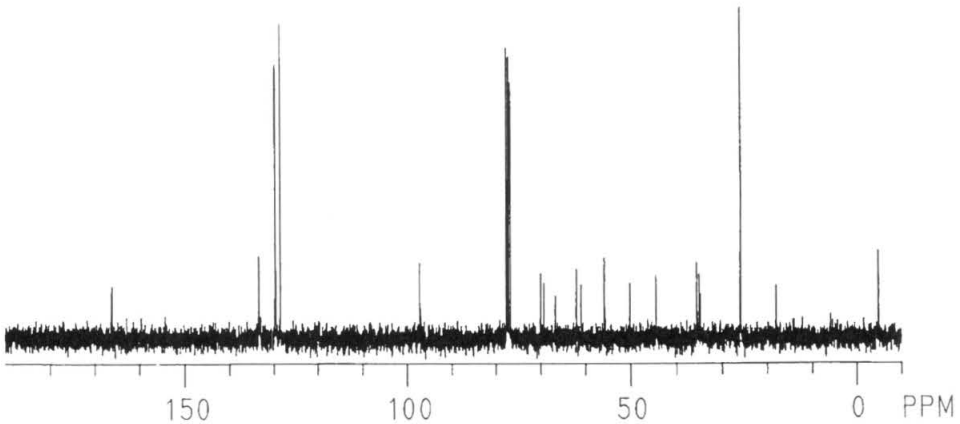
^{13}C-NMR ($CDCl_3$, 75 MHz)δ 166.2, 166.0, 133.3, 133.2, 129.54, 129.51, 129.4, 128.5, 128.40, 128.35 , 97.1, 69.8, 69.1, 66.8, 61.8, 60.8, 55.7, 50.0, 44.2, 35.3, 34.8, 34.5, 25.7, 17.9, -4.9, -5.0.

IR (thin film)ν 3372, 2955, 2857, 1722, 1602, 1452, 1271, 1110, 1044.

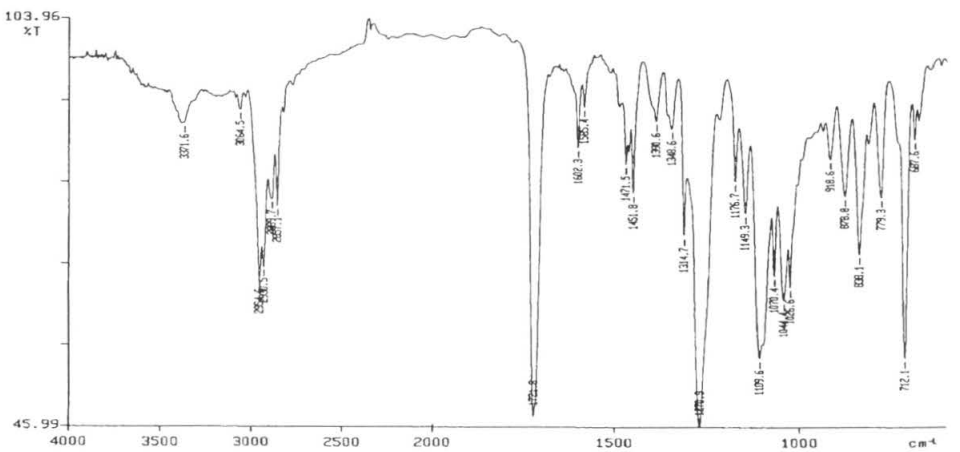
^{1}H NMR
300 MHz
$CDCl_3$

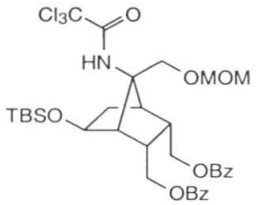


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





69. A mixture of the amine (28 mg, 48 μmol) prepared as described above and triethylamine (10 μL, 72 μmol) in 2.0 mL CH_2Cl_2 was treated with trichloroacetylchloride (7 μL, 63 μmol) at 0 °C. After 45 min the reaction was quenched by the addition of 1 mL saturated aqueous NH_4Cl, extracted 3 x 5 mL CH_2Cl_2 then dried over Na_2SO_4. Solvent removal *in vacuo* afforded a colorless oil, which was purified by chromatography on silica gel (6:1, hexanes/EtOAc) to give 0.023g (65% from **68**) of **69**.

TLC R_f = 0.48 (4:1 hexanes/EtOAc).

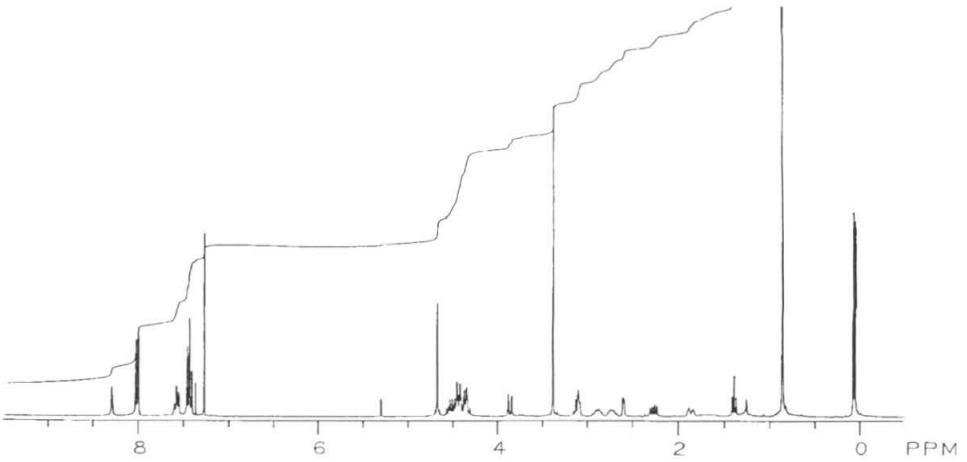
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 8.28 (s, 1H), 7.98-8.01 (m, 4H), 7.53-7.59 (m, 2H), 7.40-7.45 (m, 4H), 4.66 (s, 2H), 4.30-4.56 (m, 6H), 3.85 (d, 1H, *J*=10.9), 3.37 (s, 3H), 3.08 (t, 1H, *J*=1.6), 2.65-2.95 (m, 2H), 2.59 (d, 1H, *J*=3.3), 2.26 (dd, 1H, *J*=14.4, 7.6), 1.86 (d, 1H, *J*=14.4), 0.85 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 166.2, 166.1, 160.8, 133.2, 129.6, 129.5, 128.44, 128.42, 96.8, 93.1, 70.9, 69.6, 63.5, 62.2, 61.0, 55.5, 50.9, 43.1, 35.8, 35.0, 34.4, 26.0, 18.5,-4.7,-4.8.

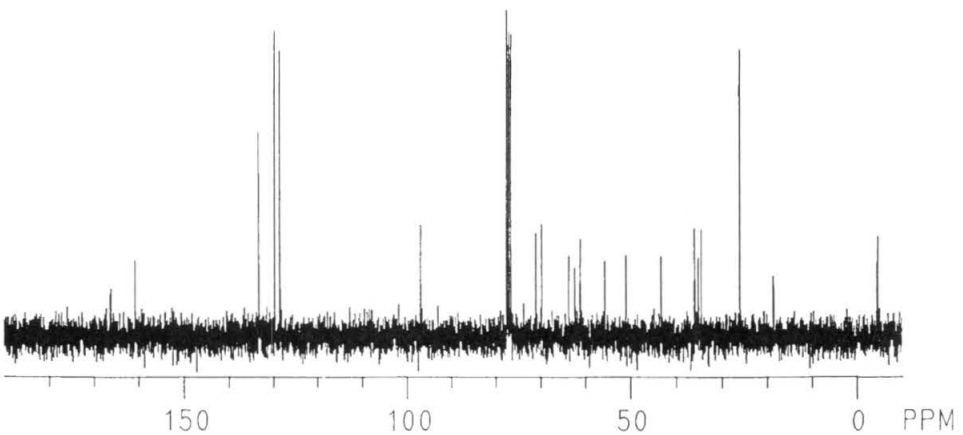
IR (thin film)ν 3362, 2955, 2858, 1716, 1603, 1515, 1452, 1270, 1110, 1043.

HRMS(EI) calc'd for $C_{34}H_{44}NO_8SiCl_3$: 728.1980; found 728.1984.

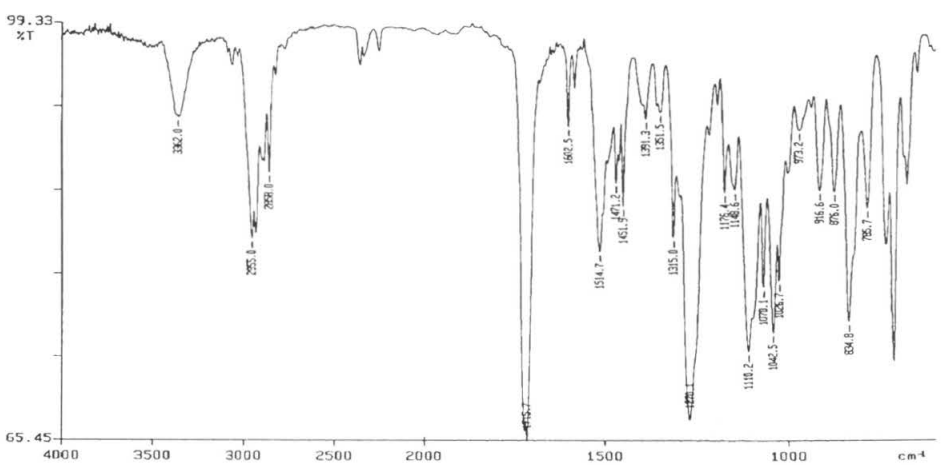
^{1}H NMR
300 MHz
$CDCl_3$

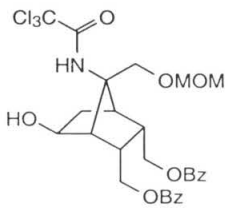


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





50. Silylether **69** (0.035g, 48 μmol) was dissolved in 2.0 mL THF, then 0.2 mL HF pyridine complex was added at 0 °C. The reaction mixture was stirred at 23 °C for 20 h, then it was poured onto 5 mL of 1 N HC1 and extracted 3 x 5 mL ether. The combined organic layers were washed with 5 mL of saturated aqueous $NaHCO_3$, 5 mL of brine then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (2:1, hexanes/EtOAc) to afford 0.0253g (86%) of **50** as a white solid.

TLC R_f = 0.41 (2:1 hexanes/EtOAc).

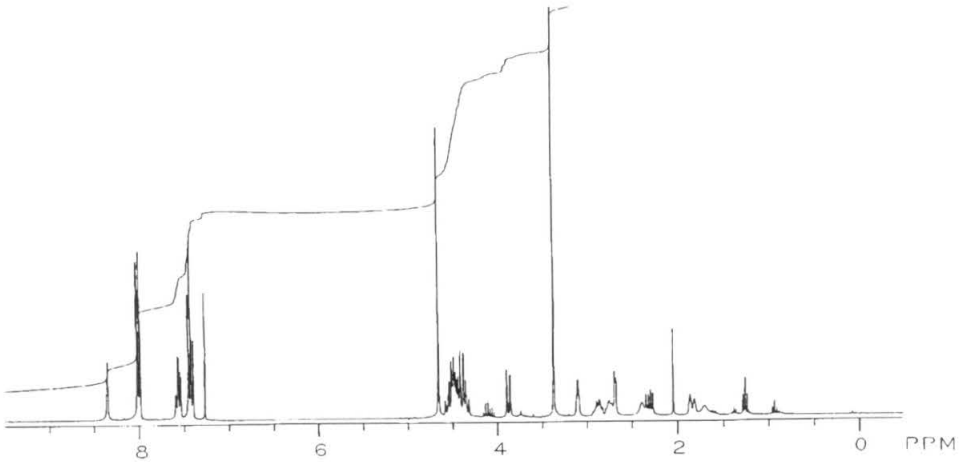
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 8.32 (s, 1H), 8.0 (d, 4H, *J*=8.1), 7.54-7.60 (m, 2H), 7.43 (t, 4H, *J*=7.3), 4.65 (s, 2H), 4.31-4.57 (m, 5H), 4.38 (d, 1H, *J*=10.9), 3.87 (d, 1H, *J*=10.9), 3.36 (s, 3H), 3.10 (t, 1H, *J*=3.4), 2.72-2.89 (m, 2H), 2.68 (d, 1H, *J*=3.3), 2.35-2.45 (s, 1H), 2.31 (dd, 1H, *J*=14.6, 7.7), 1.83 (d, 1H, *J*=14.6).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 166.3, 160.9, 133.3, 133.2, 129.61, 129.55, 128.46, 96.8, 93.0, 70.7, 68.7, 63.6, 62.2, 61.2, 55.5, 50.4, 43.3, 35.7, 34.6, 33.8.

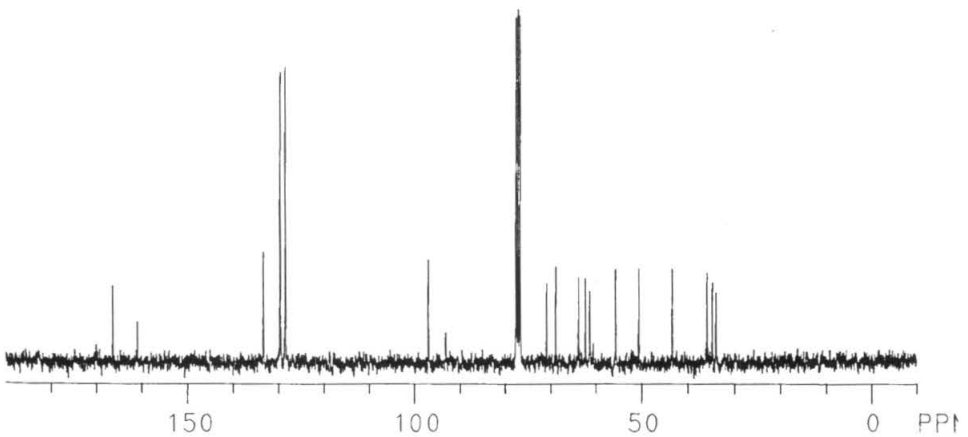
IR (thin film)ν 3468, 3362, 2953, 1715, 1602, 1520, 1452, 1271, 1111, 1040.

HRMS(EI) calc'd for $C_{28}H_{30}NO_8Cl_3$ $(M+H)^+$: 614.1115; found 614.1123.

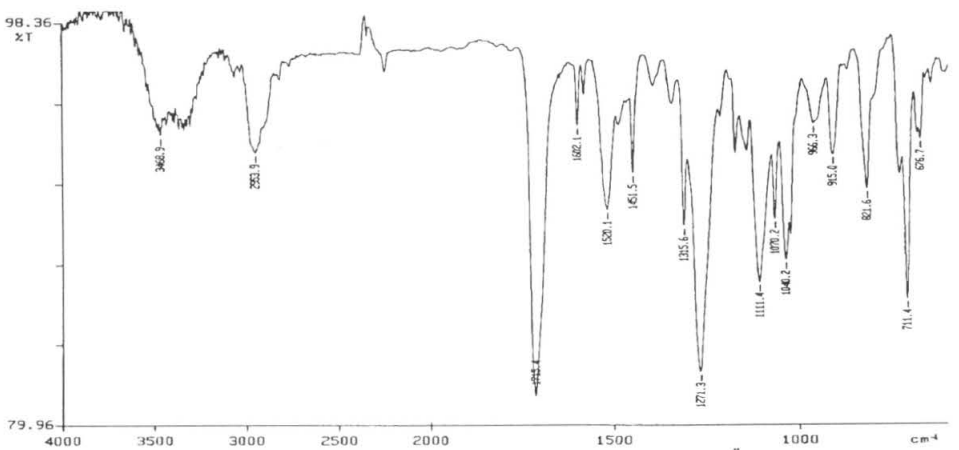
^{1}H NMR
300 MHz
$CDCl_3$

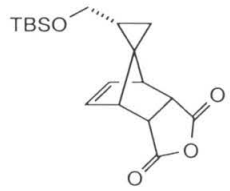


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





74. To a solution of imide **52** (5.01g, 12.3 mmol) in 350 mL THF at room temperature was added aqueous LiOH (0.1 M, 365 mL, 36.5 mmol) dropwise. The reaction was stirred for 45 min then quenched by dropwise addition of aqueous $NaHSO_4$ (1.0 M, 37 mL, 37 mmol). The resulting mixture was diluted with 300 mL saturated aqueous NaCl, extracted 1 x 300 mL CH_2Cl_2, then 3 x 100 mL CH_2Cl_2 and the combined organic layers were dried over sodium sulfate. Solvent removal *in vacuo* yielded a colorless solid. The solid mixture of isomeric acid-amides was dissolved in 1.5 L toluene upon heating the heterogeneous mixture to 70 °C. The temperature was maintained at 70 °C for 4 h then the solution was cooled to room temperature and poured onto 1 L of ice-cold 1 M HC1 and shaken vigorously. The aqueous layer was discarded and the organic layer was then washed with saturated aqueous NaC1 and dried over sodium sulfate. Solvent removal *in vacuo* afforded the desired anhydride **74** as a colorless solid. 3.91g (95%)

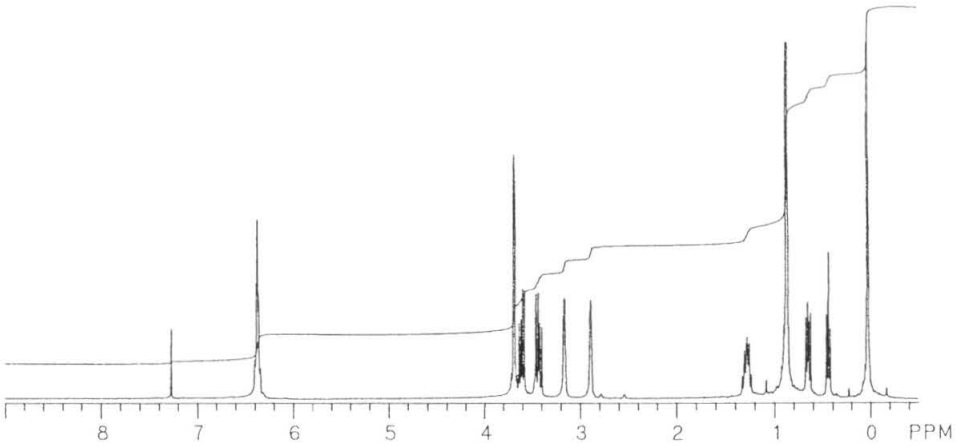
$\mathbf{R_f}$= 0.91 (1: 1 hexanes/EtOAc).

^{1}H-NMR ($CDC1_3$, 300 MHz) δ 6.37 (m, 2H), 3.68 (m, 2H), 3.61 (dd, 1H, *J*= 11, 9), 3.42 (dd, 1H, *J*= 11, 9), 3.16 (s, 1H), 2.88 (s, 1H), 1.27 (m, 1H), 0.87 (s, 9H), 0.65 (dd, 1H, *J*= 9.9, 5.6), 0.42 (dd, IH, *J*= 5.5, 5.5), 0.03 (s, 6H).

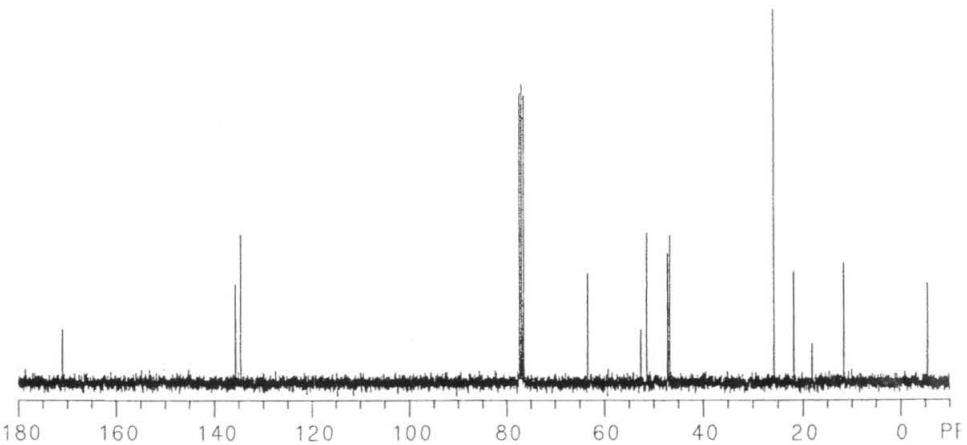
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 170.89, 134.58, 134.52, 63.26, 52.48, 51.28, 47.08, 47.04, 46.61, 25.65, 21.72, 11.53, -5.52, -5.57.

IR (thin film) ν 2927, 2855, 1792, 1472, 1255, 1222, 1083, 935, 913, 836, 775, 668, 620.

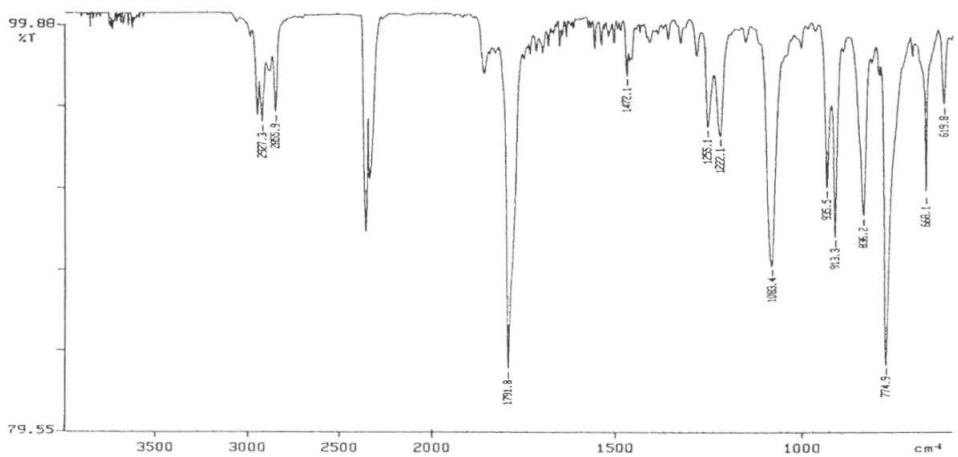
^{1}H NMR
300 MHz
$CDCl_3$

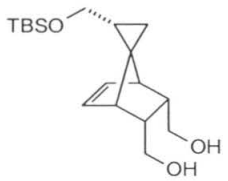


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





75. To a solution of anhydride **74** (3.61g, 10.8 mmol) in 220 mL diethyl ether cooled -10°C was added a THF solution of LAH (1 M, 15mL, 60 mmol hydride) dropwise. The reaction was warmed to room temperature and stirred 3.5 h then cooled to 0 °C and treated sequentially with water (0.57 mL), aqueous NaOH (15%, 0.57 mL), then water (1.7mL). The resulting slurry was immediately vacuum filtered through celite and the filter cake pulverized then washed ten times with 50 mL portions of CH_2Cl_2. The combined filtrates were evaporated *in vacuo* to give the desired diol **75** as a colorless solid that was purified by recrystallization from hexanes. 3.1lg (89%)

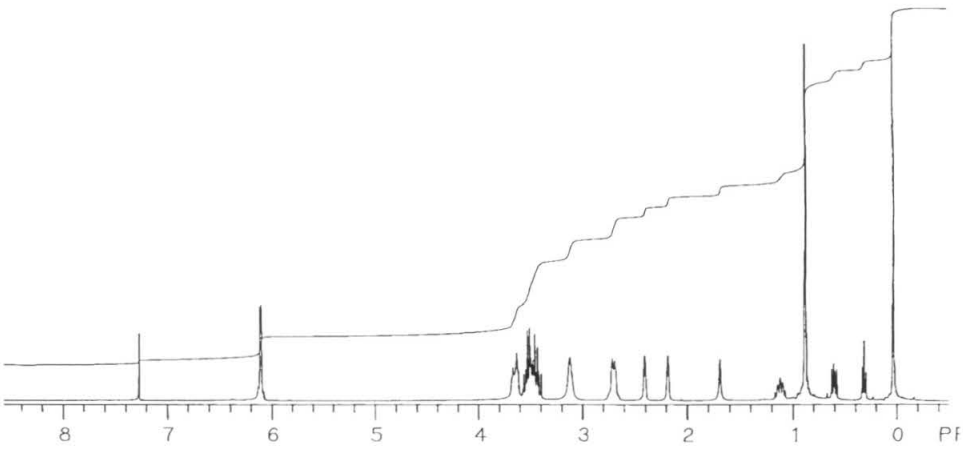
$\mathbf{R_f}$= 0.18 (l: 1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.10 (m, 2H), 3.65 (m, 2H), 3.4-3.6 (m, 4H), 3.11 (s,12H), 2.71 (m, 2H), 2.39 (s, lH), 2.18 (s, 1H), 1.68 (s, lH), 1.11 (m, 1H), 0.86 (s, 9H), 0.60 (dd, 1H, *J*= 9.5, 5.4), 0.31 (dd, 1H, *J*= 5.4, 5.4), 0.03 (s, 6H).

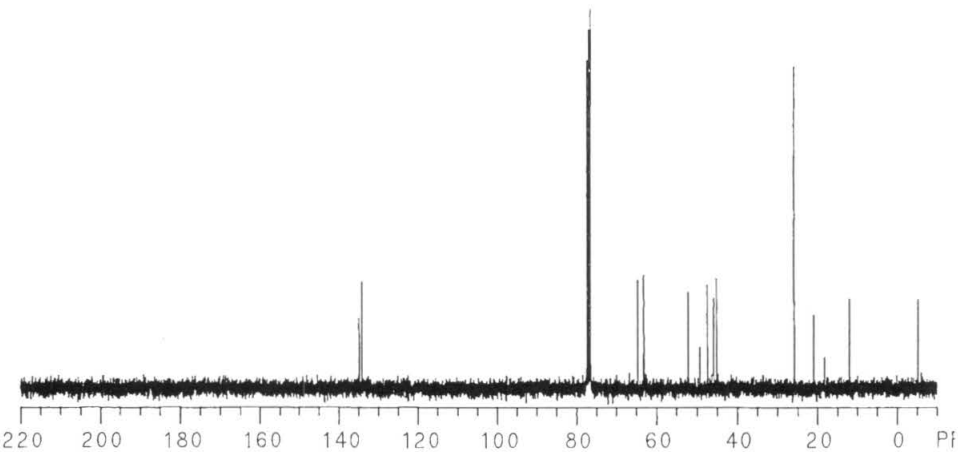
^{13}C-NMR ($CDCl_3$, 75 MHz) δ, 134.69, 133.97, 64.48, 62.92, 51.97, 49.07, 47.16, 45.63, 44.96, 25.74, 20.78, 18.14, 11.83, -5.40.

IR (thin film) ν 3280, 2928, 2857, 1472, 1253, 1220, 1022, 836, 773.

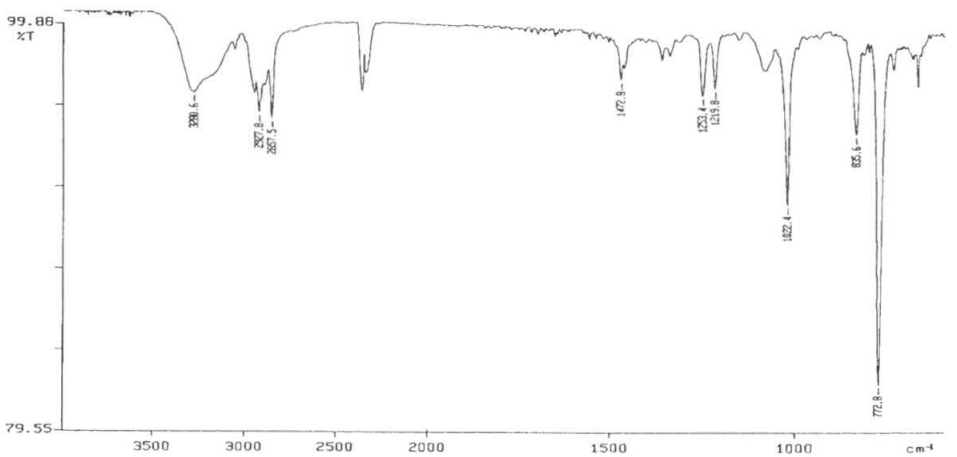
^{1}H NMR
300 MHz
$CDCl_3$

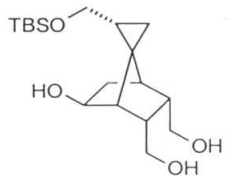


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





76. To a stirring solution of **75** (0.188g, 0.579 mmol) in 10 mL THF cooled to –10 °C was added a solution of borane-THF complex in THF (1M, 1.5 mL, 1.5 mmol). Gas evolution was observed. The reaction was maintained at –10 °C for 1 h then warmed to room temperature and allowed to react for 45 min. A 2 mL portion of 1:1 v/v THF/EtOH was then added, followed by 1 mL pH=7 buffer (0.05 M phosphate), and 1 mL 30% hydrogen peroxide and the mixture was stirred 12 h. The reaction was then diluted with 20 mL saturated aqueous NaCl, and 20 mL aqueous 1N NaOH, then extracted 3 x 20 rnL CH_2Cl_2. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give a colorless solid mixture of regioisomeric triols **76** in a 3:1 ratio (determined by ^{1}H-NMR). 0.193g (97%)

Major Isomer **76**

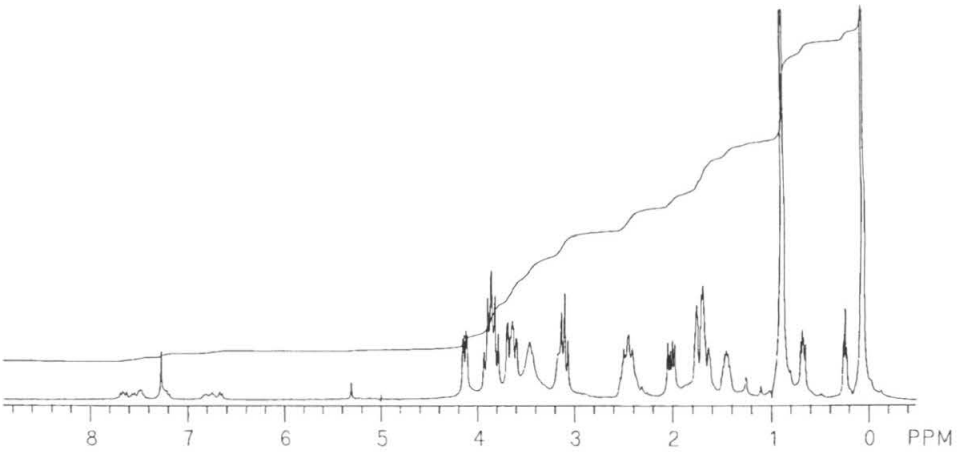
$\mathbf{R_f}$= 0.35 (EtOAc).

^{1}H-NMR (d_6-DMSO, 300 MHz) δ 4.41(m, 2H), 3.78 (m, 2H), 3.66 (dd, 1H, *J* = 10, 6), 3.45 (m, 3H), 2.10 (m, 2H), 1.89 (m, 1H), 1.68 (s, 1H), 1.41 (s, 1H), 1.29 (m, 1H), 0.89 (s, 9H), 0.46 (dd, 1H, *J* = 8, 4.5), 0.14 (dd, 1H, *J* = 5, 5), 0.01 (s, 6H).

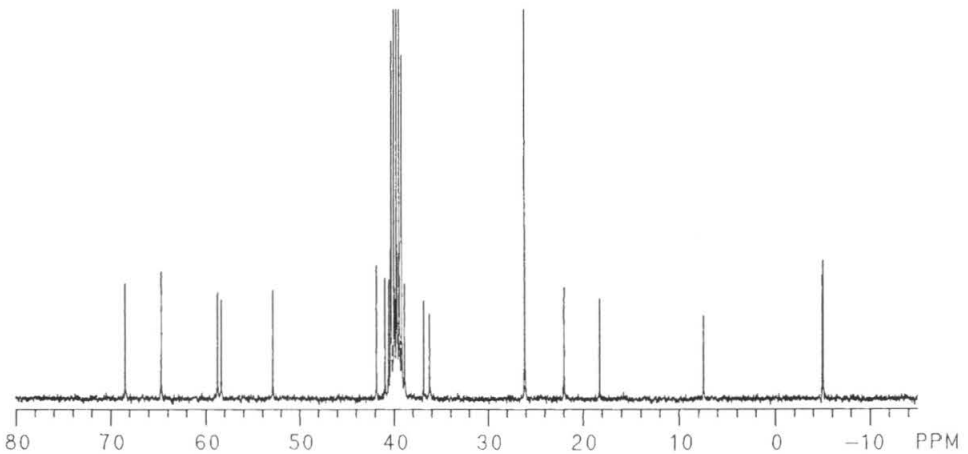
^{13}C-NMR (d_6-DMSO, 75 MHz) δ, 68.43, 64.61, 58.66, 58.26, 52.79, 41.82, 40.88, 40.30, 36.78, 36.15, 26.06, 21.90, 18.16, 7.37, -5.02, -5.12.

IR (thin film) ν 3330, 2953' 2858, 1471, 1361, 1255, 1080, 1016, 939, 837, 775, 668.

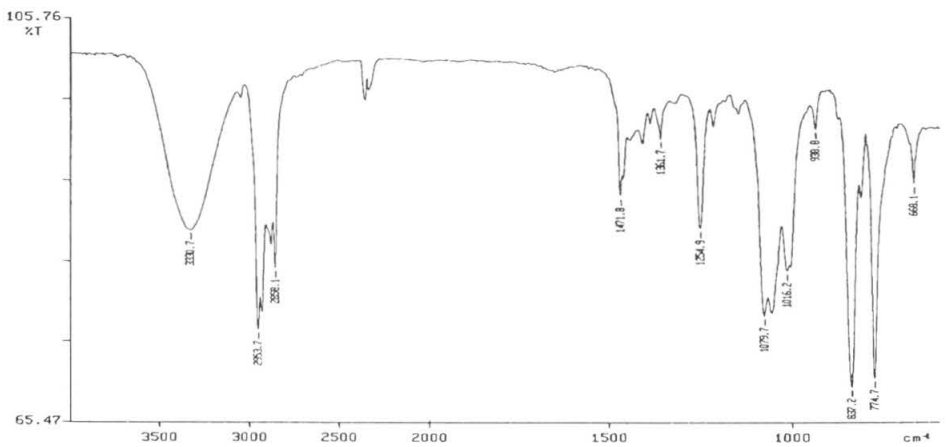
^{1}H NMR
300 MHz
d_6-DMSO

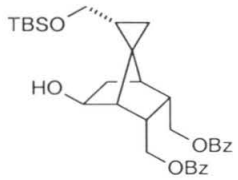


^{13}C NMR
75 MHz
d_6-DMSO



FTIR
thin film





77. To a solution of **76** (3.06g, 8.95 mmol) in 100 mL dichloromethane at 23 °C was added DMAP (2.22g, 18.2 mmol), and benzoic acid (2.20g, 18.2 mmol) followed by EDC (3.50g, 18.2 mmol) and the reaction was stirred for 6 h. The reaction was then diluted with 200 mL CH_2Cl_2 and washed 2 x 200 mL aqueous lN HCI, l x 200 mL saturated aqueous sodium bicarbonate, l x saturated aquoues NaCl, then dried over sodium sulfate. Concentration *in vacuo* gave a colorless glass. Chromatography on silica gel (5:1 hexanes/EtOAc) gave 4.80g (97%) of **77** as a 3:1 mixture of mono-ol regioisomers.

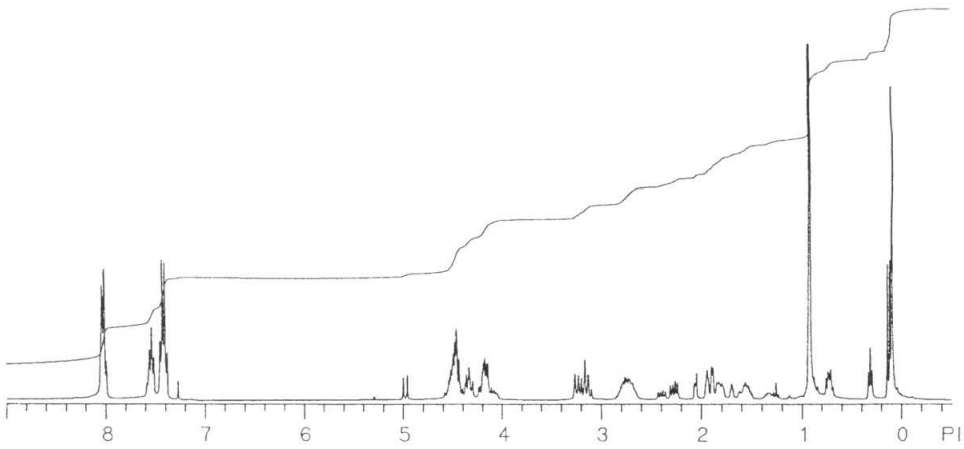
Major Isomer **77**

$\mathbf{R_f}$= 0.35 (4: 1 hexanes/EtOAc).

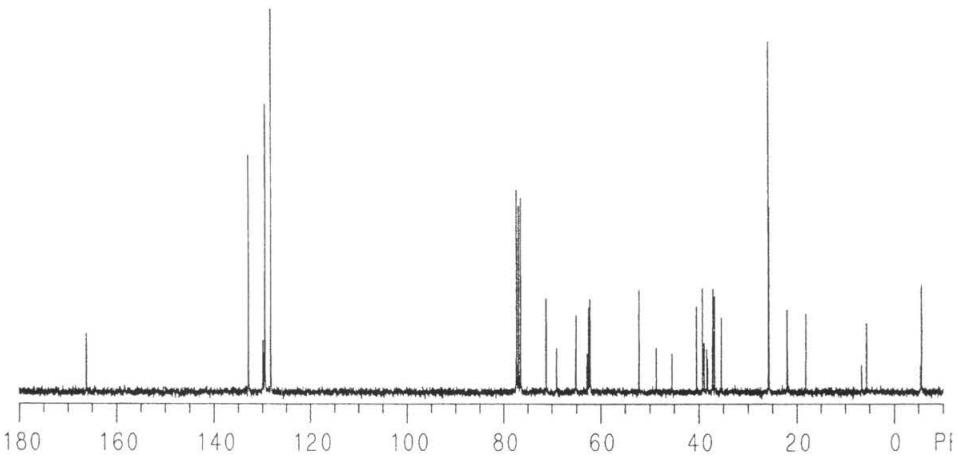
^{1}H-NMR ($CDC1_3$, 300 MHz) δ 8.00 (d, 4H, *J*= 7.0), 7.54 (m, 2H), 7.38 (m, 4H), 4.4-4.5 (m, 3H), 4.31 (dd, 1H, *J*= 11.1, 2.4), 4.15 (m, 2H), 3.24 (d, 1H, *J*= 10.9), 3.14 (dd, 1H, *J*= 10.5), 2.6-2.8 (m, 2H), 2.25 (dd, 1H, *J*= 14.4, 7.0), 1.7-2.0 (m, 2H), 1.65 (m,1H), .88 (s, 9H), 0.72 (dd, 1H, *J*= 9.5, 5.4), 0.30 (dd, 1H, *J*= 5.4, 5.4), 0.06 (s, 6H).

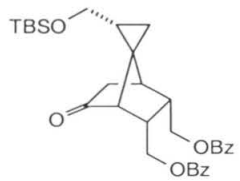
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 166.12, 166.08, 132.75, 129.85, 129.71, 129.34, 129.32, 128.13, 71.05, 64.92, 62.40, 62.10, 52.05, 40.31, 39.13, 37.01, 36.65, 35.33, 25.69, 21.90, 18.04, 5.49, -5.69, -5.73.

^{1}H NMR
300 MHz
$CDCl_3$



^{13}C NMR
75 MHz
$CDCl_3$





TBS-Ketone (between **77** and **78**). To a solution of **77** (4.80g, 8.71 mmol) in 200 mL CH_2Cl_2 at room temperature was added crushed 4Å molecular sieves (9.2g, oven dried at 130 °C > two weeks) and the suspension was stirred for 15 min. Pyridinium chlorochromate (PCC) (4.2g, 19 mmol) was then added and the dark brown heterogeneous reaction was stirred for 4 h. The reaction mixture was then filtered through silica gel, washing with 10 x 30 mL portions of 3:1 hexanes/EtOAc. The combined filtrates were concentrated *in vacuo* to give a dark oil. The oil solidified on standing and was purified by chromatography on silica gel (6:1 hexanes/EtOAc) to give 3.46g (72%) of the desired ketones.

Major Isomer

R_f= 0.45 (4: 1 hexanes/EtOAc).

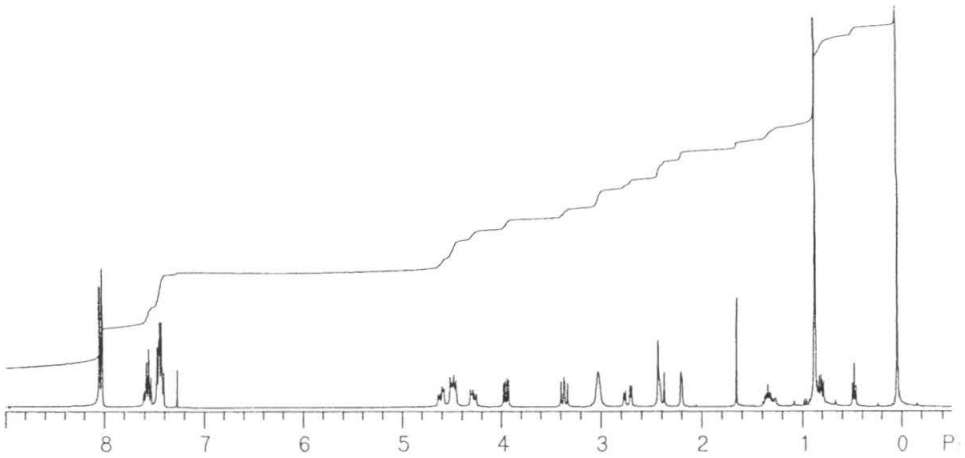
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, 4H, *J*= 7.0), 7.56 (m, 2H), 7.42 (m, 4H), 4.59 (m, 1H), 4.49 (m, 2H), 4.28 (dd, 1H, *J*= 11.6, 4.0), 3.94 (dd, 1H, *J*= 11.0, 5.0), 3.36 (dd, 1H, *J*= 11.0, 8.7), 3.02 (s, 1H), 2.72 (dd, 1H, *J*= 18.2, 4.6), 2.40 (d, 2H, *J*= 18.2), 2.20 (s, 1H), 1.33 (m, 1H), 0.85 (s, 9H), 0.78 (dd, 1H, *J*= 9.5, 5.4), 0.47 (dd, 1H, *J*=5.4, 5.4), 0.04 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ, 213.42, 166.00, 165.86, 132.90, 132.82, 129.59, 129.39, 129.36, 128.19, 63.86, 62.82, 62.16, 59.51, 41.07, 40.12, 38.82, 38.64, 38.08, 25.66, 20.71, 17.96, 8.84, -5.47, -5.65.

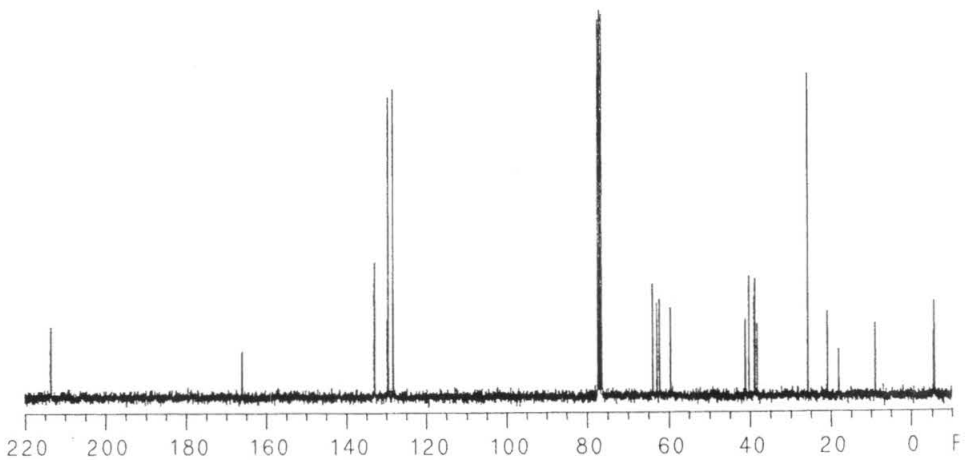
IR (thin film) ν 2955, 2857, 1748, 1721, 1451, 1270, 1111, 1026, 838, 775, 711.

^{1}H NMR

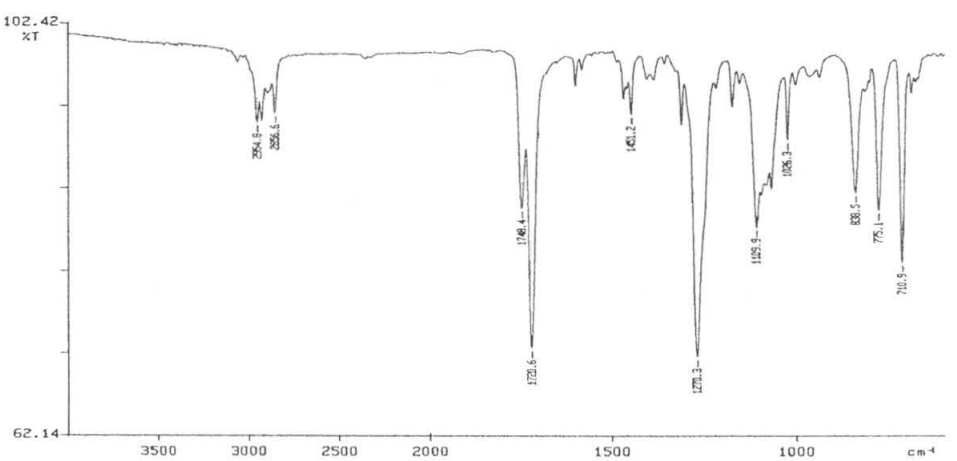
300 MHz
$CDCl_3$

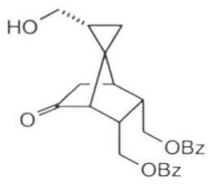


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





78. To a solution of **77** (1.2g) in 20 mL THF at room temperature was added 80 mL 48% HF/CH_3CN/water (5:95:1.5 v/v/v) and the reaction was stirred 2 h. Saturated aqueous sodium bicarbonate was then carefully added portionwise until bubbling ceased and pH was approximately neutral (by pH paper). The reaction was then extracted 3 x 50 mL CH_2Cl_2 and the combined organic layers were washed 1 x 100 mL saturated aqueous NaC1 then dried over sodium sulfate. Concentration *in vacuo* afforded a 3:1 mixture of isomers **78** as a colorless foam. 0.92g (97%).

Major isomer **78**

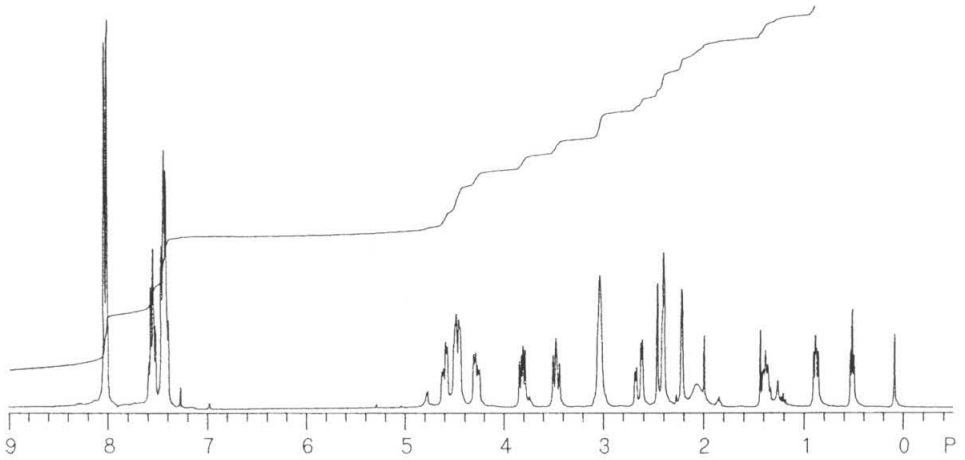
$\mathbf{R_f}$= 0.60 (2:7 hexanes/EtOAc).

^{1}**H-NMR** ($CDC1_3$, 300 MHz) δ 8.02 (d, 4H, *J*= 7.0), 7.58 (m, 2H), 7.41 (m, 4H), 4.59 (m, 1H), 4.48 (m, 2H), 4.29 (m, 1H), 3.81 (dd, 1H, *J*= 11.0, 5.0), 3.46 (dd, 1H, *J*=11.0, 8.7), 3.02 (s, 2H), 2.61 (dd, 1H, *J*= 18.2, 4.6), 2.45 (d, 2H, *J*= 18.2), 2.20 (s, 1H), 1.39 (m, 1H), 0.87 (dd, 1H, *J*= 9.5, 5.4), 0.51 (dd, 1H, *J*=5.4, 5.4).

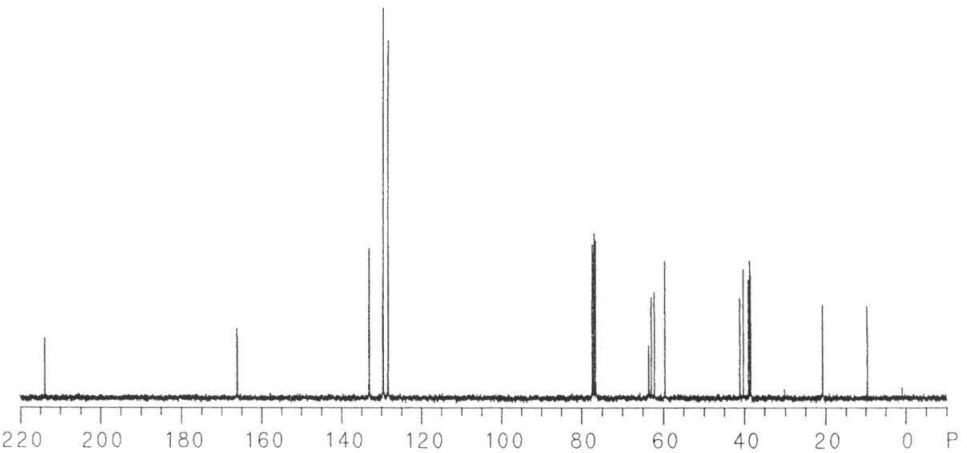
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 9.53, 20.66, 38.26, 38052, 38.85, 40.09, 40.97, 59.45, 62.07, 62.80, 63.43, 128.20, 128.23, 129.37, 129.50, 132.89, 165.90, 166.05, 213.77.

IR (thin film) ν 3484, 2917, 1719, 1602, 1451, 1272, 1177, 1112, 1070, 1026, 966, 755, 711.

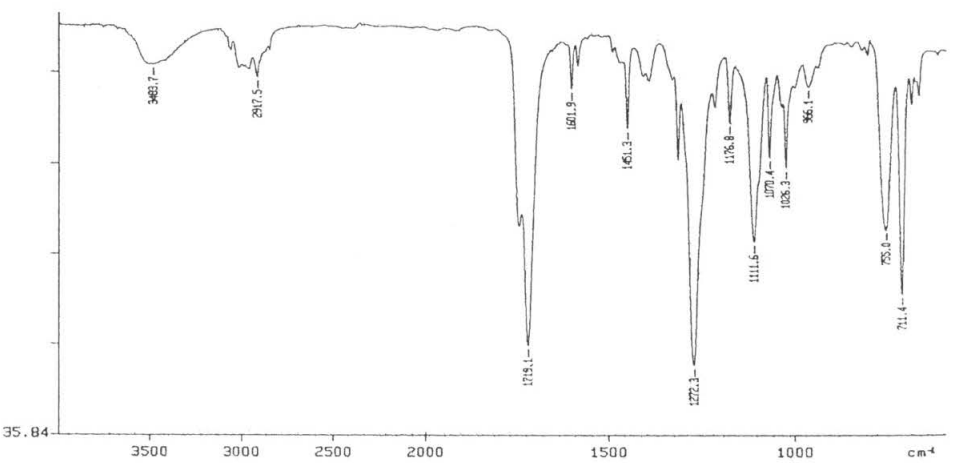
^{1}H NMR
300 MHz
$CDCl_3$

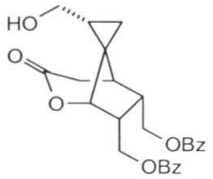


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





79. To a solution of keto-alcohol isomers **78** (0.l0g, 0.24 mmol) in 10 mL dichloromethane at room temperature was added *m*CPBA (0.089g, 0.51 mmol) in one portion. The reaction was stirred for 13 h then treated with 10% aqueous sodium bisulfite (l0mL) and extracted 3 x 20 mL CH_2Cl_2. The combined organic extracts were washed with 30 mL saturated aqueous sodium bicarbonate then dried over sodium sulfate. Solvent removal *in vacuo* afforded the 3:1 isomeric mixture **79** as a foamy white solid that was purified by chromatography on silica gel (3: 1 hexanes/EtOAc) to give **79** in 99% yield. Leading fractions of the pure major isomer were obtained for characterization.

Major Isomer **79**

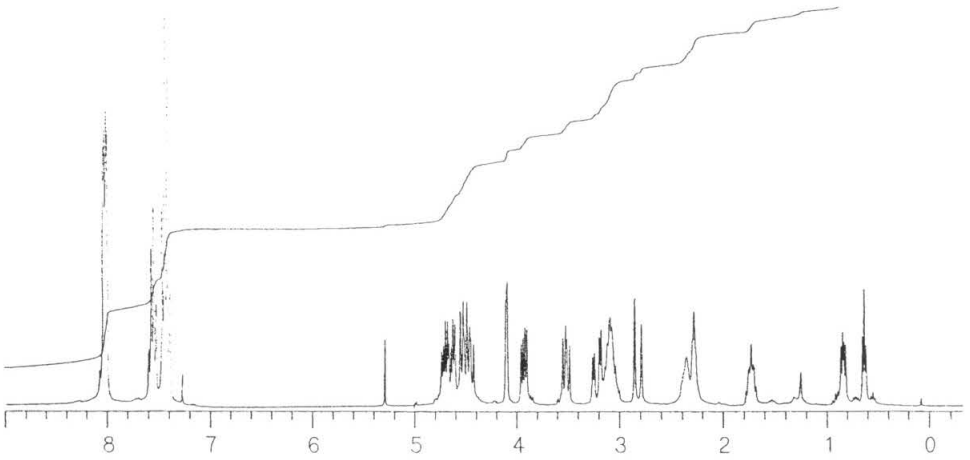
R_f= 0.45 (2:7 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.03 (m, 4H), 7.58 (m, 2H), 7.46 (m, 4H), 4.73-4.42 (m, 5H), 4.09 (s, 1H), 3.93 (dd, 1H, *J* = 11, 6), 3.50 (dd, 1H, *J* = 11, 8), 3.23 (dd, 1H, *J* = 18, 5), 3.2-3.0 (m, 2H), 2.81 (d, 1H, *J* = 18), 2.4-2.2 (bm, 3H), 1.71 (m, 1H), 0.84 (dd, lH, *J*=9, 5), 0.62 (dd, 1H, *J*= 11, 5).

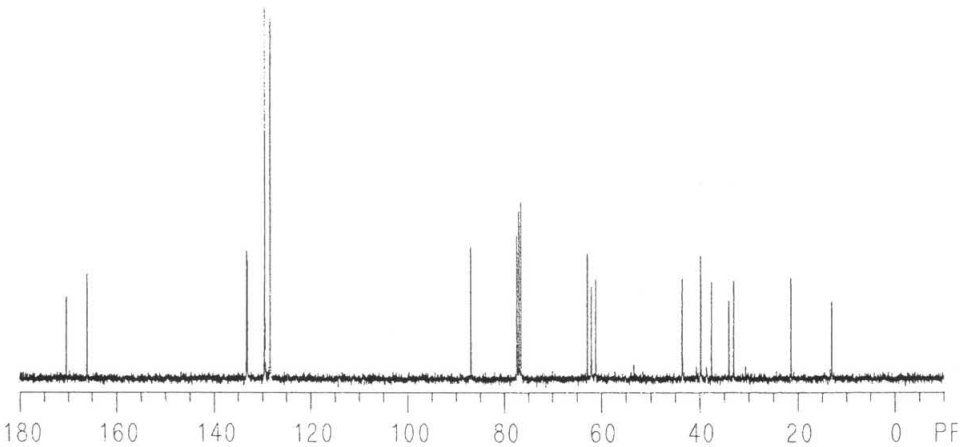
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 12.94, 21.32, 32.91, 33.89, 37.44, 39.63, 43.43, 61.04, 61.95, 62.74, 86.85, 128.19, 128.29, 129.38, 129.46, 132.95, 133.10, 165.92, 170.23.

IR (thinfilm) ν 3468, 2959, 2923, 1720, 1451, 1361, 1315, 1273, 1176, 1112, 1071, 1026, 981, 913, 712.

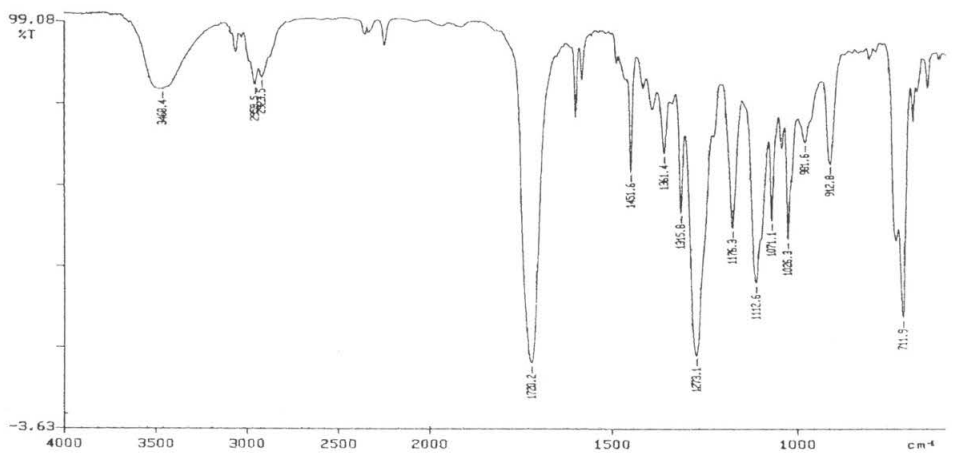
^{1}H NMR
300 MHz
$CDCl_3$

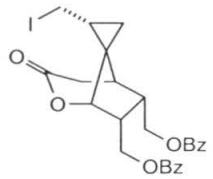


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





80. To a solution of **79** (0.11g, 0.24 mmol) in 1 mL CH_3CN and 5 mL Et_2O at 23 °C was added triphenylphosphine (0.10g, 0.39 mmol), and imidazole (0.036g, 0.53 mmol). Once the mixture became homogenous, iodine (0.10g, 0.40 mmol) was added and the reaction was stirred until it reached a translucent orange/brown color (10 min.). The solution was decolorized with 6 mL 10% aqueous sodium thiosulfate then extracted 3 x 20 mL Et_2O. The combined ethereal layers were then washed 1 x 30 mL 10% aqueous copper (II) sulfate, 5 x 30 mL water, 1 x 50 mL saturated aqueous NaCl, and dried over sodium sulfate. Concentration *in vacuo* produced a colorless solid that was purified by chromatography on silica gel (3:1 hexanes/EtOAc) to give 0.112g (82%) of a 5:1 mixture of isomers **80** as a colorless solid.

$\mathbf{R_f}$= 0.94 (1: 1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.02 (m, 4. 8H), 7.4-7.6 (m, 7.2H), 4.40-4.78 (m, 5H), 4.09 (s, 1H), 3.46 (dd, 1H, *J* = 10, 6), 3.34 (m, 0.4H), 3.13 (m, 3.2H), 2.93 (s, 2H), 2.27 (s, 1H), 2.03 (m, 1H), 1.81 (m, 0.2H), 1.18 (dd, 0.2H, *J* = 8, 5), 1.06 (dd, 1H, *J* =8, 5), 0.63 (dd, 0.2H, J=5,5), 0.62 (dd, lH, *J*=5, 5).

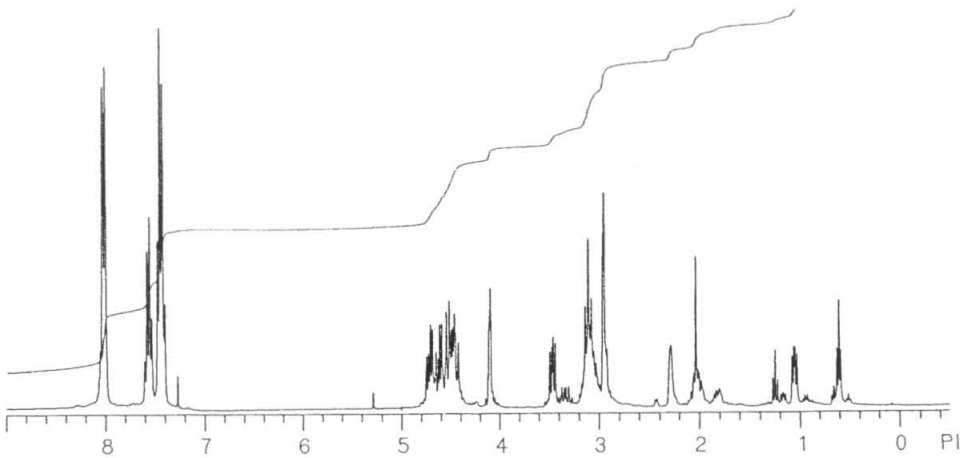
Major isomer 28a:

^{13}C-NMR ($CDCl_3$, 75 MHz) δ 4.90, 19.27, 23.99, 34.53, 37.53, 38.89, 39.55, 43.19, 60.77, 61.61, 86.29, 128.21, 128.31, 129.19, 129.38, 132.99, 133. 15, 165.79, 168.74.

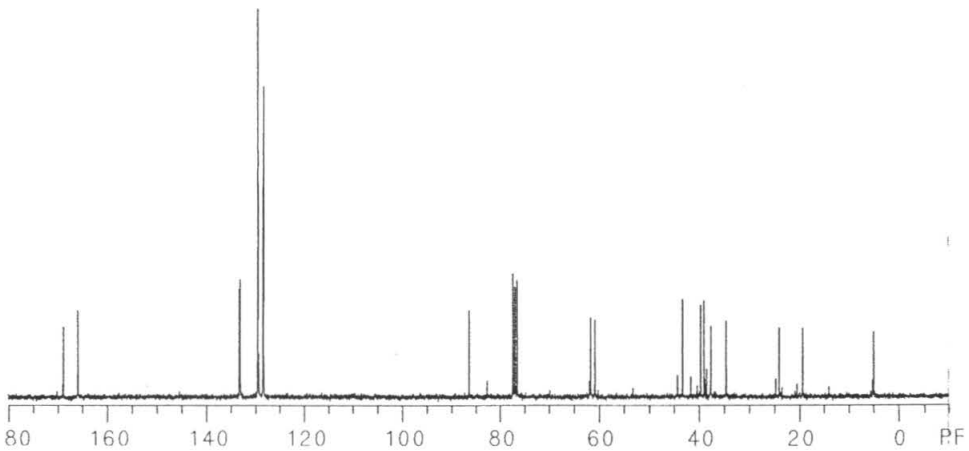
Minor isomer 28b:

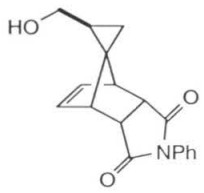
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 4.91, 14.11, 20.12, 23.65, 24.83, 38.41, 38.76, 40.27, 41.58, 44.24, 62.44, 83.01, 128.21, 128.31, 129.19, 129.38, 132.99, 133. 15, 168.23, 170.09.

^{1}H NMR
300 MHz
$CDCl_3$



^{13}C NMR
75 MHz
$CDCl_3$





Alcohol (between **52** and **78**). To a solution of **52** (10.6g) in 30 ml THF at 23 °C was added 150 ml 48% HF / acetonitrile / water (5:95:1.5 v/v/v) and the reaction stirred one hour. Saturated $NaHCO_3$ was then added portionwise until bubbling ceased and pH was approximately neutral (by pH paper). The reaction was extracted 5 x 100 ml dichloromethane and the combined extracts washed 1 x 300 ml saturated aqueous NaCl and dried over Na_2SO_4. Solvent removal *in vacuo* afforded analytically pure product in quantitative yield as a colorless solid.

MP 159-160 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.5-7.3 (m, 3H), 7.15 (m, 2H), 6.41 (m, 2H), 3.62 (m, 1H), 3.54 (s, 2H), 3.35 (dd, 1H, J= 11, 8), 3.13 (s, 1H), 2.91 (s, IH), 1.36 (m, 1H), 0.76 (dd, 1H, J = 8, 5), 0.44 (dd, 1H, J = 5, 5).

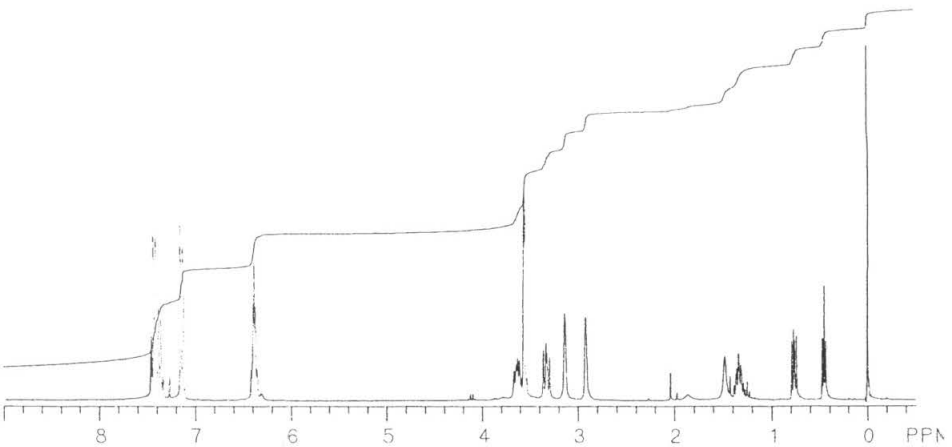
^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.85, 21.40, 45.19, 45.70, 46.28, 50.70, 52.33, 63.86, 126.36, 128.43, 128.87, 131.51, 134.22, 135.35, 176.10, 176.19.

IR (thin film) ν 3461, 2992, 2876, 1707, 1497, 1380, 1285, 1183, 1032, 913, 723.

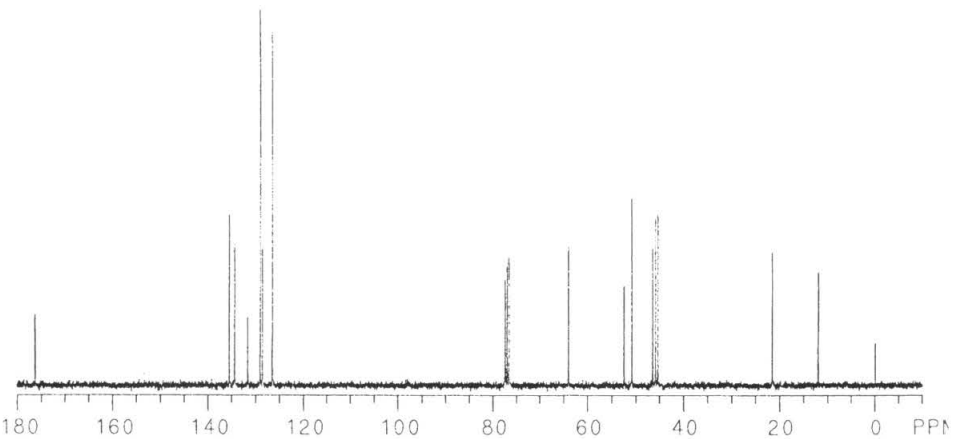
Elemental Analysis calc'd for $C_{18}H_{17}O_3N_1$: C, 73.20%, H, 5.80%, N, 4.74%; found C, 73.09%, H, 5.86%, N, 4.74%.

^{1}H NMR

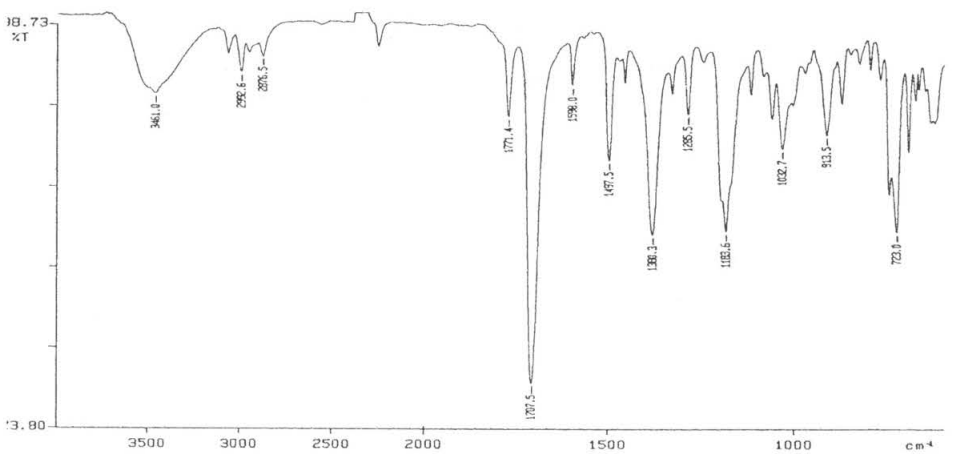
300 MHz
$CDCl_3$

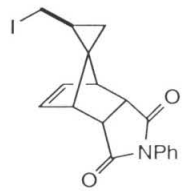


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





87. To a solution of alcohol (14.5g, 49.1 mmol), triphenylphosphine (19.2g, 73.2 mmol), and imidazole (5.12g, 75.2 mmol) in 450 ml dichloromethane cooled with an ice/salt bath was added I_2 (18.8g, 74.1 mmol) in one portion. The reaction became opaque orange-brown over 10 min then was warmed to room temperature and stirred an additional 15 min. The reaction was then treated with 50 ml of saturated aqueous Na_2SO_3 and stirred until colorless. The organic layer was washed 1 x 200 ml 10% $CuSO_4$, 2 x 200 ml water, 1 x 200 ml saturated NaCl and dried over Na_2SO_4. Partial solvent removal *in vacuo* afforded a viscous *solution* which was subjected to silica gel chromatography (1:1 hexanes/EtOAc) to give **87** as a colorless solid. 18.5g (93%)

MP 148-149 °C (dec.).

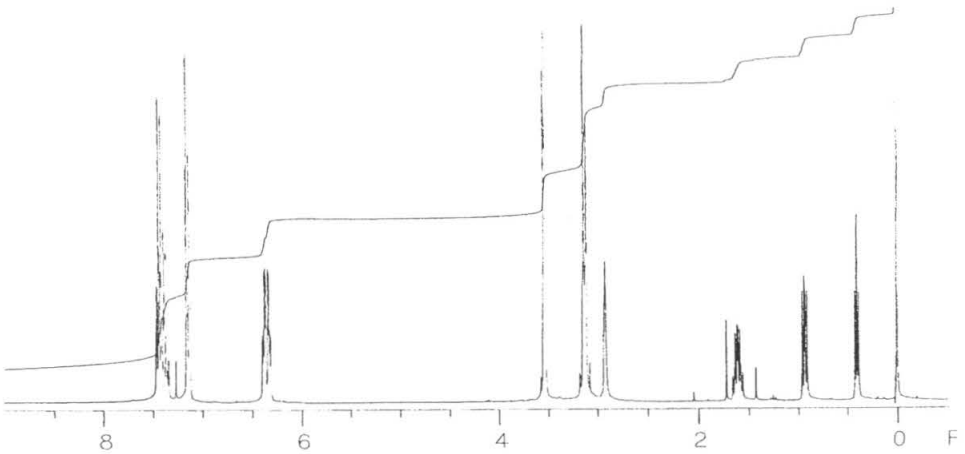
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.46-7.36 (m, 3H), 7.15 (m, 2H), 6.38 (m, 2H), 3.54 (d, 2H, J = 1), 3.14 (m, 3H), 2.92 (s, IH), 1.60 (m, 1H), 0.95 (dd, 1H, J = 8, 5), 0.42 (dd, 1H, J= 5, 5).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 7.31, 17.28, 23.51, 45.26, 45.35, 45.72, 50.66, 57.36, 126.37, 128.44, 128.88, 131.53, 133.79, 135.00, 175.90, 175.95.

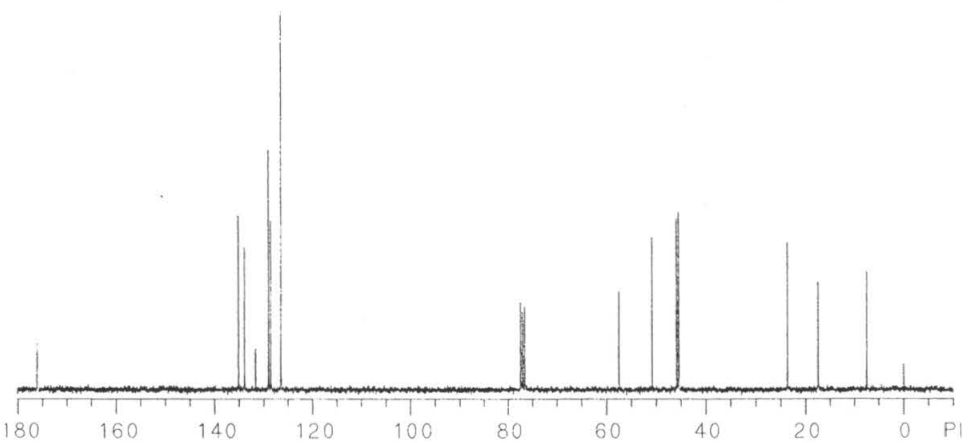
IR (thin film)ν 2989, 1772, 1710, 1598, 1499, 1455, 1378, 1285, 1182, 9l2, 874, 724.

Elemental Analysis calc'd for $C_{18}H_{16}O_2N_1I$: C, 53.35%, H, 3.98%, N, 3.46%; found C, 53.53%, H, 4.07%, N, 3.49%.

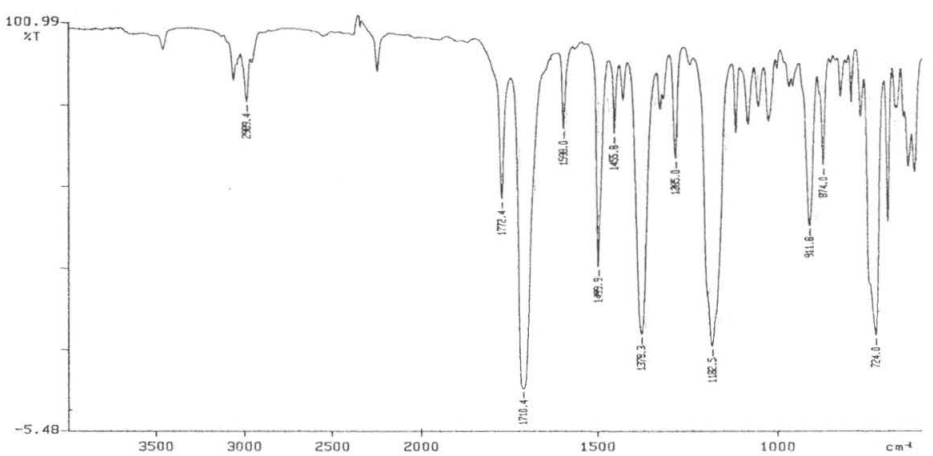
^{1}H NMR
300 MHz
$CDCl_3$

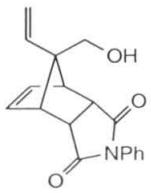


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





88. A solution of iodide **87** (30.2g, 74.5 mmol) in 700 ml benzene was vigorously aerated for 30 min with dry air passing through a fritted glass dispersion tube. While aeration continued, Bu_3SnH (50.0g, 172 mmol, diluted to 100 ml with benzene) was added dropwise *via* pressure equalizing addition funnel over a period of 2 h. Aeration was stopped when **87** was consumed (as indicated by TLC). The orange reaction was then stirred an additional 15 h during which time some white precipitate formed. With stirring, 750 ml hexanes was added and the resulting copious white precipitate was collected by filtration to give 15.8g of **88**. The filtrate was concentrated and the residue was purified by silica gel chromatography (4:1 EtOAc/hexanes) to give an additional 3.15g of **88** for a combined yield of 19.0g (86%).

MP 172-173 °C.

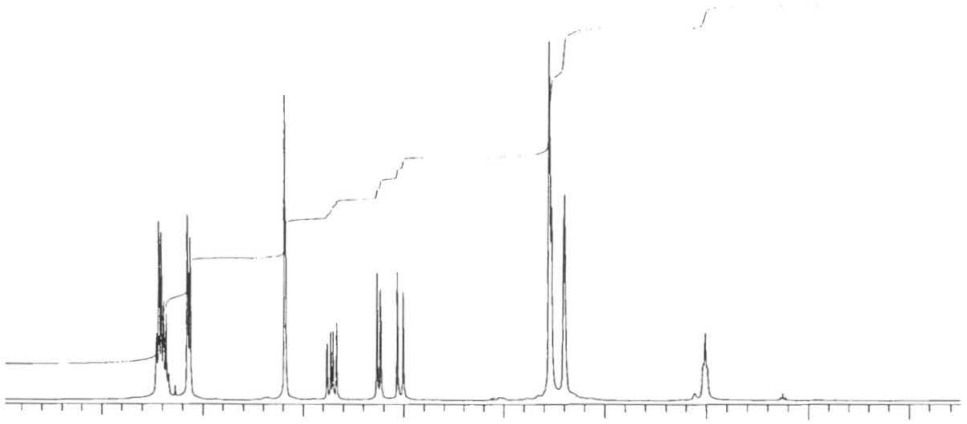
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0 7.38-7.46 (m, 3H), 7.14 (dd, 2H, J= 7, 1), 6.19 (dd, 2H, J= 2, 2), 5.72 (dd, 1H, J= 18, 11), 5.27 (dd, 1H, J= 11, 0.8), 5.06 (dd, 1H, J= 18, 0.8), 3.57 (m, 4H), 3.43 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.2O, 48.54, 62.66, 73.42, 118.67, 126.31, 128.45, 128.88, 131.52, 133.69, 137.72, 176.22.

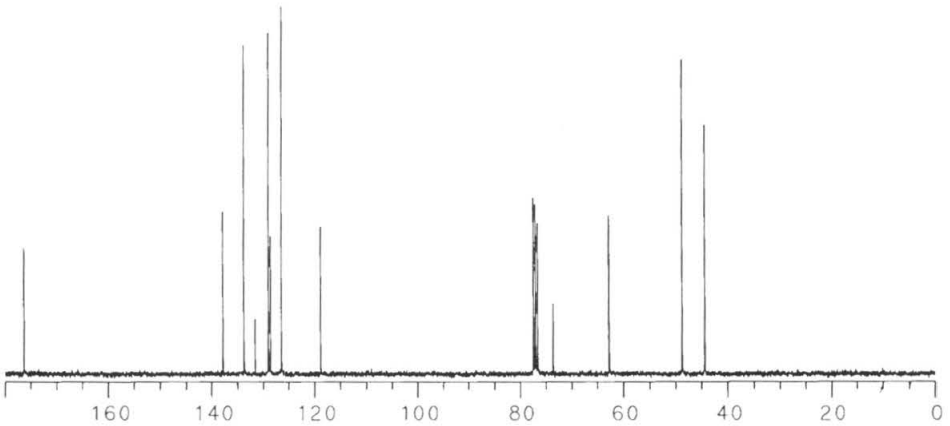
IR (thin film) ν 3456, 2979, 1772, 1706, 1469, 1381, 1185, 727, 691, 622.

Elemental Analysis calc'd for $C_{18}H_{17}O_3N_1$: C, 73.20%, H, 5.80%, N, 4.74%; found C, 73.09%, H, 5.86%, N, 4.74%.

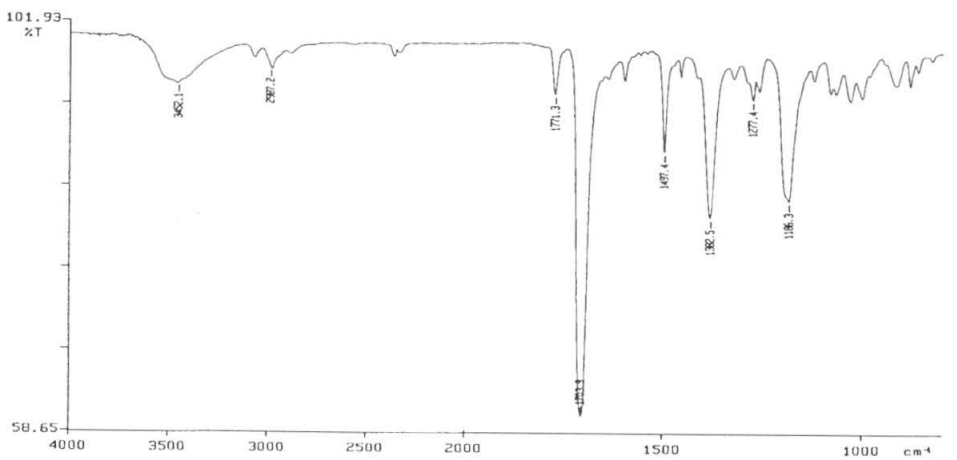
^{1}H NMR
300 MHz
$CDCl_3$

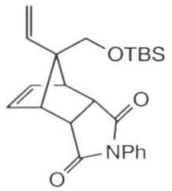


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





92. To a solution of alcohol **88** (6.0g, 20 mmol), triethylamine (5.0ml, 36 mmol), and DMAP (0.24g, 2.0 mmol), in 100 ml DMF cooled with an ice/water bath was added Me-$_2$^{t}BuSiCl (3.97g, 26 mmol). The reaction was allowed to warm to 23 °C and was stirred 5 h before quenching with 100 ml water and extracting the aqueous layer 3 x 200 ml pentane. The combined organic layers were washed 1 x 200 mL water, 1 x 200 ml 1N HCl, 1 x 200 ml saturated $NaHCO_3$, 1 x 200 ml saturated aqueous NaCl then dried over Na_2SO_4. Solvent removal *in vacuo* gave **92** as an orange oil that was purified by silica gel chromatography (4:1 hexanes/EtOAc) to give pure **92** as a colorless solid. 7.66g (92%)

MP 100-101 °C.

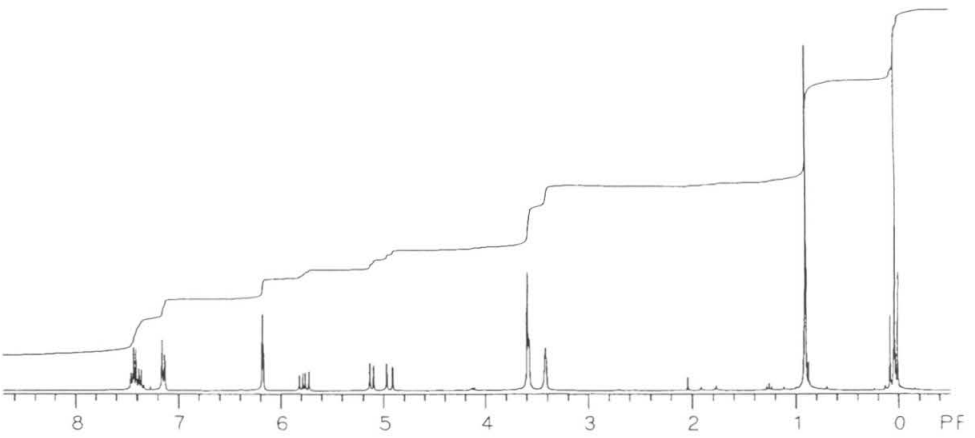
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 0 7.45-7.37 (m, 3H), 7.14 (dd, 2H, J= 7, 1.5), 6.17 (dd, 2H, J= 2, 2), 5.76 (dd, lH, J= 18, 11), 5.10 (dd, lH, J= 11, 0.8), 4.93 (dd, 1H, J= 18, 0.8), 3.57 (m, 4H), 3.41 (s, 2H), 0.90 (s, 9H), 0.01 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ-5.71, 18.02, 25.43, 44.47, 48.66, 64.33, 72.92, 116.64, 126.35, 128.35, 128.84, 131.66, 133.63, 138.65, 176.48.

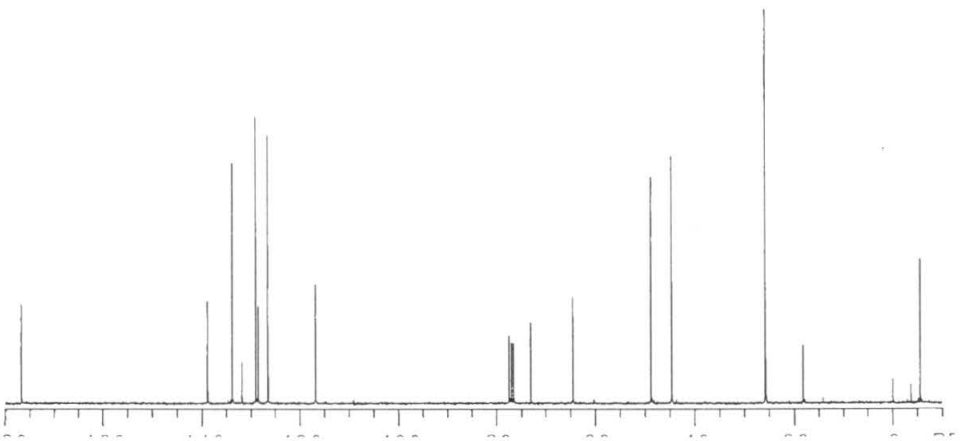
IR (thin film)ν 2928,2856, 1713, 1497, 1472, 1378, 1256, 1183, 1094, 839, 775, 726.

Elemental Analysis calc'd for $C_{24}H_{31}O_3N_1Si$: C, 70.38%, H, 7.63%, N, 3.42%; found C, 70.44%, H, 7.66%, N, 3.48%.

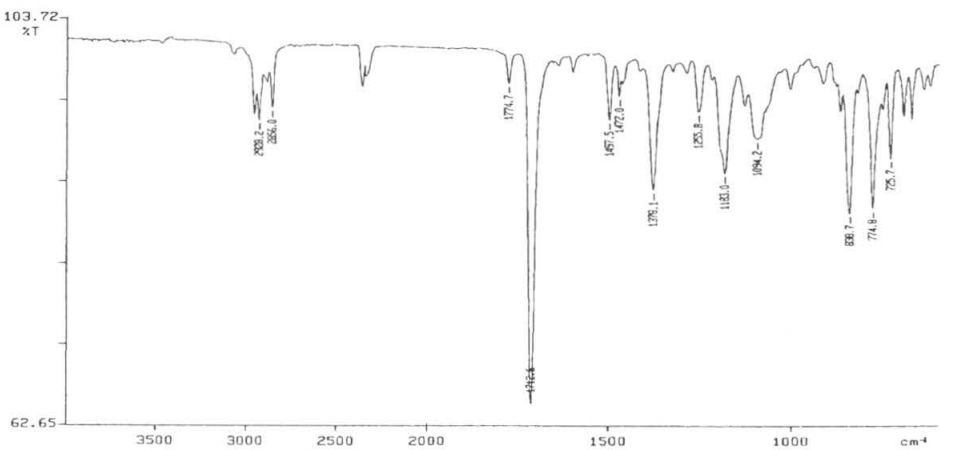
^{1}H NMR
300 MHz
$CDCl_3$

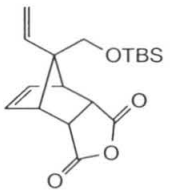


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





93. To a solution of imide **92** (3.49g, 8.52 mmol) in 100 ml THF at 23 °C was added LiOH (1M, 25 ml, 25 mmol) dropwise. The reaction was stirred for 5 min then quenched by addition of $NaHSO_4$ (1M, 25 ml, 25 mmol). The mixture was diluted with 100 ml sat. aqueous NaCl, extracted 3 x 100 mL CH_2Cl_2, and the organic layers dried over Na_2SO_4. Solvent removal *in vacuo* yielded a colorless solid that was dissolved in 700 ml toluene at 23 °C. After 2 h the reaction was poured onto 1L of ice cold 1M HCl and shaken vigorously. The organic layer was then washed 1 x 500 ml sat. NaCl and dried over Na_2SO_4. Solvent removal *in vacuo* afforded pure **93** as a colorless solid. 2.71g (95%). An analytical sample was obtained by recrystallization from hexanes.

MP 98-99 °C.

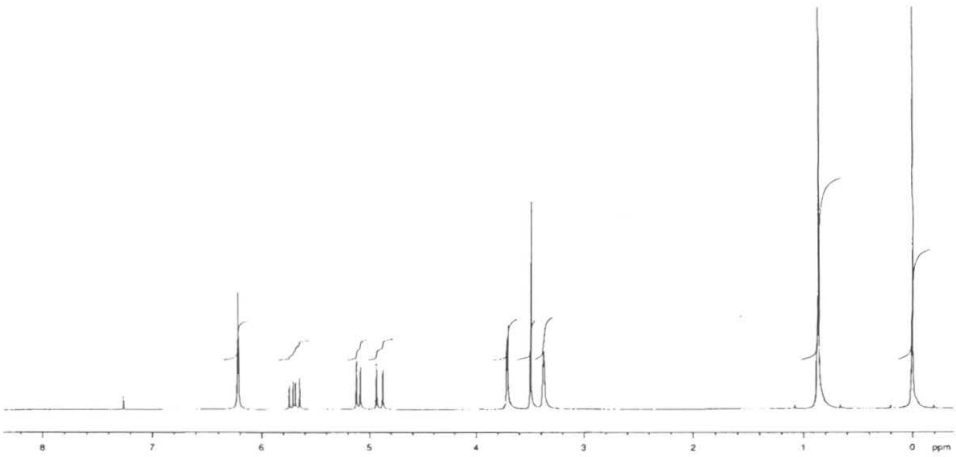
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.23 (dd, 2H, J = 2, 2), 5.72 (dd, 1H, J = 17, 11), 5.12 (d, 1H, J = 11), 4.89 (d, 1H, J = 17), 3.72 (d, 2H, J = 2), 3.50 (s, 2H), 3.40 (m, 2H), 0.91 (s, 9H), 0.04 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ -5.77, 17.95, 25.55, 45.87, 46.88, 49.11, 49.45, 64.42, 67.72, 73.58, 115.88, 117.15, 134.22, 134.65, 137.61, 139.70, 171.14, 178.00.

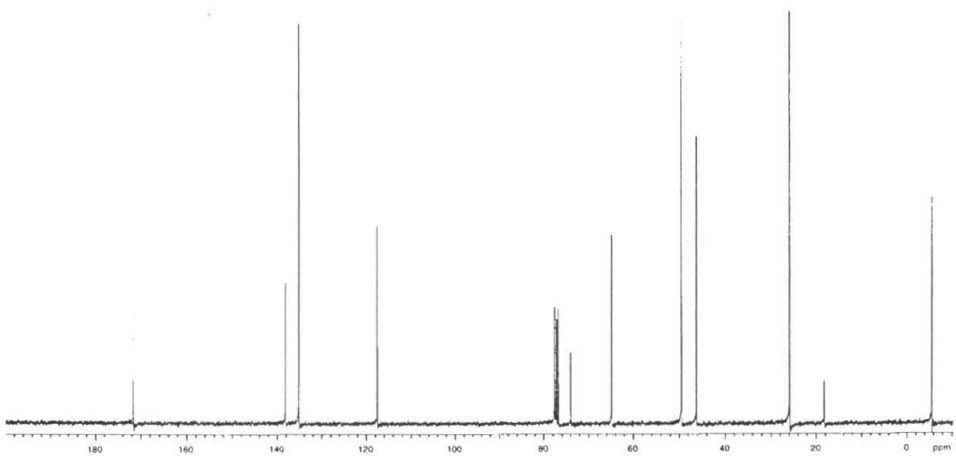
IR (thin film) ν 3081, 2955, 2929, 2857, 1782, 1717, 1472, 1416, 1254, 1092, 914, 838, 776, 735, 671.

Elemental Analysis calc'd for $C_{18}H_{26}O_4Si$: C, 64.64%, H, 7.73%, N, 0.00%; found C, 64.49%, H, 7.73%, N, 0.03%.

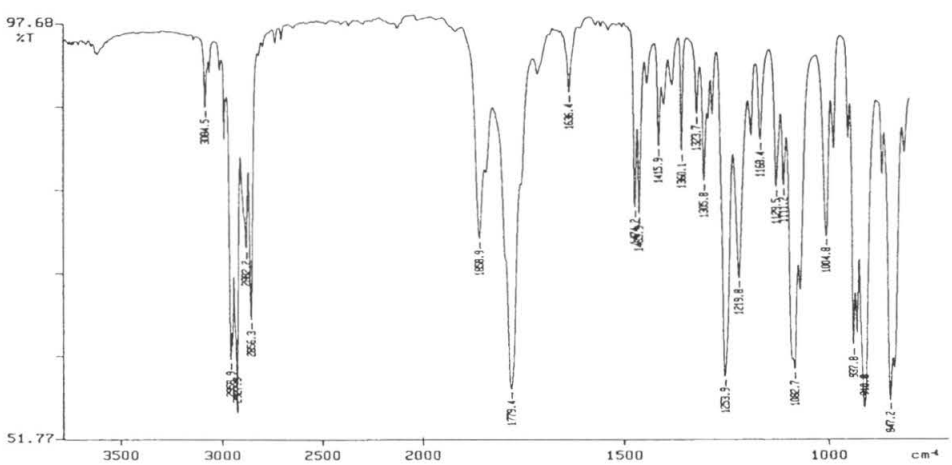
^{1}H NMR
300 MHz
$CDCl_3$

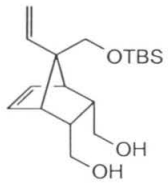


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





94. To a solution of anydride **93** (2.0g, 5.9 mmol) in 120 mL Et_2O at -10 °C was added LAH (0.45g, 12 mmol). The reaction was warmed to 23 °C and stirred 12 h then cooled to 0 °C and treated sequentially with H_2O (0.45 mL), 15% aqueous NaOH (0.45 mL), then H_2O (1.35 mL). The resulting white clurry was vacuum filtered through celite and the filter cake was pulverized and then washed 5 x 50 mL CH_2Cl_2. The combined filtrates were concentrated *in vacuo* to give 1.9g (98%) of **93** as a colorless solid that was analytically pure.

$\mathbf{R_f}$= 0.24 (1:1 hexanes/EtOAc).

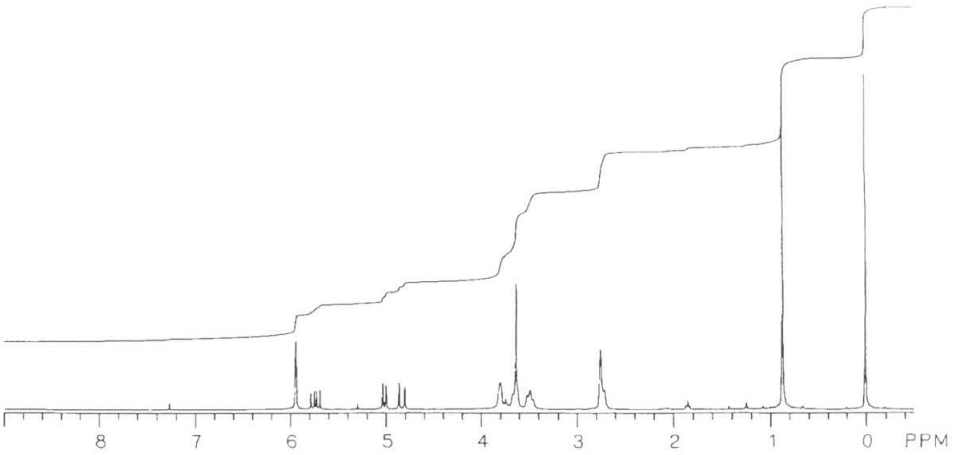
^{1}H-NMR ($CDC1_3$, 300 MHz) δ 5.93 (s, 2H), 5.73 (dd, 1H, *J*=18, 11), 5.03 (d, 1H, *J*=11), 4.83 (d, 1H, *J*=18), 3.80 (bm, 2H), 3.63 (s, 4H), 3.48 (bm, 2H), 2.75 (bm, 4H), 0.85 (s, 9H), 0.01 (s, 6H).

^{13}C-NMR ($CDC1_3$, 75 MHz) δ 140.86, 133.79, 115.17, 67.93, 64.34, 62.85, 50.00, 43.11, 25.63, 18.04, -5.69.

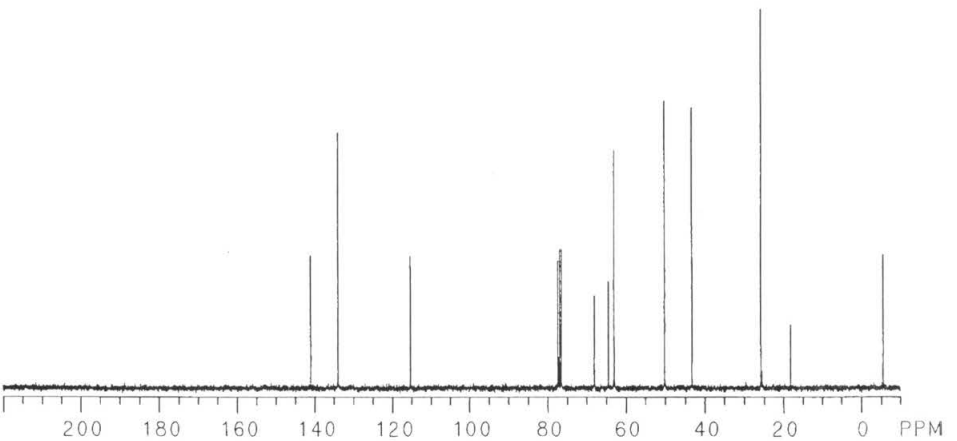
IR (thin film) ν 3301, 2928, 2854, 1472, 1256, 1095, 1033, 903, 836.

Elemental Analysis calc'd for $C_{18}H_{32}O_3Si$: C, 66.62%; H, 9.94%; N, 0.00%; found: C, 66.44%; H, 9.88%; N, 0.06%.

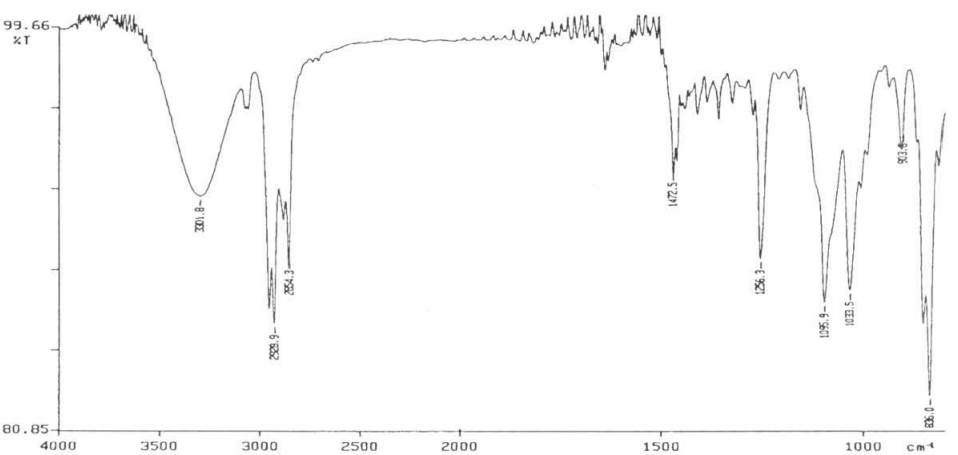
^{1}H NMR
300 MHz
$CDCl_3$

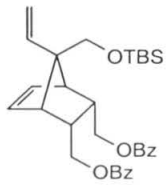


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





95. To a solution of diol **94** (3.05g, 9.41 mmol) in 40 mL CH_2Cl_2 at 0 °C was added TEA (4.0 mL, 29 mmol) followed by DMAP (0.11g, 0.94 mmol). The reaction was stirred for 4 h then diluted to 200 mL with CH_2Cl_2 and washed, 2 x 100 mL 1 M aqueous HCl, 1 x 100 mL 10% aqueous Na_2CO_3, 1 x 100 mL brine then dried over sodium sulfate. Evaporation *in vacuo* gave an orange oil that was purified by silica gel chromatography (9:1 hexanes/EtOAc) to give 4.62g (92%) of **95** as a colorless solid.

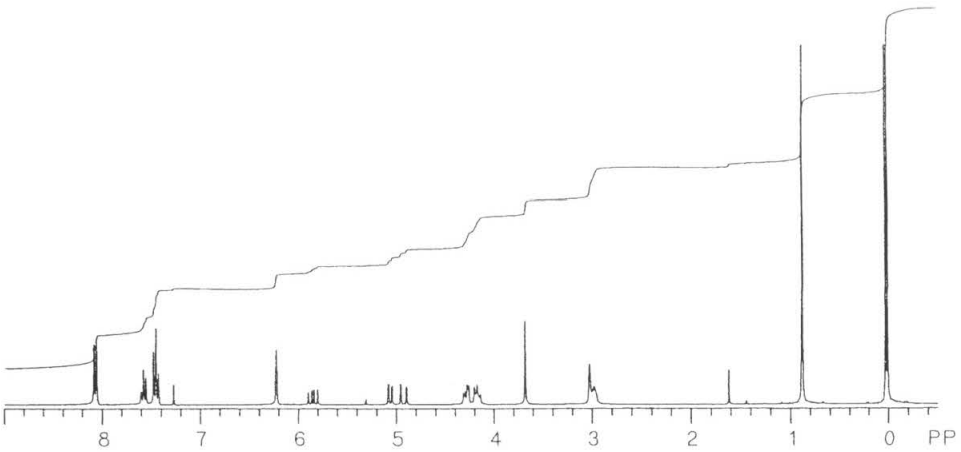
$\mathbf{R_f}$= 0.66 (6:1 hexanes/EtOAc).

^{1}H-NMR ($CDC1_3$, 300 MHz) δ 8.06 (d, 4H, *J*=7), 7.57 (t, 2H, *J*=7), 7.44 (t, 4H, *J*=7), 6.21 (t, 2H, *J*=1.8), 5.85 (dd, 1H, *J*=17, 11), 5.07 (d, 1H, *J*=11), 4.89 (d, 1H, *J*=17), 4.28 (dd, 2H, *J*=11, 6), 4.17 (dd, 2H, *J*=11, 8), 3.67 (s, 2H), 2.97-3.02 (2 x bs, 4H), 0.87 (s, 9H), 0.00 (s, 3H).

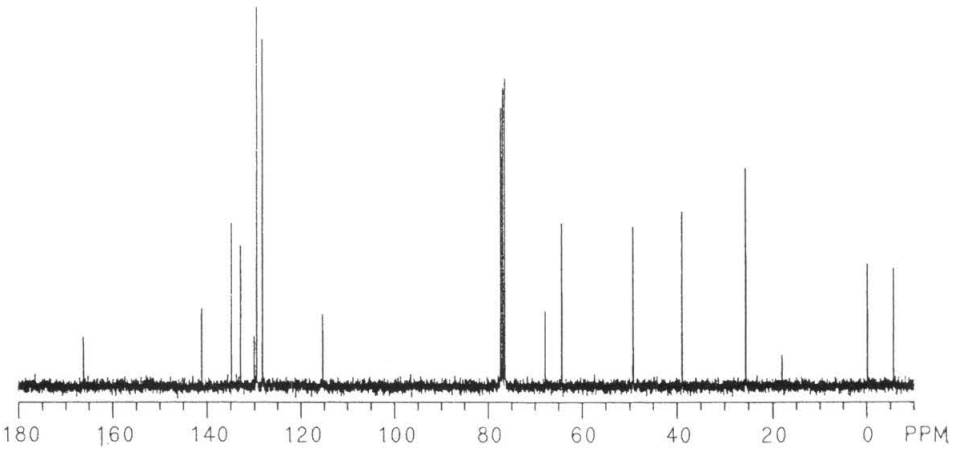
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 166.08, 141.03, 134.68, 132.73, 129.90, 129.35, 128.13, 115.25, 67.65, 64.24, 49.24, 38.89, 25.55, 17.96, -0.23, -5.71.

IR (thin film) ν 2955, 2928, 2855, 1720, 1451, 1269, 1176, 1110, 1026, 837, 775, 710.

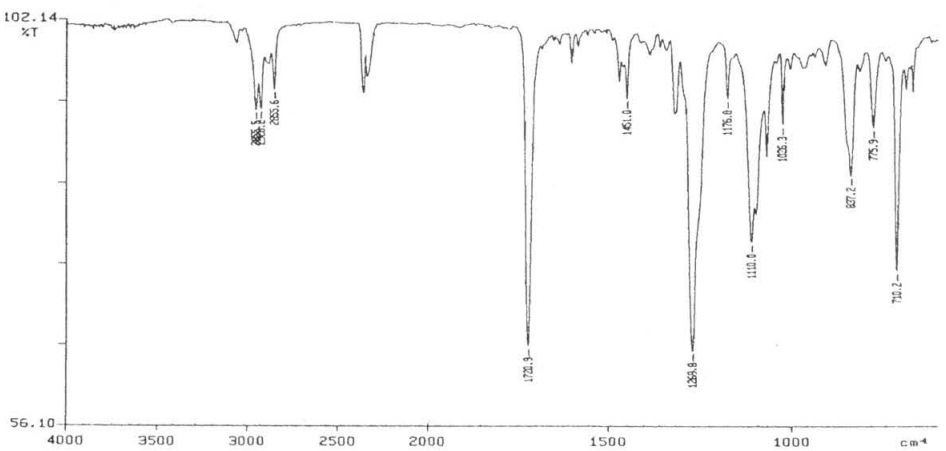
^{1}H NMR
300 MHz
$CDCl_3$

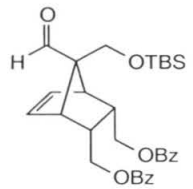


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





96. To a vigorously stirring suspension of K_2CO_3 (1.26g, 9.11 mmol) and K_3FeCN_6 (2.61g, 7.93 mmol) in 25 mL H_2O and 29 mL ^tBuOH at 23 °C was added diene **95** (1.51g, 2.83 mmol) as a solution in 25 mL THF followed by OsO_4 (0.90 mL, 4% in H_2O, 0.14 mmol). The resulting yellow heterogeneous reaction was stirred 22 h then quenched by addition of sat. aqueous Na_2SO_3 and stirred an additional hour. The mixture was extracted 2 x 100 mL EtOAc and the combined organic layers were washed 1 x 100 mL H_2O, 1 x 100 mL brine then dried over sodium sulfate. Evaporation *in vacuo* produced a green oil which was subjected to silica gel chromatography (1:1 hexanes EtOAc) to give 1.26g (79%) of the expected diol.

To a solution of diol (0.897g, 1.58 mmol) prepared as described above in 50 mL THF and 10 mL H_2O was added solid K_2CO_3 (0.65g, 4.7 mmol) followed by $NaIO_4$ (2.0g, 9.4 mmol) as a solution in 40 mL H_2O. The reaction was stirred for 1 h then it was quenched with sat. Na_2SO_3 and extracted 3 x 50 mL hexanes. The combined organic layers were washed with 1 x 100 mL brine and dried over sodium sulfate. Evaporation *in vacuo* followed by subjecting the residue to silica gel chromatography (4:1 hexanes/EtOAc) gave 0.792g (93%) of **96** as a colorless solid.

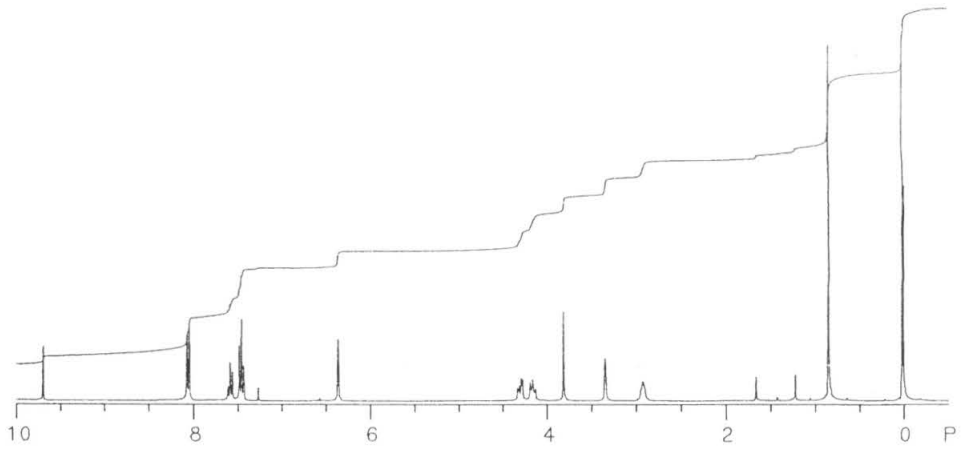
R_f= 0.6 (5:1 hexanes/EtOAc).

^{1}H-NMR ($CDC1_3$, 300 MHz) δ 9.69 (s, 1H), 8.04 (d, 4H, *J*=7), 7.58 (t, 2H, *J*=7), 7.45 (t, 4H, *J*=7), 6.35 (t, 2H, *J*=1.8), 4.30 (dd, 2H, *J*=11, 5), 4.15 (dd, 2H, *J*=11, 11), 3.81 (s, 2H), 3.34 (bs, 2H), 2.92 (bm, 2H), 0.85 (s, 9H), 0.02 (s, 6H).

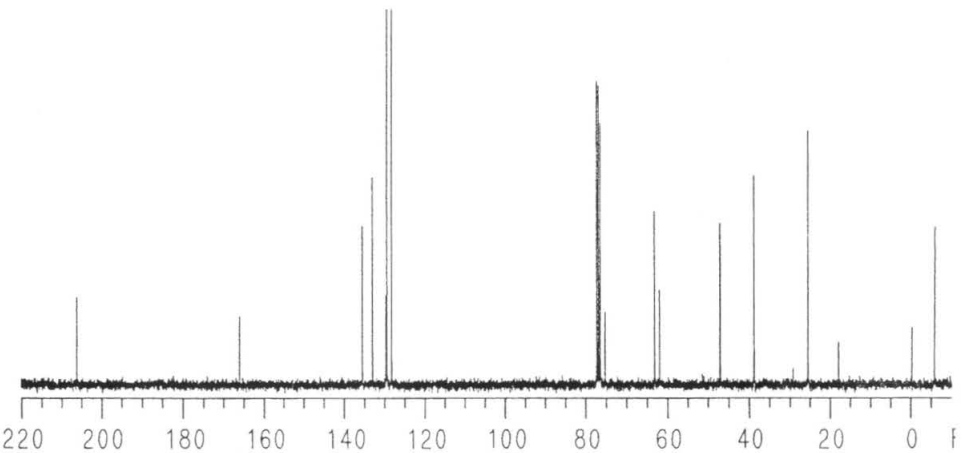
^{13}C-NMR ($CDCl_3$, 75 MHz) δ 206.17, 165.99, 135.43, 132.90, 129.64, 129.35, 128.20, 75.19, 63.11, 61.93, 47.05, 38.70, 25.44, 17.87, -0.24, -5.89.

IR (thin film) ν 2855, 2928, 2856, 1720, 1602, 1471, 1451, 1320, 1270, 1176, 1110, 1070, 1026, 838, 778, 710.

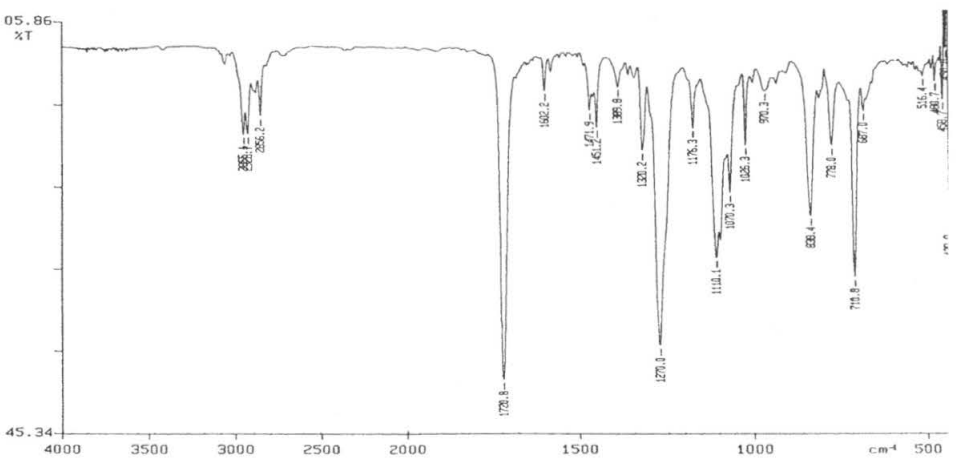
^{1}H NMR
300 MHz
$CDCl_3$

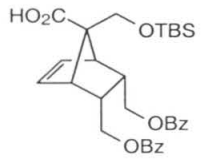


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film



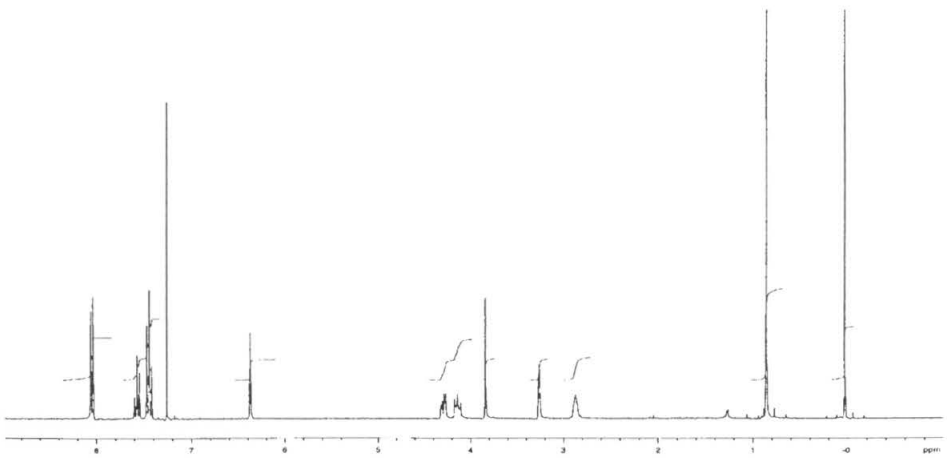


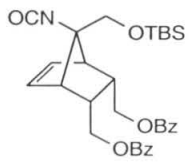
97. To a solution of aldehyde **96** (1.00g, 1.87 mmol) in 120 mL ^{t}BuOH at 23 °C was added $KMnO_4$ (0.452g, 2.86 mmol) as a solution in 85 mL pH=7 buffer (1.25 M phosphate). The purple reaction was stirred 30 min then quenched by addition of sat. Na_2SO_3 and poured on to ice-cold 1 N aqueous HCl. The aqueous phase was extracted 2 x 100 mL EtOAc and the combined organic layers were washed 1 x 100 mL H_2O, 1 x 100 mL brine then dried over sodium sulfate. Solvent removal *in vacuo* gave an oil that was purified by silica gel chromatography (8:1:1 hexanes/EtOAc/AcOH) to give 0.783g (78%) of **97** as a colorless foam.

$\mathbf{R_f}$=0.10 (5:1 hexanes/EtOAc).

^{1}H-NMR ($CDC1_3$, 300 MHz) δ 8.05 (d, 4H, *J*=7), 7.59 (t, 2H, *J*=7), 7.44 (t, 4H, *J*=7), 6.37 (t, 2H, *J*=1.8), 4.31 (dd, 2H, *J*=11, 6), 4.15 (dd, 2H, *J*=11, 10), 3.84 (s, 2H), 3.26 (s, 2H), 2.84 (bm, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

^{1}H NMR
300 MHz
$CDCl_3$





98. To a solution of carboxylic acid **97** (0.783, 1.42 mmol) in 50 mL CH_2Cl_2 at 23 °C was added HOBt (0.227g, 1.68 mmol) followed by EDC (0.320g, 1.67 mmol). The reaction was stirred for 2.5 h then it was diluted to 200 mL with EtOAc and washed 1 x 100 mL H_2O, 1 x 100 mL brine and dried over sodium sulfate. Solvent removal *in vacuo* gave 0.970g (>100%) of unpurified hydroxybenzotriazole ester as a colorless resin. This material was dissolved in 25 mL PhH and to it was added $TMSN_3$ (0.30 mL, 2.3 mmol) and DMAP (0.27g, 2.2 mmol) and the reaction was heated to refluxed for 6.25 h then cooled to 23 °C. Once cooled it was directly subjected to silica gel chromatography (5:1 hexanes/EtOAc) to yield 0.504g (65% two steps) of **98** as a colorless amorphous solid.

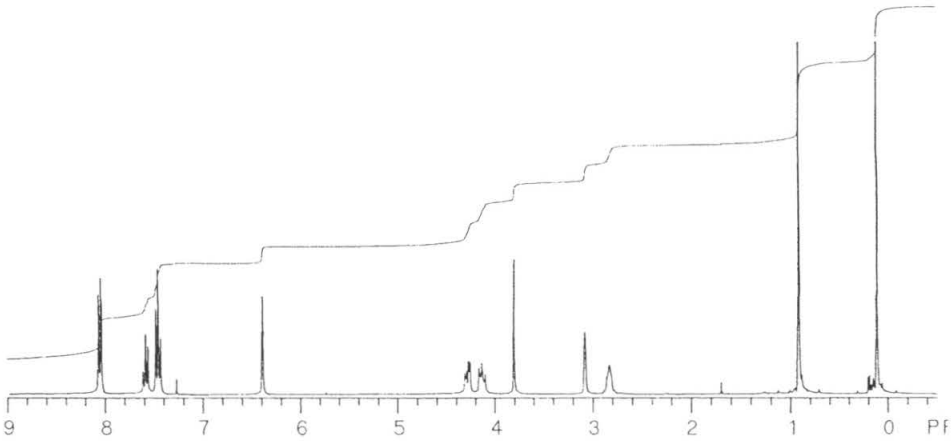
$\mathbf{R_f}$=0.55 (5:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, 4H, *J*=7), 7.57 (t, 2H, *J*=7), 7.44 (t, 4H, *J*=7), 6.39 (t, 2H, *J*=1.8), 4.28 (dd, 2H, *J*=11, 6), 4.14 (dd, 2H, *J*=11, 10), 3.79 (s, 2H), 3.08 (bs, 2H), 2.83 (bm, 2H), 0.92 (s, 9H), 0.11 (s, 6H).

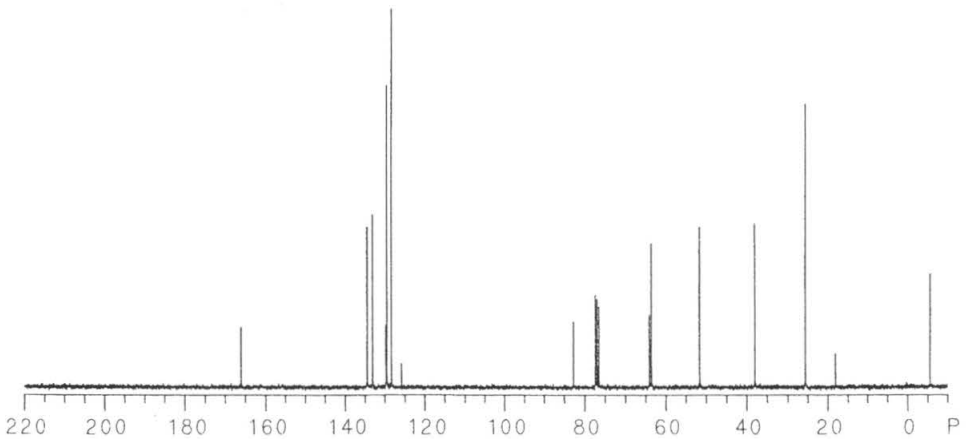
^{13}C-NMR ($CDCl_3$, 75 MHz) δ 165.90, 134.27, 132.93, 129.59, 129.34, 128.21, 82.59, 63.90, 63.44, 51.46, 37.84, 25.47, 17.95, -5.69.

IR (thin film) ν 2929, 2857, 2247, 1720, 1451, 1320, 1269, 1176, 1109, 1070, 1026, 837, 778, 710.

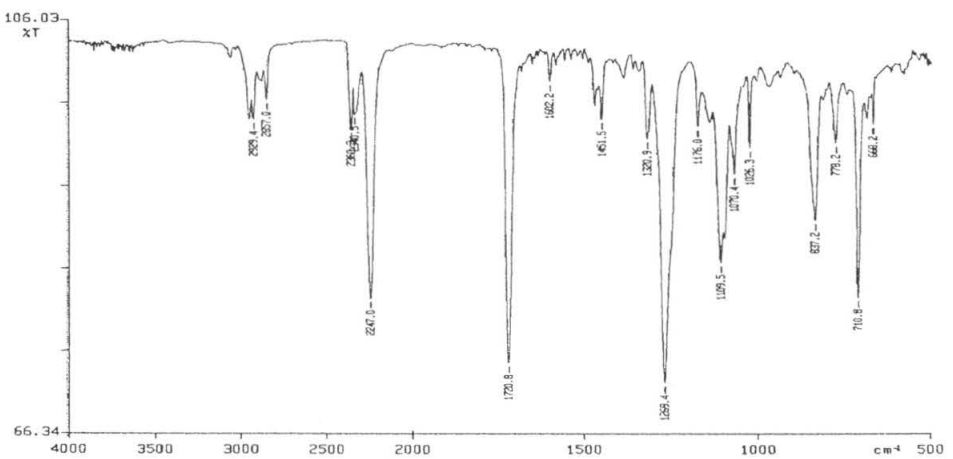
^{1}H NMR
300 MHz
$CDCl_3$

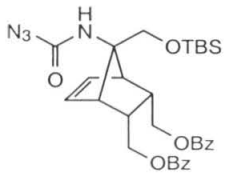


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film

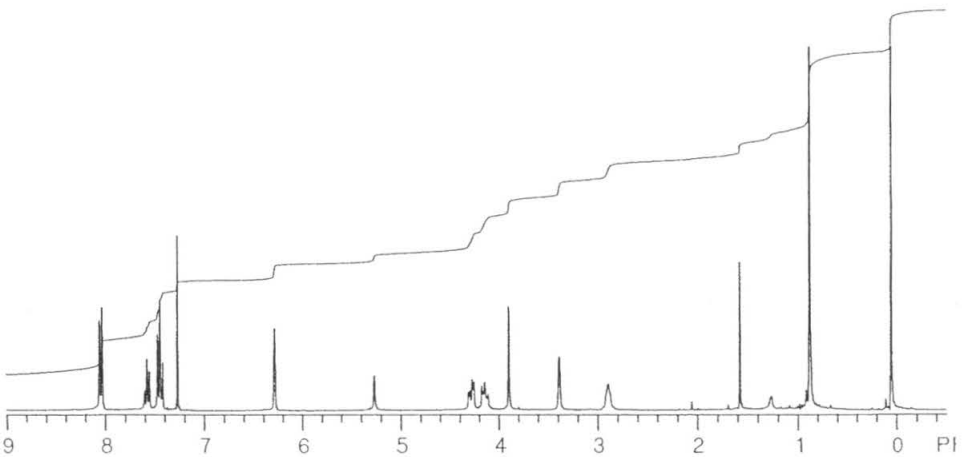




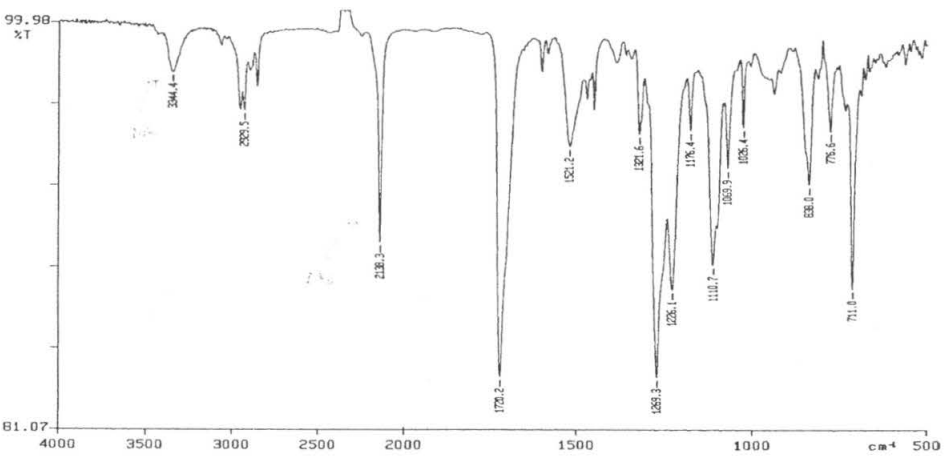
^{1}H-NMR ($CDC1_3$, 300 MHz) δ 8.05 (d, 4H, *J*=7), 7.57 (t, 2H, *J*=7), 7.44 (t, 4H, *J*=7), 6.28 (s, 2H), 5.26 (bs, 1H), 4.28 (dd, 2H, *J*=11, 6), 4.15 (dd, 2H, *J*=11, 10), 3.89 (s, 2H), 3.38 (s, 2H), 2.87 (bm, 2H), 0.87 (s, 9H), 0.05 (s, 6H).

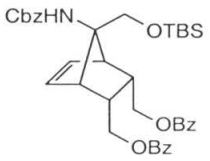
IR (thin film) ν 3344, 2929, 2138, 1720, 1521, 1321, 1269, 1226, 1176, 1110, 1026, 838.

^{1}H NMR
300 MHz
$CDCl_3$



FTIR
thin film





91. Isocyanate **98** (0.480g, 0.876 mmol) was dissolved in 8 mL BnOH and to it was added DMAP (0.011g, 0.088 mmol). The reaction was heated to 100 °C for 1 h then the solvent was distilled of under hivac (<1 torr) to give an orange gelatinous residue that was subjected to silica gel chromatography (4:1 hexanes/EtOAc) to give 0.532g (93%) of **91** as a colorless foam.

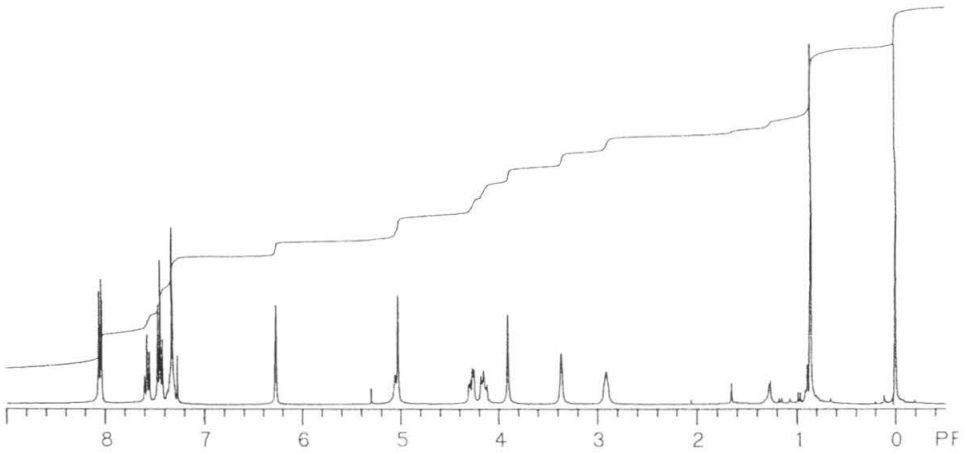
$\mathbf{R_f}$=0.73 (5:2 hexanes/EtOAc).

^{1}H-NMR ($CDC1_3$, 300 MHz) δ 8.03 (d, 4H, *J*=7), 7.59 (t, 2H, *J*=7), 7.44 (t, 4H, *J*=7), 7.34 (m, 5H), 6.26 (t, 2H, *J*=1.8), 5.05 (bs, 1H), 5.03 (s, 2H), 4.28 (dd, 2H, *J*=11, 6), 4.15 (dd, 2H, *J*=11, 10), 3.90 (s, 2H), 3.36 (s, 2H), 2.90 (bm, 2H), 0.88 (s, 9H), 0.00 (s, 6H).

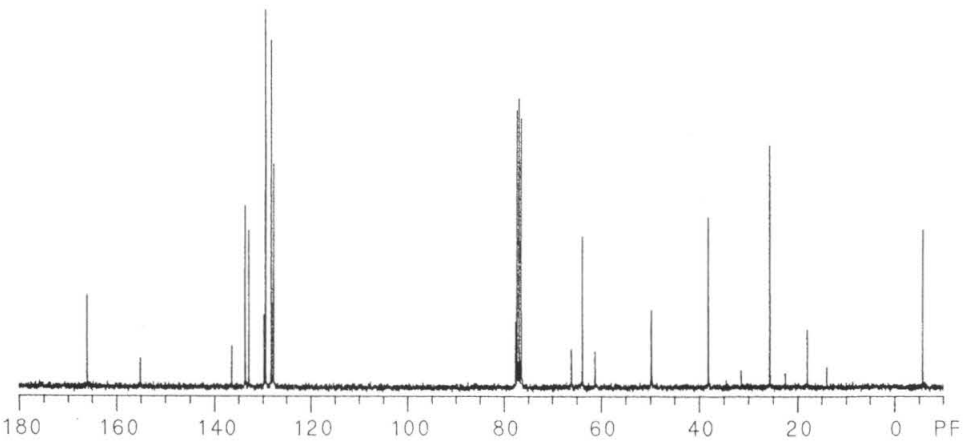
^{13}C-NMR ($CDC1_3$, 75 MHz) δ 166.00, 155.06, 136.35, 133.58, 132.81, 129.70, 129.36, 128.21, 128.15, 127.74, 127.68, 77.51, 65.97, 63.75, 61.18, 49.66, 38.03, 25.56, 17.93, 13.90, -5.79.

IR (thin film) ν 3400, 2928, 1721, 1452, 1268, 1110, 1068, 1026, 837, 776, 710.

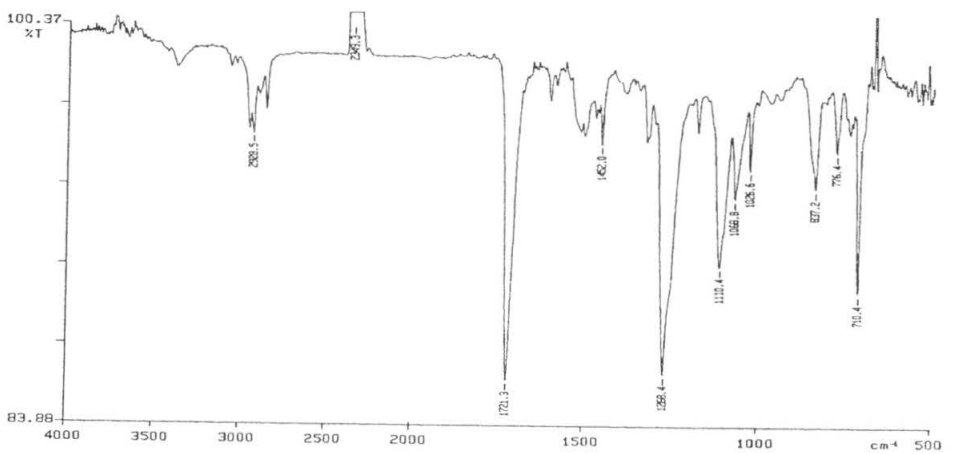
^{1}H NMR
300 MHz
$CDCl_3$

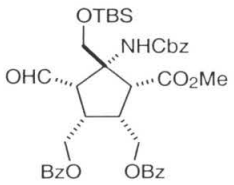


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





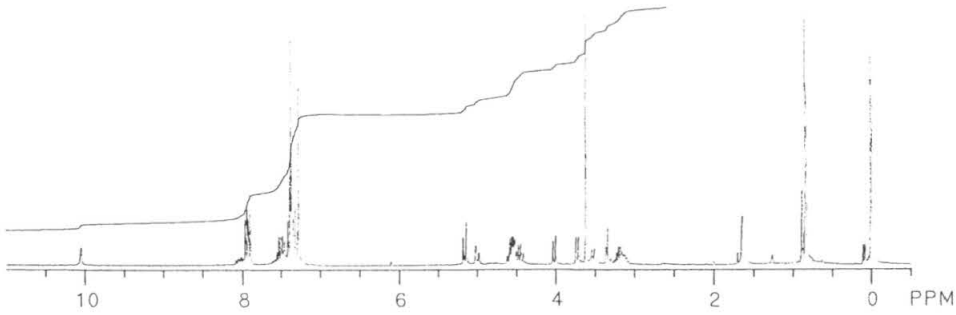
100. Into a solution of olefin **91** (0.447g, 0.682 mmol) in 20 mL CH_2Cl_2 and 7 mL of MeOH cooled to -78 °C was bubbled a dilute stream of O_3 in O_2 until the reaction became a persistent blue color. The reaction was purged with N_2 until it became colorless, then it was warmed to 23 °C and solvent was removed *in vacuo*. The residue was flash azeotroped 3 x 10 mL PhH then dissolved in 20 mL CH_2Cl_2 and cooled to 0 °C. To this was added TEA (0.29 mL, 2.1 mmol) followed by Ac_2O (0.07 mL, 0.7 mmol) and the reaction was stirred for 12 h. The reaction was diluted to 100 mL with EtOAc and washed 2 x 50 mL 1 N aqueous HCl, 1 x 50 mL 10% aqueous K_2CO_3, 1 x 50 mL brine then dried over sodium sulfate. Solvent removal *in vacuo* followed by silica gel chromatography (7:1 hexanes/EtOAc) gave 0.251g (51%) of **100** as a colorless foam.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 10.05 (s, 1H), 7.92 (m, 4H), 7.43-7.52 (m, 2H), 7.28-7.40 (m, 9H), 5.16 (d, 1H, *J*=12), 5.01 (d, 1H, *J*=12), 4.42-4.58 (m, 4H), 4.02 (d, 1H, *J*=10), 3.71 (d, 1H, *J*=10), 3.60 (s, 3H), 3.51 (bd, 1H, *J*=10), 3.33 (d, 1H, *J*=6), 3.16 (m, 2H), 0.87 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H).

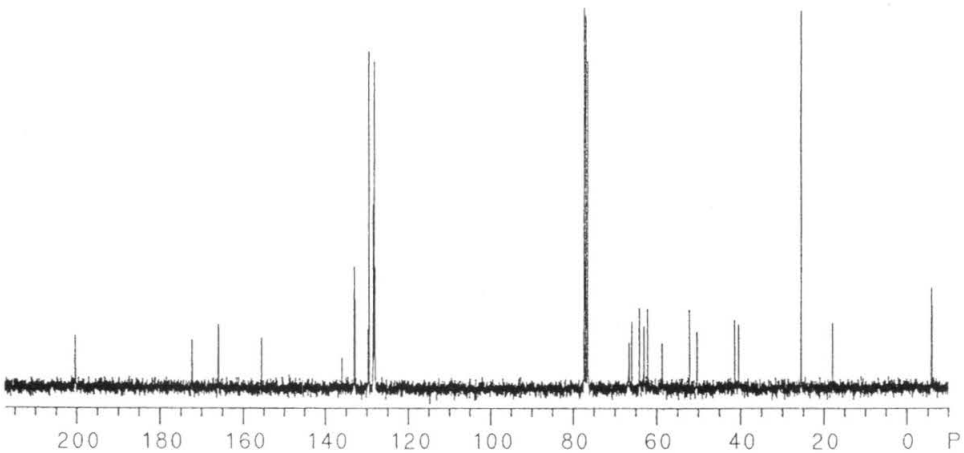
^{13}C-NMR ($CDCl_3$, 75 MHz) δ 200.19, 172.16, 165.82, 165.78, 155.40, 135.80, 132.85, 132.70, 129.50, 129.41, 129.32, 129.24, 128.35, 128.30, 128.24, 128.06, 127.96, 127.89, 66.43, 65.74, 63.93, 62.86, 62.01, 58.55, 51.95, 50.14, 41.17, 40.20, 25.37, 17.80, -5.96, -6.13.

IR (thin film) ν 3352, 2954, 2857, 1720, 1498, 1452, 1271, 1176, 1110, 1070, 1026, 838, 779.

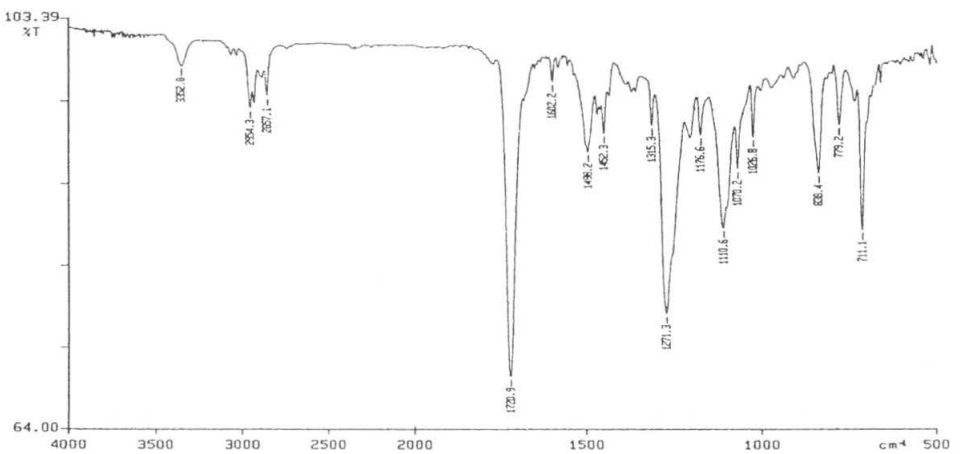
^{1}H NMR
300 MHz
$CDCl_3$

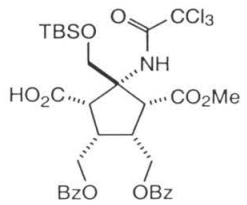


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





To a solution of aldehyde **100** (0.039g, 0.054 mmol) in 3 mL ^{t}BuOH at 23 °C was added $KMnO_4$ (0.023g, 0.15 mmol) as a solution in 2 mL of pH=7 buffer (1.25 M phosphate). The purple reaction was stirred for 0.5 h then quenched by addition of sat. Na_2SO_3 and poured onto ice-cold 1 N aqueous HCl. The aqueous phase was extracted 3 x 5 mL CH_2Cl_2 and the combined organic layers were washed 1 x 10 mL brine and dried over sodium sulfate. Solvent removal *in vacuo* gave 0.040g of a colorless foam. This material was dissolved in 1 mL MeOH and to it was added 10% Pd/C (0.001g) and the mixture was stirred at 23 °C under a balloon of H_2. After 5 h the mixture was filtered through celite and solvent removal *in vacuo* yielded 0.029g of a colorless waxy solid. The solid was dissolved in 2 mL CH_2Cl_2 and cooled to -78 °C. To this solution was added TEA (0.05 mL, 0.36 mmol) followed by TCAA (0.018 mL, 0.058 mmol) and the reaction was stirred for 10 min then quenched by addition of H_2O and warming it to 23 °C. The reaction was then diluted to 10 mL with CH_2Cl_2 and washed 2 x 5 mL 1 N aqueous HCl, 1 x 5 mL brine then dried over sodium sulfate. Solvent removal *in vacuo* gave a colorless oil that was purified by silica gel chromatography (3:1 hexanes/EtOAc) to give 0.016g (40% from **100**) of **72** as a colorless film.

R_f= 0.23 (3:1 hexanes/EtOAc).

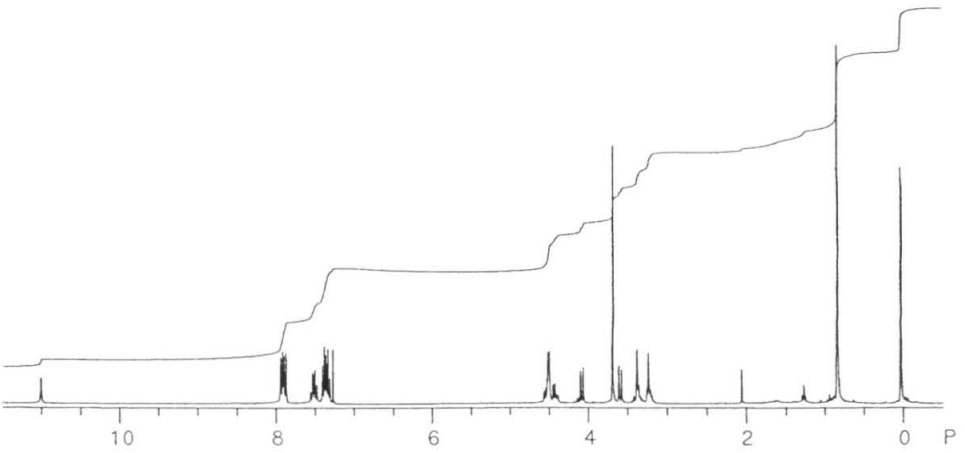
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 11.00 (bs, 1H), 7.92 (d, 2H, *J*=7), 7.90 (d, 2H, *J*=7), 7.52 (t, 1H, *J*=7), 7.50 (t, 1H, *J*=7), 7.40 (t, 2H, *J*=7), 7.35 (t, 2H, *J*=7), 4.48 (dd+s, 3H,

J(dd)=5, 10), 4.42 (dd, 1H, *J*=10,7), 4.09 (d, 1H, *J*=10), 3.68 (s, 3H), 3.58 (d, 1H, *J*=10), 3.36 (m, 2H), 3.23 (m, 2H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

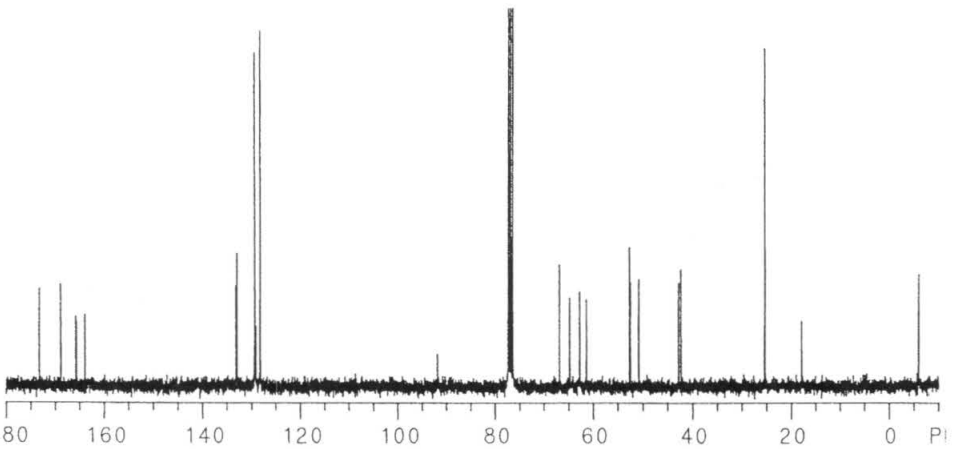
^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.16, 168.79, 165.69, 165.58, 163.83, 133.04, 132.88, 129.27, 129.24, 129.20, 128.97, 128.14, 128.12, 91.73, 66.76, 64.70, 62.65, 61.30, 52.57, 52.37, 50.74, 42.68, 42.20, 25.26, 17.77, -6.03, -6.07.

IR (thin film) ν ~3100 b, 2955, 2930, 2857, 1722, 1517, 1452, 1373, 1272, 1207, 1177, 1111, 1070, 1026, 911, 839, 779, 733, 711, 685.

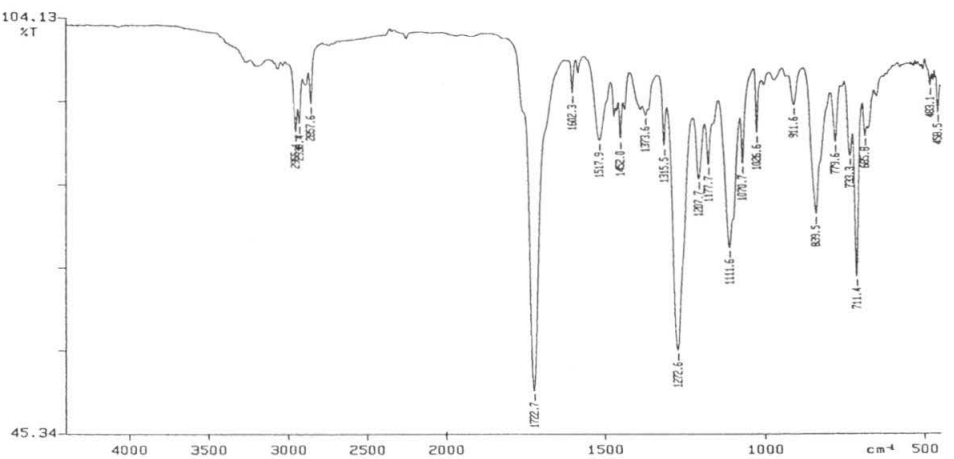
^{1}H NMR
300 MHz
$CDCl_3$

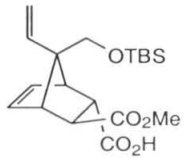


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





127. To a suspension of anhydride **93** (2.54g, 7.61 mmol) in 25 ml CCl_4 and 25 ml toluene cooled with an ice/water bath was added methanol (0.90 ml, 22 mmol) followed by quinine (2.71g, 8.35 mmol). The heterogeneous white mixture became homogeneous over two hours and was then diluted with 200 ml EtOAc and washed 2 x 200 ml 1N HCl, 1 x 200 ml brine and dried over Na_2SO_4. Solvent removal *in vacuo* gave quantitative return of cis acid-ester **126** as a colorless oil that was used without further purification ($[\alpha]_{Na}$ -2.13 (c = 0.825, $CDCl_3$)). To a solution of lithium diisopropylamide (20.0 ml 1.6M BuLi/hexane + 4.6 ml diisopropylamine, 32 mmol) in 50 ml Et_2O cooled with an ice/water bath was added acid-ester **126** (2.25g, 6.15 mmol) dropwise as a solution in 20 ml Et_2O over 15 min. The reaction gradually turned yellow and, after 30 min, was poured onto 150 ml ice-cold 1N $NaHSO_4$ then extracted 2 x 200 ml EtOAc. The combined organic layers were washed 1 x 200 ml water, 1 x 200 ml brine then dried over Na_2SO_4. Solvent removal *in vacuo* gave acid-ester **16** as a yellow oil that was purified by silica gel chromatography (30:1 CH_2Cl_2/HOAc) to give 1.64g (73%) of pure **127** as a colorless oil that crystallized on standing.

MP 99-100 °C.

Optical rotation: $[\alpha]_{Na}$ +7.20 (c = 0.957, $CDCl_3$).

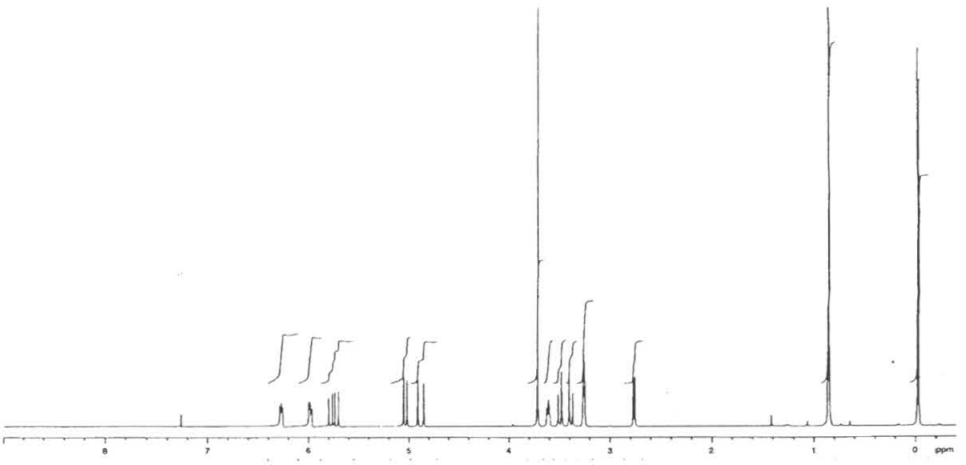
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.27 (m, 1H), 5.98 (m, 1H), 5.70-5.80 (dd, 1H, *J*=17.7, 10.9), 5.05 (dd, 1H, *J*=10.9, 1.4), 4.90 (dd, 1H, *J*=17.7, 1.4), 3.72 (s, 3H), 3.62 (m, 1H), 3.51 (d, 1H, *J*=10.6), 3.34 (d, 1H, *J*=10.6), 3.26 (s, 2H), 2.76 (d, 1H, *J*=5.0), 0.85 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 179.84, 173.67, 140.38, 138.27, 133.40, 115.91, 69.09, 64.56, 52.25, 50.00, 49.58, 47.87, 45.50, 25.83, 18.26, -5.47, -5.69.

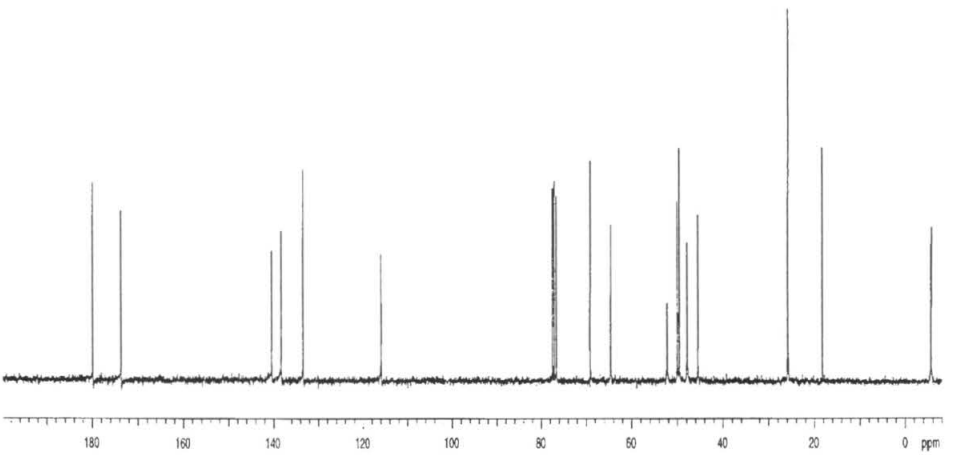
IR (thin film)ν 3077, 2953, 2856, 1737, 1732, 1708, 1471, 1435, 1417, 1314, 1257, 1229, 1198, 1093, 1070, 1005, 912, 838, 775.

Elemental Analysis calc'd for $C_{19}H_{30}O_5Si$: C, 62.26%, H, 8.25%, N, 0.00%; found C, 62.29%, H, 8.16%, N, 0.00%.

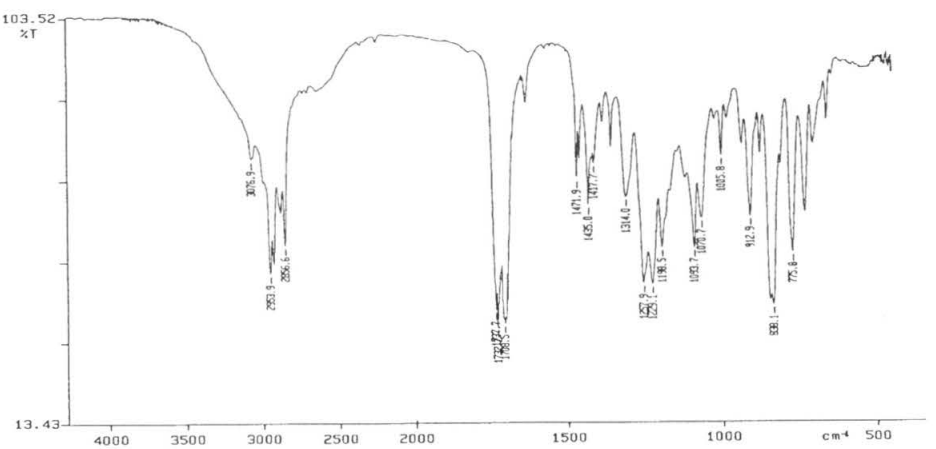
^{1}H NMR
300 MHz
$CDCl_3$

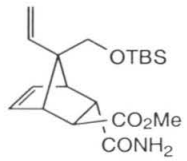


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





128. To a solution of acid/ester **127** (0.101g, 0.276 mmol) in 5 mL CH_2Cl_2 at 23 °C was added HOBt (0.047g, 0.35 mmol) followed by EDC (0.086g, 0.45 mmol) and the reaction was stirred for 20 min then 25% aqueous NH_3 (0.5 mL) was added in one portion. The resulting clear colorless biphase was partitioned between 10 mL CH_2Cl_2 and 10 mL H_2O and the organic layer was washed 2 x 10 mL 1 N aqueous HCl, 1 x 10 mL H_2O, 1 x 10 mL sat. $NaHCO_3$, 1 x 10 mL brine and dried over sodium sulfate. Solvent removal *in vacuo* yielded 0.100g (99%) of **128** as a colorless oil.

R_f: 0.41 (1:2 hexanes/EtOAc).

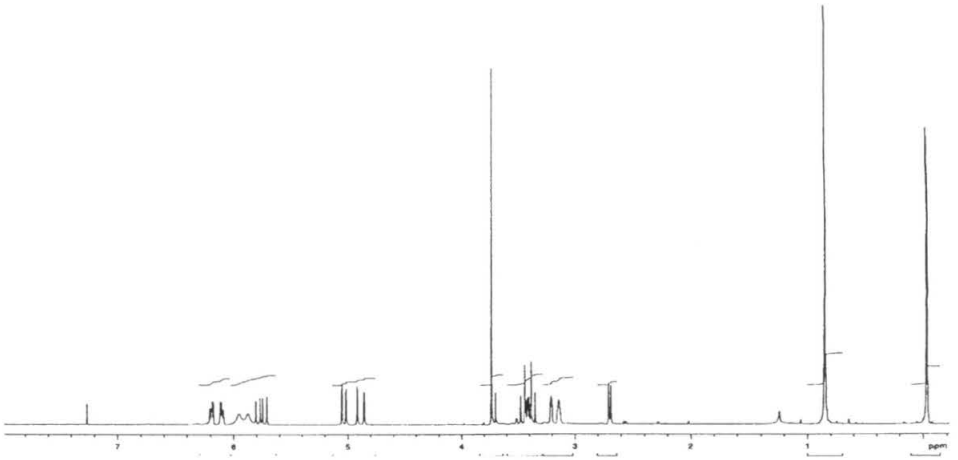
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.19 (dd, 1H, *J*=8, 4), 6.10 (dd, 1H, *J*=6, 3), 5.95 (bs, 1H), 5.87 (bs, 1H), 5.75 (dd, 1H, *J*=18, 11), 5.05 (d, 1H, *J*=11), 4.86 (d, 1H, *J*=18), 3.73 (s, 3H), 3.44 (d, 1H, *J*=10), 3.40 (m, 1H), 3.37 (d, 1H, *J*=10), 3.21 (s, 1H), 3.14 (s, 1H), 2.68 (d, 1H, *J*=6), 0.86 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 175.31, 174.71, 140.62, 136.54, 134.65, 115.82, 68.74, 64.76, 52.33, 49.53, 49.05, 46.41, 25.85, 18.29, -5.47, -5.67.

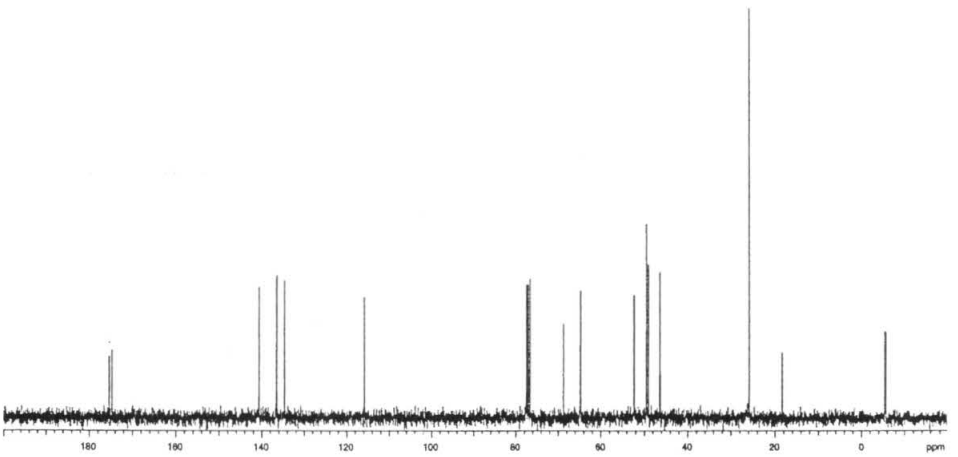
IR (thin film)ν 3347, 3196, 3077, 2954, 2856, 1731, 1672, 1612, 1472, 1435, 1406, 1344, 1256, 1229, 1199, 1094, 1070, 1006, 911, 838.

Elemental Analysis calc'd for $C_{19}H_{31}NO_4Si$: C, 62.43%, H, 8.55%, N, 3.83%; found C, 62.48%, H, 8.77%, N, 4.11%.

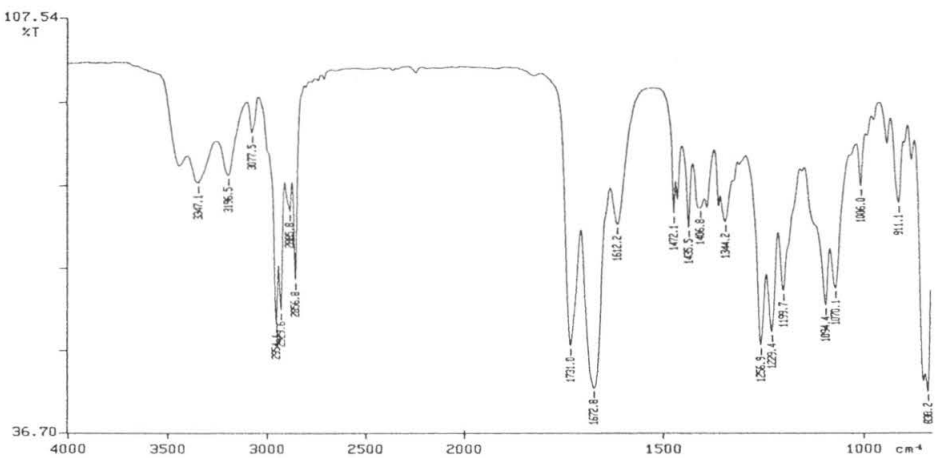
^{1}H NMR
300 MHz
$CDCl_3$

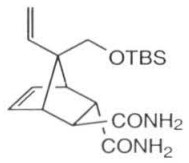


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





130. To a solution of amide/ester **128** (0.740g, 2.03 mmol) in 200 mL THF and 50 mL H_2O at 23 °C was added KOH (1.2g, 21 mmol) and the reaction was heated to 50 °C. After 12 h the reaction was cooled to 23 °C and partitioned between 500 mL 1 N aqueous $NaHSO_4$ and 200 mL EtOAc. The aqueous layer was then extracted 2 x 100 mL EtOAc and the combined organic layers were washed 1 x 100 mL H_2O, 1 x 100 mL brine and dried over sodium sulfate. Concentration *in vacuo* gave 0.712g of a colorless foam. This material was dissolved in 20 mL CH_2Cl_2 at 23 °C and to it was added HOBt (0.324g, 2.40 mmol) followed by EDC (0.625g, 3.26 mmol). The reaction was stirred for 15 min then 25% aqueous NH_3 (5 mL) was added and the resulting clear colorless biphase was extracted 2 x 50 mL CH_2Cl_2. The combined organic layers were washed 2 x 50 mL 1 N aqueous KH_2PO_4, 1 x 50 mL sat. aqueous $NaHCO_3$, 1 x 50 mL brine then dried over sodium sulfate. Concentration *in vacuo* gave a yellow solid that was purified by silica gel chromatography (100% EtOAc) to give 0.602g (83% from **127**) of **130** as a colorless solid.

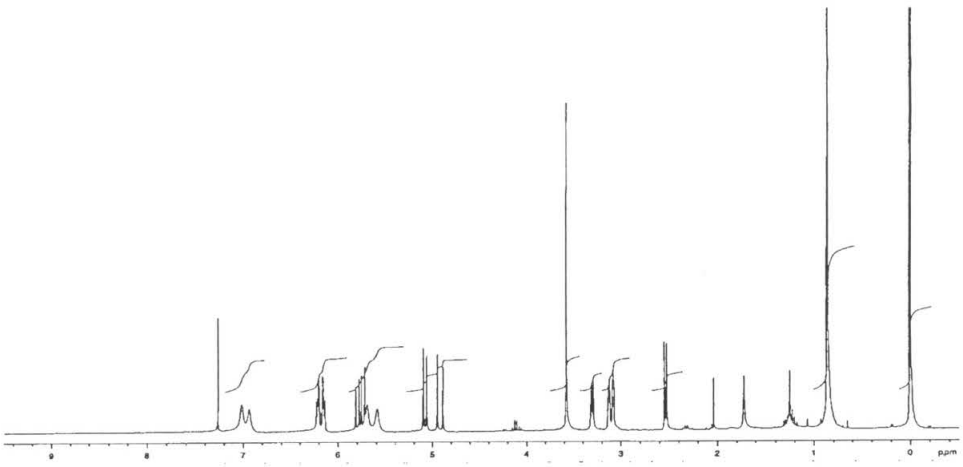
$\mathbf{R_f}$: 0.25 (EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.05-6.90 (2 x bs, 2H), 6.21 (dd, 1H, *J*=4, 3), 6.11 (dd, 1H, *J*=5, 3), 5.75 (dd, 1H, *J*=18, 10), 5.70 (bs, 1H), 5.58 (bs, 1H), 5.08 (d, 1H, *J*=10), 4.90 (d, 1H, *J*=18), 3.58 (s, 2H), 3.30 (dd, 1H, *J*=6, 3), 3.13 (bs, 1H), 3.08 (bs, 1H), 2.53 (d, 1H, *J*=6), 0.87 (s, 9H), -0.09 (s, 3H), -0.18 (s, 3H).

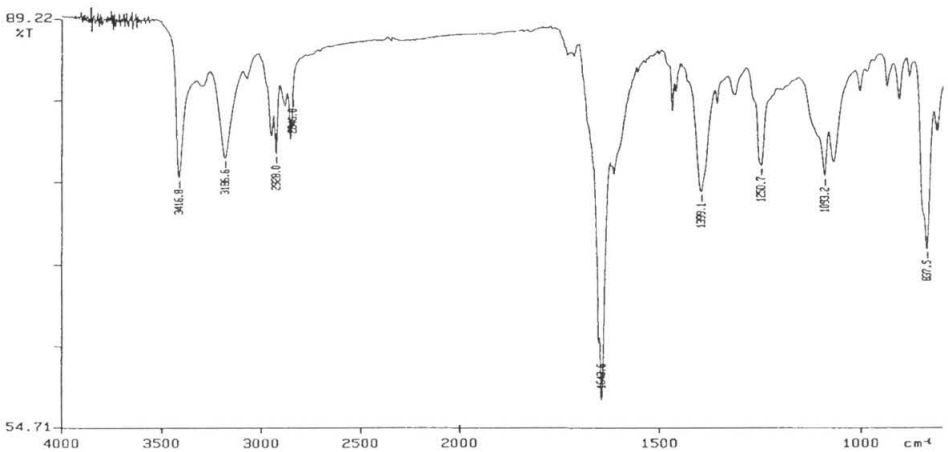
IR (thin film)ν 3416, 3186, 2928, 2846, 1643, 1399, 1250, 1093, 837.

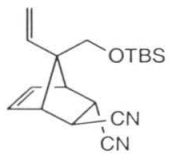
Elemental Analysis calc'd for $C_{18}H_{30}N_2O_3Si$: C, 61.68%, H, 8.63%, N, 7.99%; found C, 61.62%, H, 8.39%, N, 7.89%.

^{1}H NMR
300 MHz
$CDCl_3$



FTIR
thin film



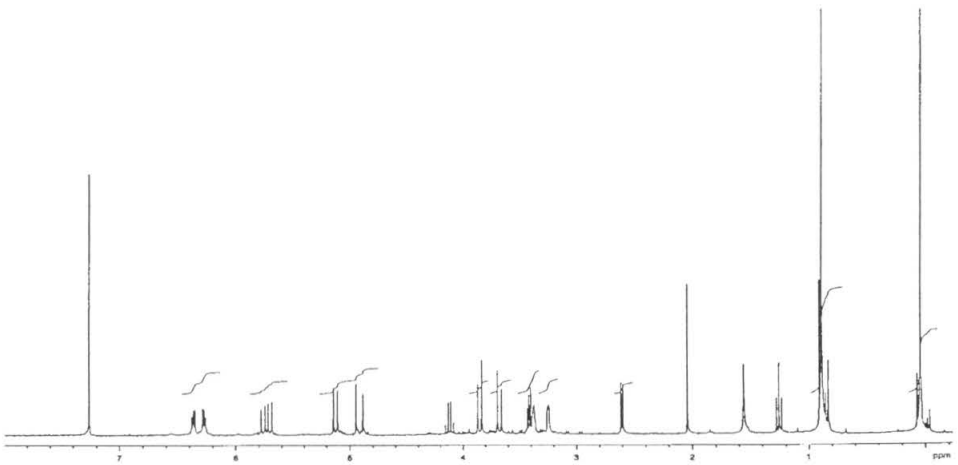


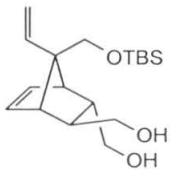
131. To a solution of bisamide **130** (0.279g, 0.797 mmol) in 15 mL THF at -78 °C was added pyridine (1.3 mL, 16 mmol) followed by TFAA (0.23 mL, 1.6 mmol) dropwise over 5 min. The reaction was stirred for 5 min then quenched by addition of 5 mL pH=7 buffer (1.25 M phosphate) and warming the reaction to 23 °C. The reaction was then diluted to 50 mL with EtOAc and washed 2 x 50 mL 1 N aqueous HCl, 1 x 50 mL H_2O, 1 x 50 mL sat. aqueous $NaHCO_3$, 1 x 50 mL brine then dried over sodium sulfate. Concentration *in vacuo* gave 0.233g (93%) of **131** as a colorless solid.

$\mathbf{R_f}$: 0.89 (1:1 hexanes/EtOAc).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.38 (dd, 1H, *J*=4, 3), 6.28 (dd, 1H, *J*=5, 3), 5.75 (dd, 1H, *J*=18, 10), 5.14 (d, 1H, *J*=10), 4.90 (d, 1H, *J*=18), 3.84 (d, 1H, *J*=11), 3.68 (d, 1H, *J*=11), 3.41 (dd, 1H, *J*=5, 4), 3.38 (bs, 1H), 3.25 (bs, 1H), 2.61 (d, 1H, *J*=5), 0.89 (s, 9H), 0.04 (s, 6H).

^{1}H NMR
300 MHz
$CDCl_3$





135. To a solution of acid ester **127** (0.974g, 2.66 mmol) in 30 ml Et_2O cooled with an ice bath was added LAH (0.306g, 8.06 mmol) portionwise over 10 minutes. Some gas evolution was noted. The reaction was allowed to warm to room temperature and after 1.5 h it was cooled again with an ice bath and sequentially treated with 0.3 ml water (gas evolution!), 0.3 ml 15% NaOH, and 0.9 ml water. The resulting grey slurry was warmed to room temperature and stirred (~5 min) until it turned white and it was filtered through celite. The filter cake was pulverized and rinsed 10 x 20 ml CH_2Cl_2. The colorless filtrate was evaporated *in vacuo* to yield 0.701g (81%) of **135** as a single compound by ^{1}H-NMR.

R_f: 0.17 (1:1 hexanes/EtOAc).

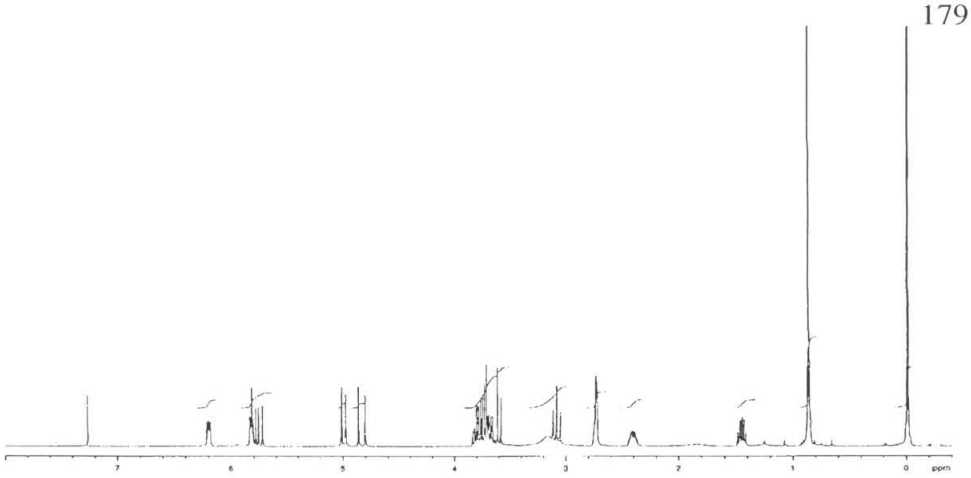
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 6.19 (dd, 1H, *J*=4, 3), 5.82 (dd, 1H, *J*=4, 3), 5.75 (d, 1H, *J*=17, 10), 5.00 (d, 1H, *J*=10), 4.86 (d, 1H, *J*=10), 3.84-3.65 (m, 4H), 3.61 (d, 1H, *J*=10), 3.19 (bs, 2H), 3.09 (t, 1H, *J*=10), 2.73 (bs, 2H), 2.39 (m, 1H), 1.46 (q, 1H, *J*=5), 0.86 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 142.88, 138.53, 131.28, 114.83, 68.44, 66.21, 65.05, 64.64, 49.26, 49.01, 48.98, 45.05, 25.86, 18.21, -5.43.

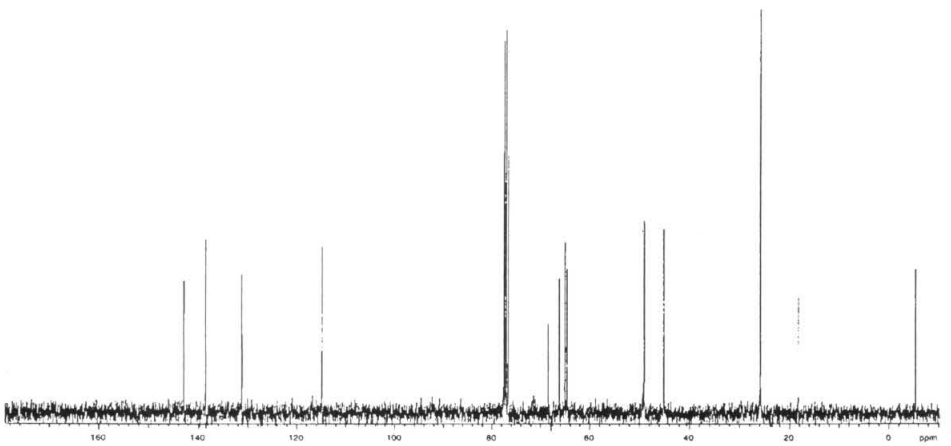
IR (thin film)ν 3288, 2954, 2857, 1471, 1255, 1094, 1072, 1029, 837.

^{1}H NMR

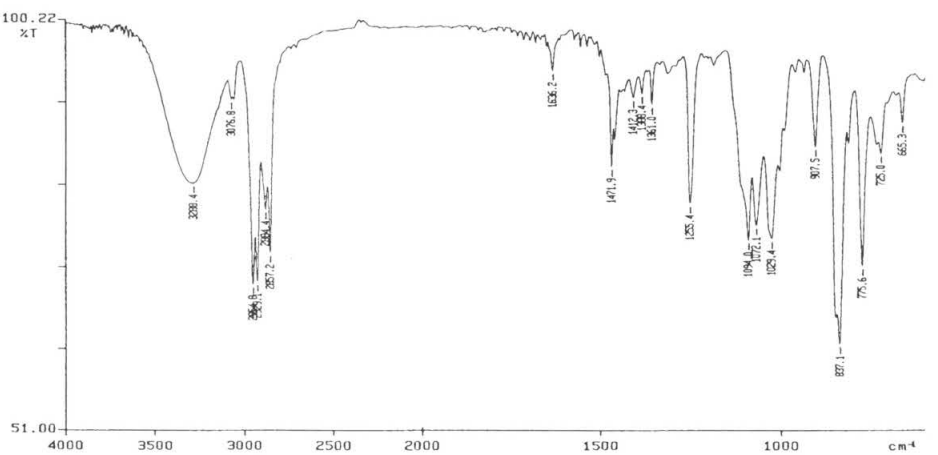
300 MHz
$CDCl_3$

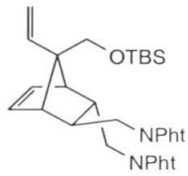


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





136. To a solution of **135** (1.22g, 3.76 mmol), prepared as described above, in 60 ml THF at room temperature was added PPh_3 (2.47g, 9.42 mmol) and phthalimide (1.12g, 7.61 mmol) followed by diethylazodicarboxylate (1.5 ml, 9.5 mmol) dropwise over 5 min. The yellow reaction was stirred for 30 min then it was diluted with 300 ml EtOAc and washed 1 x 100 ml 10% Na_2SO_3, and 2 x 100 ml 10% K_2CO_3. The combined aqueous washes were back extracted 1 x 50 ml EtOAc and the combined organic layers were then washed 1 x 100 ml brine and dried over Na_2SO_4. Rotary evaporation gave a viscous yellow oil that was purified by silica gel chromatography (gradient 5:1 $\rightarrow$ 2:1 hexane/EtOAc) to yield 1.92g (88%) **136** as a colorless foam.

MP 140-142 °C.

Optical rotation: $[\alpha]_{Na}$ -46.9 (c = 0.925, $CDCl_3$).

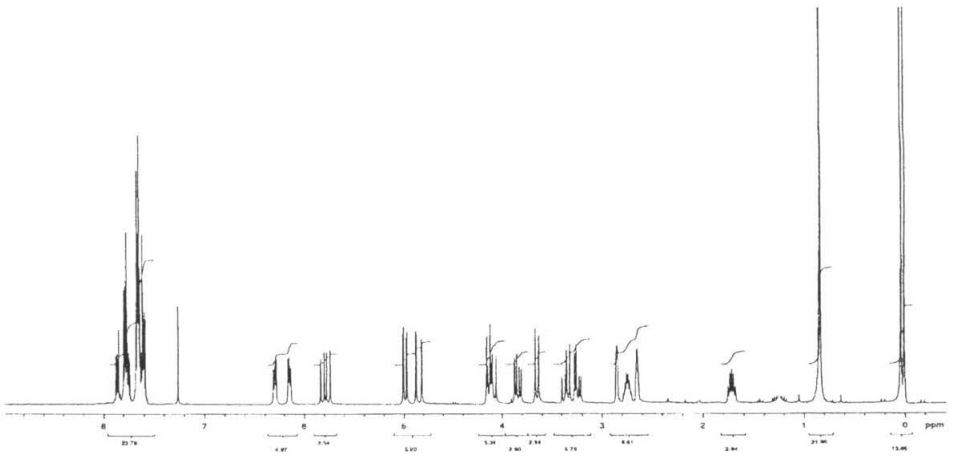
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.73-7.79 (m, 2H), 7.58-7.67 (m, 6H), 6.30 (dd, 1H,*J*=5.6, 3.4), 6.15 (dd, 1H, *J*=5.6, 2.8), 5.79 (dd, 1H, *J*=17.7, 10.9), 5.01 (dd, 1H, *J*=10.9, 1.6), 4.85 (dd, 1H, *J*=17.7, 1.6), 4.06-4.16 (m, 2H), 3.85 (dd, 1H, *J*=14.0, 6.2), 3.63 (d, 1H, *J*=10.9), 3.36 (dd, 1H, *J*=13.7, 9.0), 3.22 (dd, 1H, *J*=13.4, 5.3), 2.85 (s, 1H), 2.72 (m, 1H), 2.65 (s, 1H), 1.72 (m, 1H), 0.84 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 168.66, 168.07, 142.99, 138.42, 134.31, 133.76, 133.68, 132.84, 132.19, 131.96, 123.60, 123.19, 123.08, 114.80, 68.49, 64.74, 49.69, 49.47, 44.69, 41.58, 41.26, 40.52, 25.85, 18.18, -5.33, -5.49.

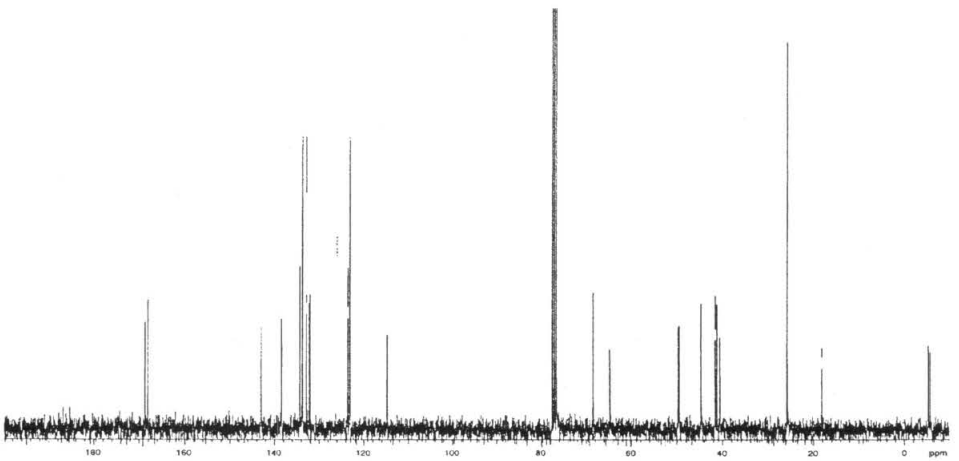
IR (thin film)ν 2928, 2884, 2854, 1772, 1715, 1467, 1435, 1397, 1347, 1302, 1255, 1188, 1093, 1070, 1002, 912, 837, 777, 713.

Elemental Analysis calc'd for $C_{34}H_{38}O_5N_2Si$: C, 70.07%, H, 6.57%, N, 4.81%; found C, 69.88%, H, 6.68%, N, 4.63%.

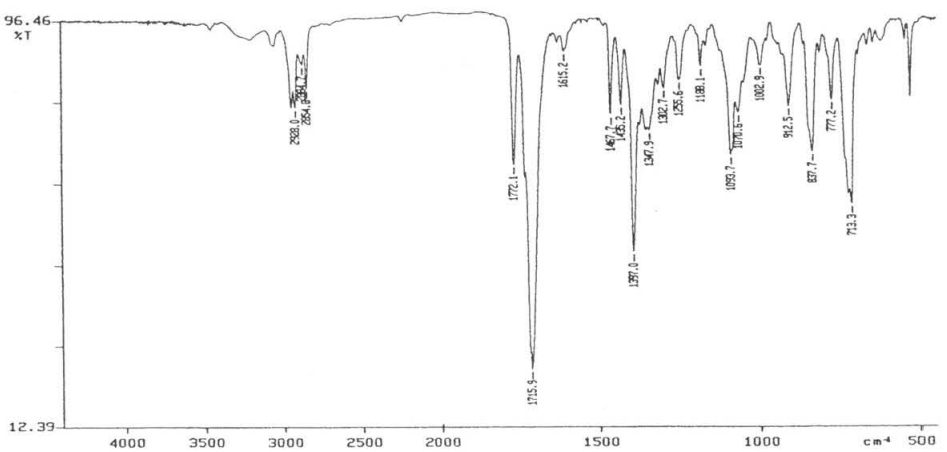
^{1}H NMR
300 MHz
$CDCl_3$

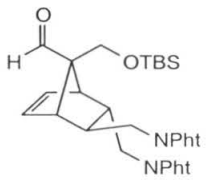


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





137. To a vigorously stirring mixture of NMO (0.79g, 6.7 mmol), $(DHQD)_2PHAL$ (0.11g, 0.13 mmol), and OsO_4 (0.45 ml, 4% in water, 0.07 mmol) in 15 ml water and 5 ml THF was added diene **136** (1.36g, 2.33 mmol) dropwise as a solution in 5 ml THF. The reaction was stirred at 23 °C for 23 h then 5 ml sat. aq. Na_2SO_3 was added and the reaction was stirred 1 h. It was then extracted 3 x 50 ml CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. Concentration *in vacuo* gave an oil which was purified by silica gel chromatography (1:1 CH_2Cl_2/EtOAc) to give 1.31g (98%) of a 6:5 mixture of two diastereomeric diols.

To a solution of diol (1.03g, 1.67 mmol), prepared as described above, in 30 ml THF and 20 ml water was added K_2CO_3 (0.42g, 3.0 mmol) followed by $NaIO_4$ (1.06g, 4.95 mmol, in 2 ml water). The mixture stirred for 1 h during which time some white precipitate formed, then it was extracted 3 x 100 ml EtOAc and the combined organics were washed 1 x 100 ml 10% Na_2SO_3, 1 x 100 ml brine and dried over Na_2SO_4. Concentration *in vacuo* followed by purification by silica gel chromatography (1:1 hexane/EtOAc) gave 0.900g (92%) aldehyde **137** as a colorless foam.

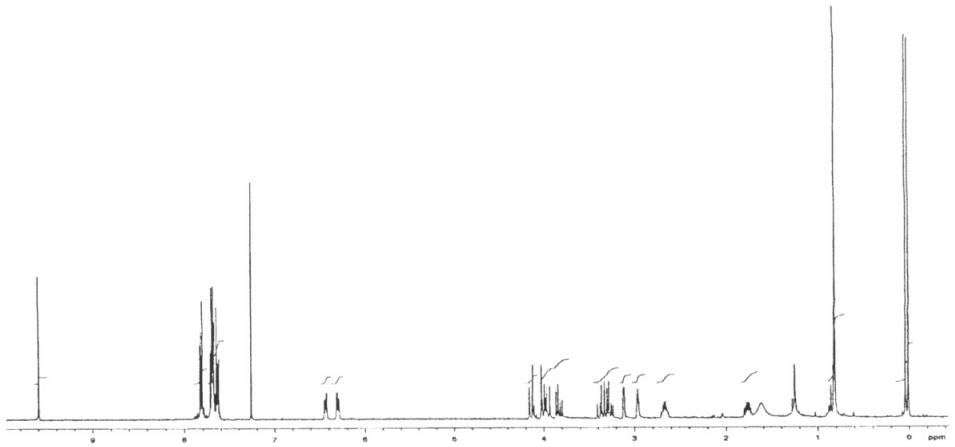
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 9.60 (s, 1H), 7.79-7.83 (m, 2H), 7.62-7.72 (m, 6H), 6.43 (dd, 1H, *J*=3.4, 5.6), 6.31 (dd, 1H, *J*=2.8, 5.6), 4.15 (d, 1H, *J*=10.9), 3.93-4.06 (m, 2H), 3.84 (dd, 1H, *J*=14.0, 6.8), 3.23-3.41 (m, 2H), 3.11 (s, 1H), 2.97 (s, 1H), 2.65-2.69 (m, 1H), 1.73-1.80 (m, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 206.27, 168.56, 167.99, 138.58, 133.94, 133.86, 132.03, 131.83, 123.32, 123.18, 76.16, 62.20, 47.74, 47.04, 44.26, 41.10, 40.37, 39.95, 26.90, 25.70, 18.06, -5.57, -5.77.

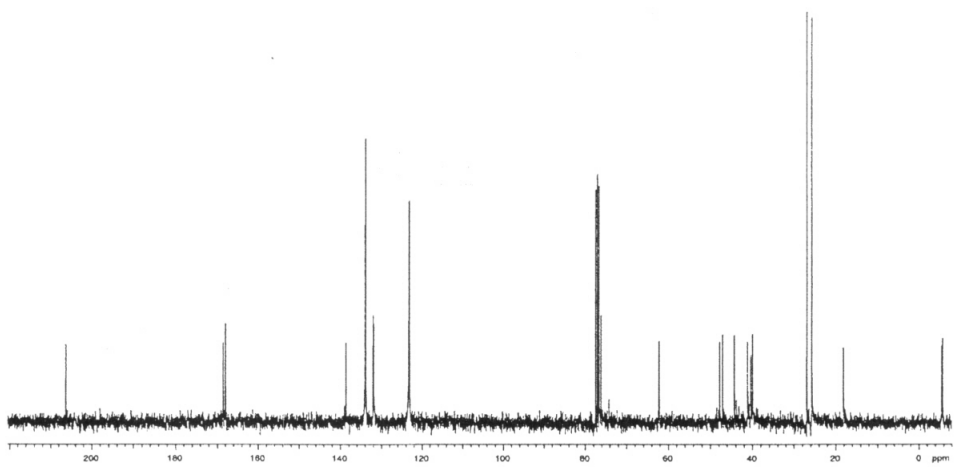
IR (thin film)ν 2928, 2855, 1770, 1715, 1467, 1397, 1257, 1087, 838, 778, 713.

HRMS(MALDI) calc'd for $(C_{33}H_{36}O_6N_2SiNa)^+$, 607.2240; found, 607.2236.

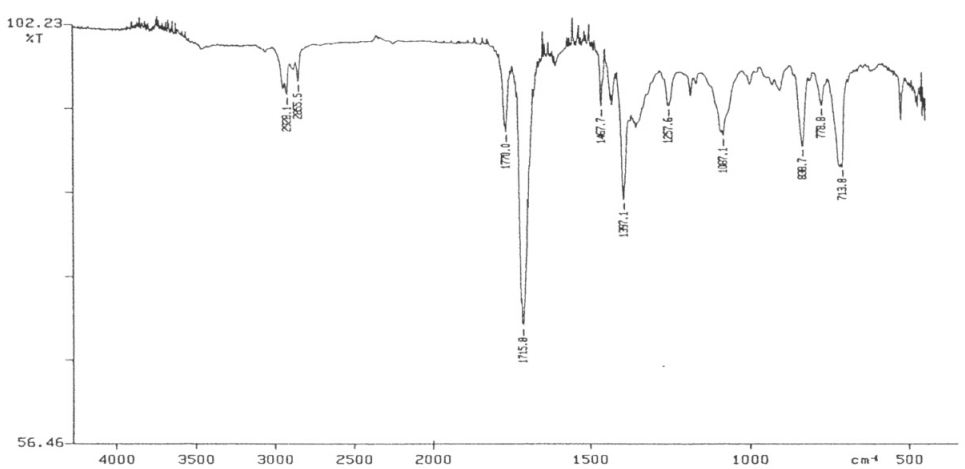
^{1}H NMR
300 MHz
$CDCl_3$

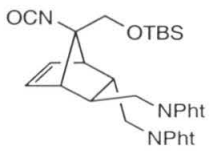


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





141. To a solution of aldehyde **137** (0.431g, 0.737 mmol) in 20 ml ^{t}BuOH and 0.2 ml DMSO was added dropwise a solution of $NaClO_2$ (0.343g, 3.79 mmol) and KH_2PO_4 (1.01g, 7.45 mmol) in 4 ml water. The resulting yellow reaction was stirred until colorless (~1 h), then it was further acidified with 1N $NaHSO_4$ (7.5 ml, 7.5 mmol) and extracted 3 x 100 ml EtOAc. The combined organic layers were then washed 1 x 100 ml water, 1 x 100 ml brine and dried over Na_2SO_4. Concentration *in vacuo* gave a colorless solid (0.58g, >100%) that was purified by silica gel chromatography (1:1 hexane/EtOAc with 5% HOAc) to give 0.418g (94%) of the corresponding carboxylic acid **138**. In practice, the crude material was found to contain ~5% of the acid chloride **139** and thus was carried on to subsequent steps unpurified.

To a solution of unpurified carboxylic acid **138** (0.214g, 0.356 mmol), prepared as described above, in 10 ml CH_2Cl_2 was added $(COCl)_2$ (0.037 ml, 0.42 mmol) dropwise followed by one drop of DMF (~0.005 ml). Gas evolution was noted and the reaction was stirred for 1.5 h then concentrated *in vacuo* to give a yellow solid residue. The residue was dissolved in 4 mL dry DMSO and NaN_3 (0.056g, 0.86 mmol) was added. The solution was stirred for 1.5 h then it was diluted with 10 ml water and extracted 3 x 10 ml EtOAc. The combined organics were washed 5 x 10 ml water, 1 x 10 ml brine then dried over Na_2SO_4. Concentration *in vacuo* gave a yellow oily residue that was redissolved in 15 ml benzene and heated to reflux for 2 h. (Completion of the reaction was determined by FTIR as evidenced by the disappearance of the N_3 stretch and appearance of the NCO stretch.) Evaporation of solvent *in vacuo* yielded a yellow solid that was purified by silica

gel chromatography (3:2 hexane/EtOAc) to give 0.144g (67%, 4 steps) of isocyanate **141** as a white solid.

Optical rotation: $[\alpha]_{Na}$ -33.0 (c = 1.08, $CDCl_3$).

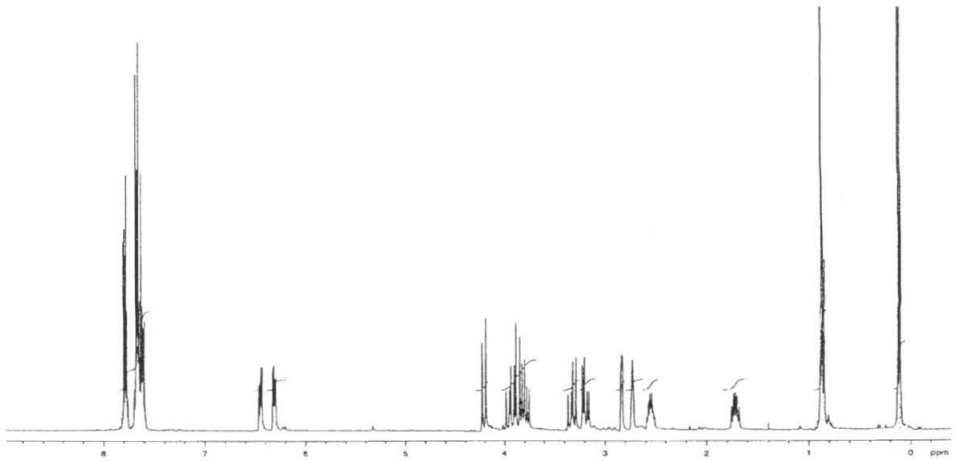
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.78-7.81 (m, 2H), 7.59-7.77 (m, 6H), 6.44 (dd, 1H, *J*=3.1, 5.6), 6.31 (dd, 1H, *J*=3.2, 5.6), 4.21 (d, 1H, *J*=10.9), 3.75-3.98 (m, 3H), 3.33 (dd, 1H, *J*=13.7, 9.0), 3.20 (dd, 1H, *J*=13.7, 5.6), 2.83 (s, 1H), 2.73 (s, 1H), 2.52-2.57 (m, 1H), 1.68-1.75 (m, 1H), 0.87 (s, 9H), 0.11 (s, 3H), 0.072 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ 168.54, 167.91, 137.64, 133.98, 133.87, 132.56, 131.99, 131.78, 125.54, 123.34, 123.19, 83.47, 64.82, 52.22, 51.33, 42.72, 41.23, 39.70, 39.65, 25.76, 18.13, -5.36, -5.52.

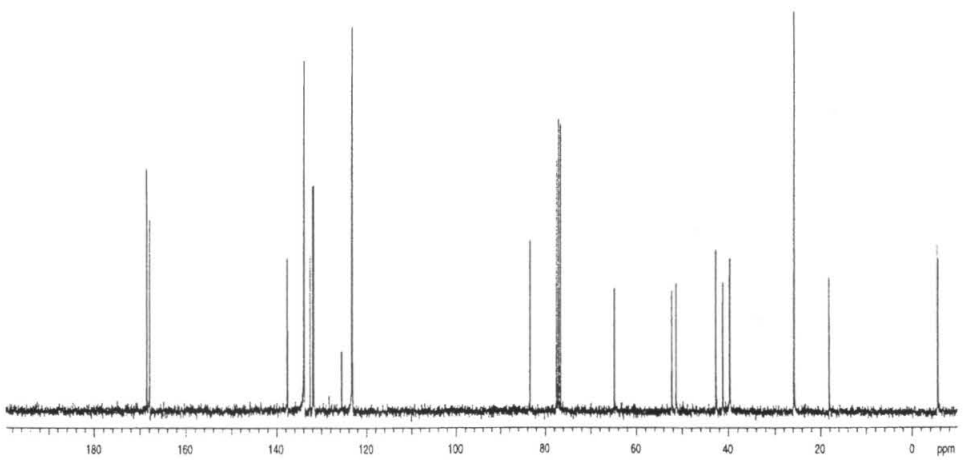
IR (thin film) ν 2928, 2855, 2249, 1771, 1715, 1467, 1435, 1396, 1348, 1085, 838, 779, 724.

Elemental Analysis calc'd for $C_{33}H_{35}N_3O_6Si$: C, 66.31%, H, 5.90%, N, 7.03%; found C, 66.06%, H, 6.03%, N, 7.02%.

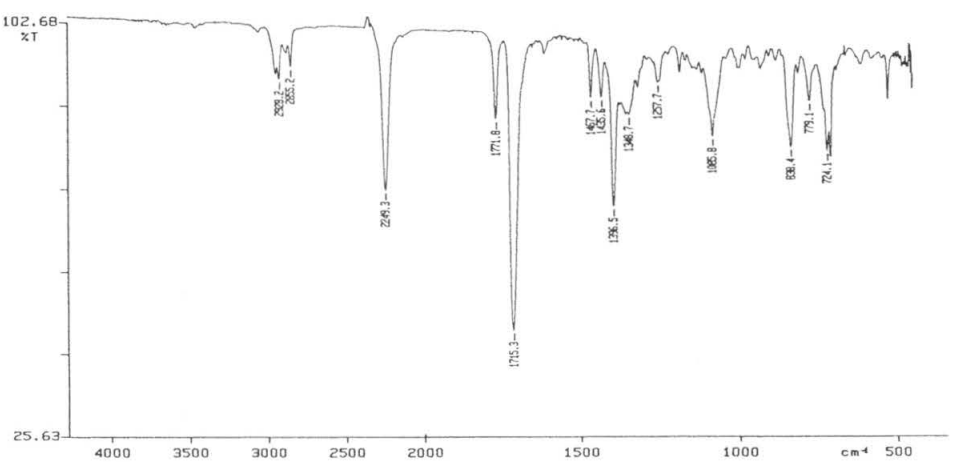
^{1}H NMR
300 MHz
$CDCl_3$

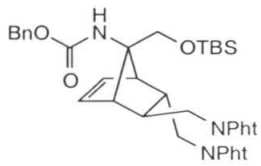


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





142. Isocyanate **141** (0.503g, 0.841 mmol) was dissolved in 5 ml THF and added via cannula to a solution of BnOLi (0.102g BnOH + 0.6 mL 1.6M BuLi) in 20 mL THF at 0 °C. The reaction was poured onto 20 mL ice-cold 1N $NaHSO_4$ and extracted 2 x 20 mL EtOAc. The combined organic layers were washed 1 x 20 mL sat. $NaHCO_3$ and 1 x 20 mL sat. NaCl then dried over Na_2SO_4. Removal of solvent *in vacuo* gave a colorless resin that was purified by silica gel chromatography (grad. 3:1 → 1:1 hexanes/EtOAc) to give **142** as 0.450g (76%) of colorless foam.

Optical rotation: $[\alpha]_{Na}$ -27.1 (c = 0.700, $CDCl_3$).

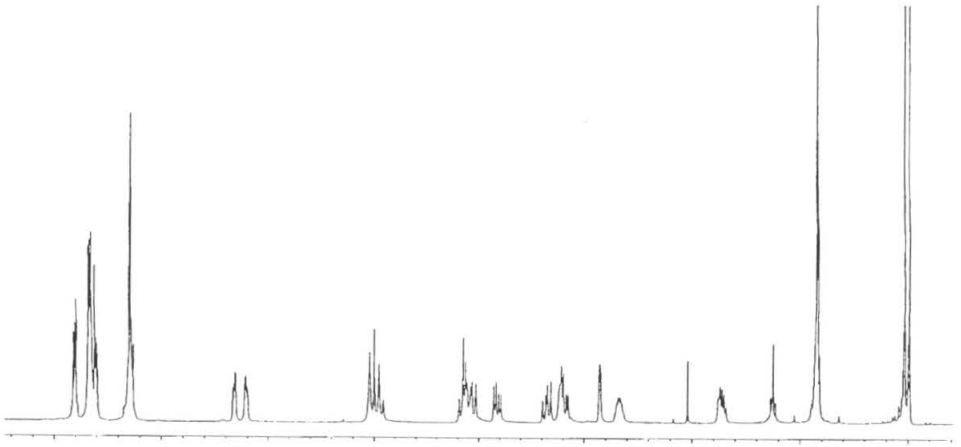
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.82 (m, 2H), 7.59-7.77 (m, 6H), 7.35 (m, 5H), 6.31 (dd, 1H, *J*=5.7, 3.1), 6.21 (dd, 1H, *J*=5.7, 3.1), 5.04 (bs, 1H), 5.00 (d, 1H, *J*=12.5), 4.91 (d, 1H, *J*=12.5), 4.18-4.03 (m, 3H), 3.81 (dd, 1H, *J*=14, 6.2), 3.35 (dd, 1H, *J*=13.7, 9.7), 3.23-3.15 (m, 2H), 2.85 (s, 1H), 2.65 (m, 1H), 1.75 (m, 1H), 0.87 (s, 9H), 0.12 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 168.58, 167.91, 154.94, 136.65, 136.23, 133.86, 133.73, 132.40, 132.13, 131.92, 128.47, 128.06, 127.98, 123.27, 123.16, 78.20, 66.18, 61.86, 50.79, 48.90, 42.61, 41.38, 40.41, 39.89, 25.85, 18.18, -5.46, -5.57.

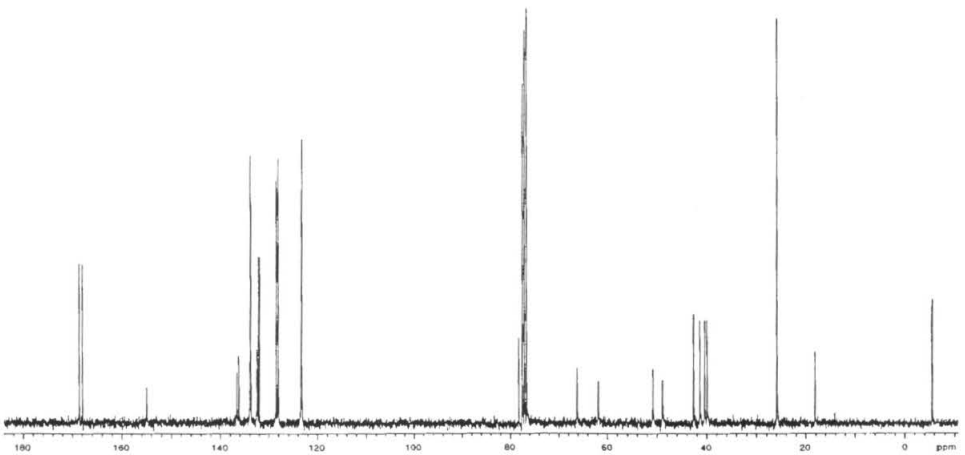
IR (thin film)ν 3369, 2945, 2929, 2846, 1771, 1716, 1468, 1435, 1397, 1347, 1251, 1069, 834.

Elemental Analysis calc'd for $C_{40}H_{43}O_7N_3Si$: C, 68.06%, H, 6.14%, N, 5.95%; found C, 67.93%, H, 6.38%, N, 5.94%.

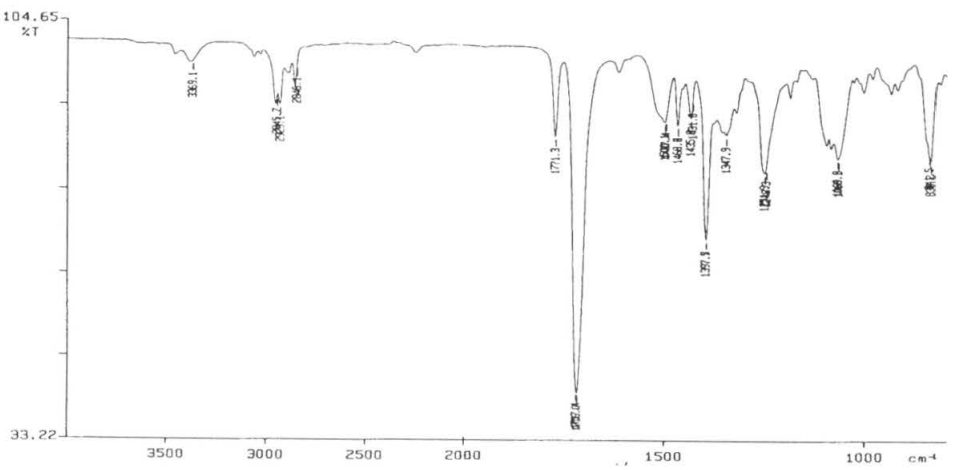
^{1}H NMR
300 MHz
$CDCl_3$

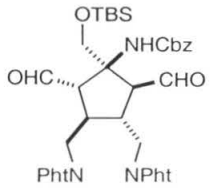


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





144. Into a solution of **142** (0.447g, 0.634 mmol) in 10 ml CH_2Cl_2 cooled to –78 °C was bubbled a dilute stream of O_3 in O_2 until the solution became blue. It was then flushed with N_2, and PPh_3 (0.201g, 0.766 mmol) was added and the reaction was warmed to 23 °C. After 30 min, K_2CO_3 (0.3g, 2 mmol) was added to the solution and it was stirred an additional 2 h. The reaction was then filtered through celite and concentrated *in vacuo* to give a pale yellow oil that was purified by silica gel chromatography (3:2 hexane/EtOAc) to give 0.410g (88%) of pure **144** as a colorless foam.

Optical rotation: $[\alpha]_{Na}$ +19.9 (c = 0.600, $CDCl_3$).

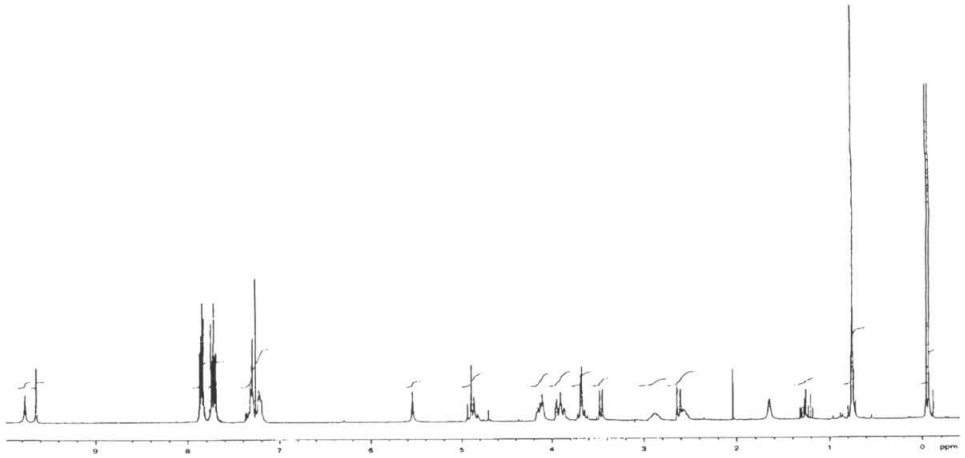
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 9.76 (s, 1H), 9.64 (d, 1H, *J*=1.2), 7.85 (m, 4H), 7.75 (m, 4H), 7.36 (m, 3H), 7.20 (m, 2H), 5.54 (bs, 1H), 4.91 (d, 1H, *J*=12.2), 4.84 (d, 1H, *J*=12.2), 4.08-4.15 (bm, 2H), 3.85-3.95 (m, 2H), 3.64-3.72 (m, 2H), 3.47 (d, 1H, *J*=8.4), 2.88 (bm, 1H), 2.62 (d, 1H, *J*=11.2), 2.58 (bm, 1H), 0.76 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ 200.63, 199.72, 168.96, 168.9, 154.98, 134.20, 134.02, 131.98, 131.90, 128.52, 128.21, 123.57, 123.44, 67.98, 66.75, 64.76, 60.24, 58.35, 41.02, 39.32, 38.51, 38.38, 25.60, 17.97, -5.83, -5.80.

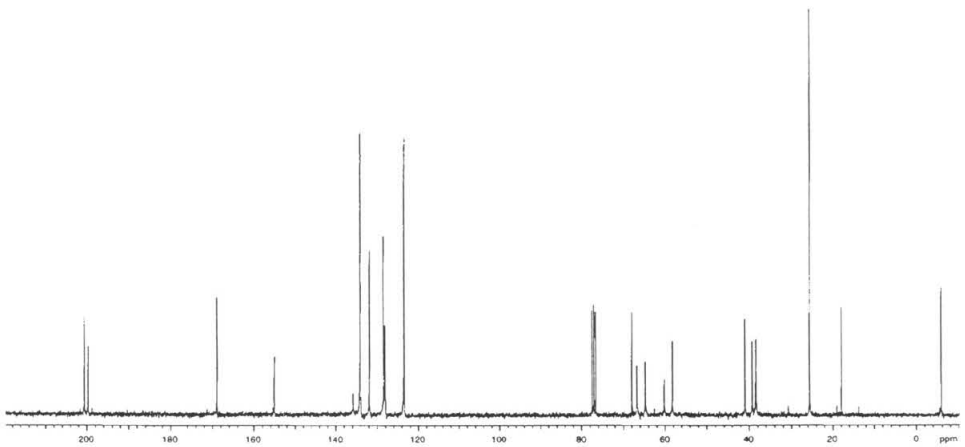
IR (thin film) ν 3369, 2929, 2856, 1712, 1506, 1467, 1433, 1391, 1352, 1251, 1084, 913, 839, 779, 723.

Elemental Analysis calc'd for $C_{40}H_{43}N_3O_9Si$: C, 65.11%, H, 5.87%, N, 5.69%; found C, 64.88%, H, 5.98%, N, 5.44%.

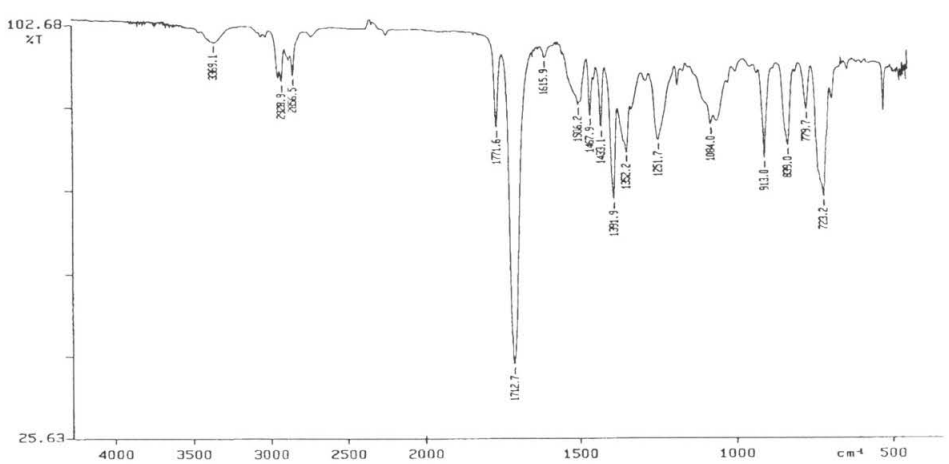
^{1}H NMR
300 MHz
$CDCl_3$

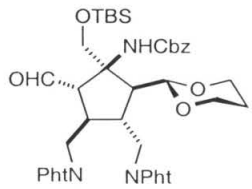


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





149. To a vigorously stirring solution of distilled 1,3-propanediol (0.2 mL) in 5 mL dry ether was added dialdehyde **144** (0.101g, 0.137 mmol) and PPTS (0.097g, 0.380 mmol). After 1.5 h the reaction was treated with 0.1g $NaHCO_3$ and filtered through celite. The filtrate was concentrated *in vacuo* and the residue purified by silica gel chromatography (grad. 2:1 → 1:1 hexanes/EtOAc) to give 0.015g (15%) of starting dialdehyde **144** and 0.055g (59% based on unrecovered **144**) of **149** as a colorless foam.

Optical rotation: $[\alpha]_{Na}$ +20.3 (c = 1.65, $CDCl_3$).

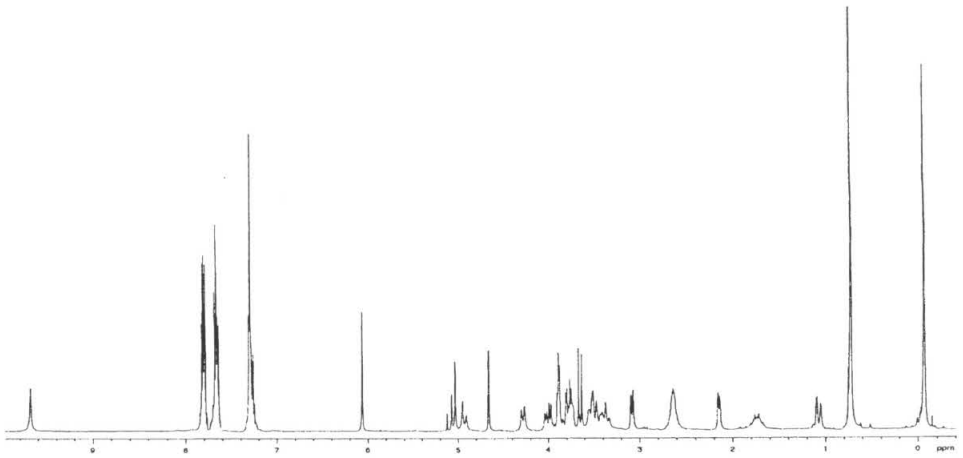
^{1}H-NMR ($CDCl_3$, 300 MHz)δ 9.68 (s, 1H), 7.84-7.80 (m, 4H), 7.70-7.77 (m, 4H), 7.24-7.30 (m, 5H), 6.06 (bs, 1H), 5.12 (d, 1H, *J*=14.3), 4.95 (d, 1H, *J*=14.3), 4.66 (d, 1H, *J*=2.5), 4.27 (bd, 1H, *J*=10.3), 3.99 (dd, 1H, *J*=14, 6.2), 3.89 (m, 2H), 3.77 (m, 2H), 3.65 (d, 1H, *J*=10.3), 3.37-3.55 (bm, 3H), 3.08 (d, 1H, *J*=8.1), 2.55-2.70 (bm, 2H), 2.13 (dd, 1H, *J*=6.8, 2.2), 1.61-1.82 (bm, 1H), 1.07 (bd, 1H, *J*=12.1), 0.86 (s, 9H), -0.28 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz)δ 199.84, 168.71, 155.00, 133.83, 133.71, 132.27, 132.03, 128.44, 128.20, 127.99, 123.28, 123.10, 100.74, 67.91, 66.75, 66.70, 66.23, 62.40, 60.92, 48.73, 40.38, 40.22, 39.33, 39.25, 25.61, 18.00, -5.76, -5.81.

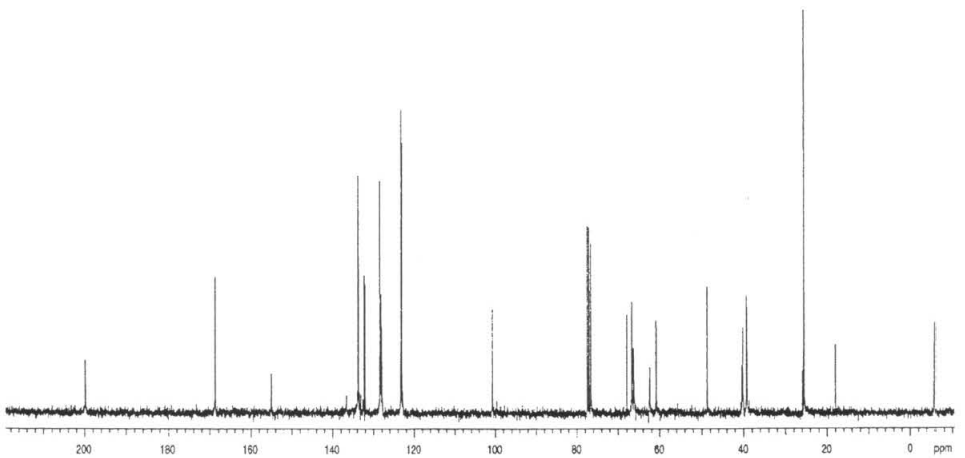
IR (thin film)ν 3365, 2930, 2856, 1772, 1715, 1512, 1468, 1435, 1397, 1362, 1251, 1086, 1002, 913, 875, 838.

HRMS(MALDI) calc'd for $(C_{43}H_{49}N_3O_{10}SiNa)^+$, 818.3085; found, 818.3089.

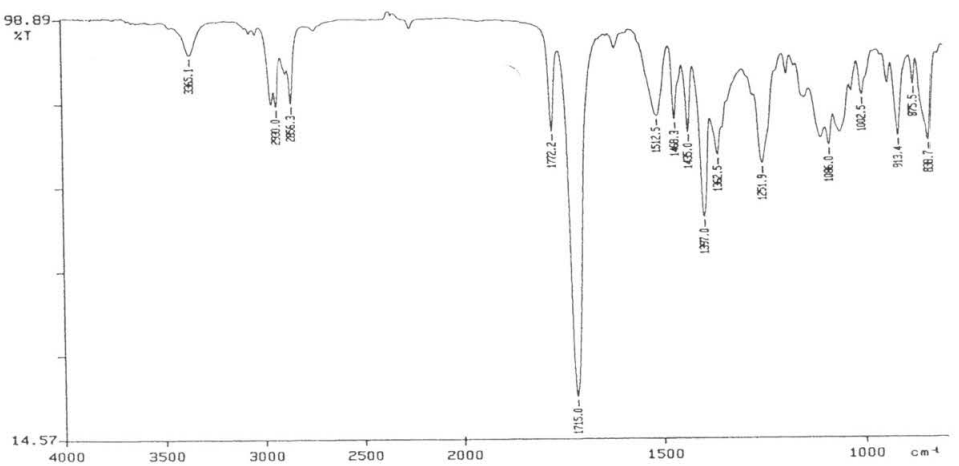
^{1}H NMR
300 MHz
$CDCl_3$

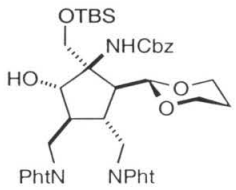


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





152. To a solution of **149** (0.060g, 0.075 mmol) in 2 mL ^{t}BuOH at 23 °C was added $KMnO_4$ (0.016g, 0.10 mmol) dissolved in 1.5 mL pH=7 buffer (1.25 M phosphate). After 45 min the reaction was poured onto 10 mL ice-cold 1 N $NaHSO_4$ and extracted 2 x 5 mL EtOAc. The combined organic layers were dried over Na_2SO_4. Solvent removal *in vacuo* gave 0.064g (quant.) of unpurified carboxylic acid **151**.

To a solution of unpurified **151** (0.030g, 0.037 mmol) in 1.5 mL $CHCl_3$ at 23 °C was added thiopyridine-*N*-oxide (0.0085g, 0.067 mmol) and EDC (0.015g, 0.078 mmol) followed by DMAP (0.0036g, 0.029 mmol). The bright yellow reaction was heated to 45 °C until it became colorless, then it was cooled to 23 °C and solvent was removed *in vacuo*. The residue was subjected to silica gel chromatography (1:1 hexanes/EtOAc) to give 0.016g (50%) of **152** as a colorless foam.

Optical rotation: $[\alpha]_{Na}$ +30.5 (c = 0.690, $CDCl_3$).

^{1}H-NMR ($CDCl_3$, 300 MHz)δ 7.84 (m, 4H), 7.67 (m, 4H), 7.29 (m, 5H), 6.38 (bs, 1H), 5.05 (d, 1H, *J*=12.5), 4.95 (d, 1H, *J*=12.5), 4.83 (d, 1H, *J*=3.4), 4,38 (d, 1H, *J*=4.4), 4.15 (dd, 1H, *J*=8.7, 3.1), 3.90 (d, 1H, *J*=6.2), 3.89-3.72 (m, 3H), 3.63-3.56 (bm, 2H), 3.49-3.41 (bm, 2H), 2.38-2.26 (bm, 3H), 1.65 (bm, 1H), 1.09 (bd, 1H, *J*=14.3), 0.087 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H).

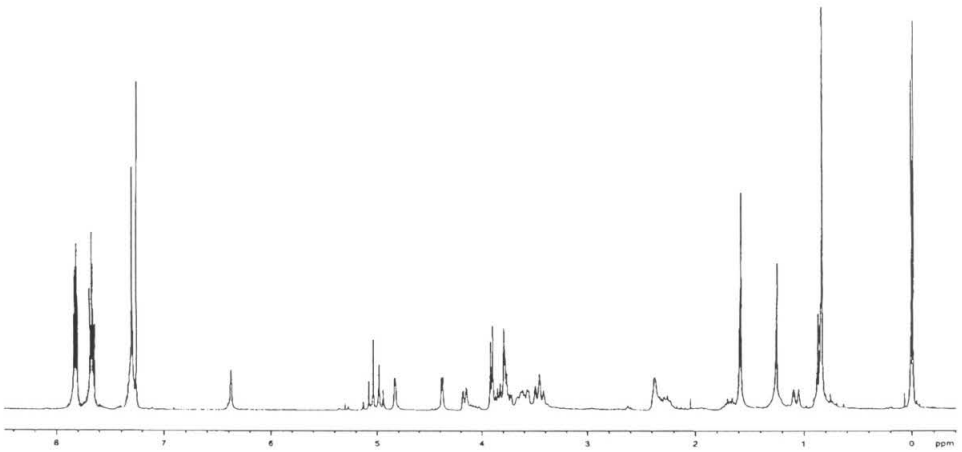
^{13}C-NMR ($CDCl_3$, 75 MHz)δ 168.64, 168.58, 156.52, 136.63, 133.58, 133.51, 132.42, 132.37, 128.44, 127.97, 127.94, 123.15, 123.02, 101.71, 81.36, 66.85, 66.47, 66.43, 65.39, 63.71, 48.03, 44.83, 41.83, 40.59, 37.79, 25.80, 25.35, 18.20, -5.57, -5.78.

IR (thin film)ν 3369, 2929, 2854, 1767, 1713, 1518, 1464, 1435, 1356, 1256, 1086, 912, 841.

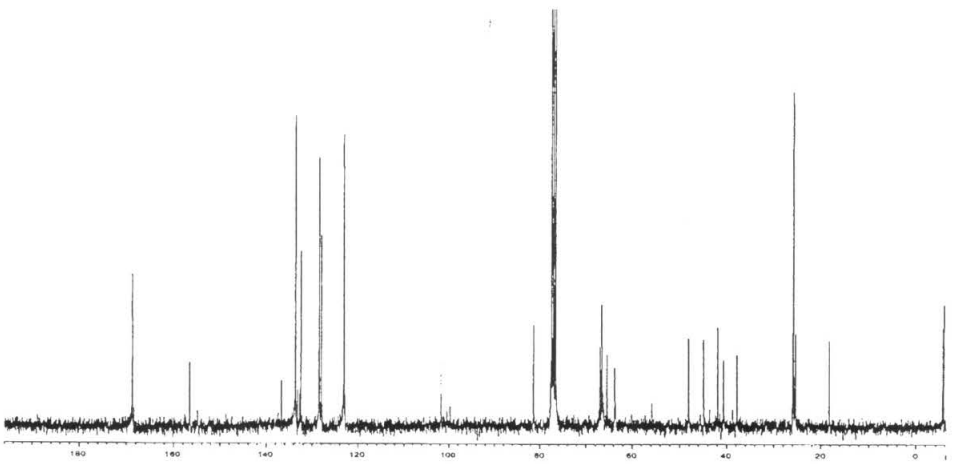
Elemental Analysis calc'd for $C_{41}H_{47}N_3O_{10}Si$: C, 64.46%, H, 5.88%, N, 5.33%; found C, 64.16%, H, 6.93%, N, 5.08%.

HRMS(MALDI) calc'd for $C_{41}H_{47}N_3O_{10}Si$ $[M+Na]^+$, 806.3080; found 806.3222.

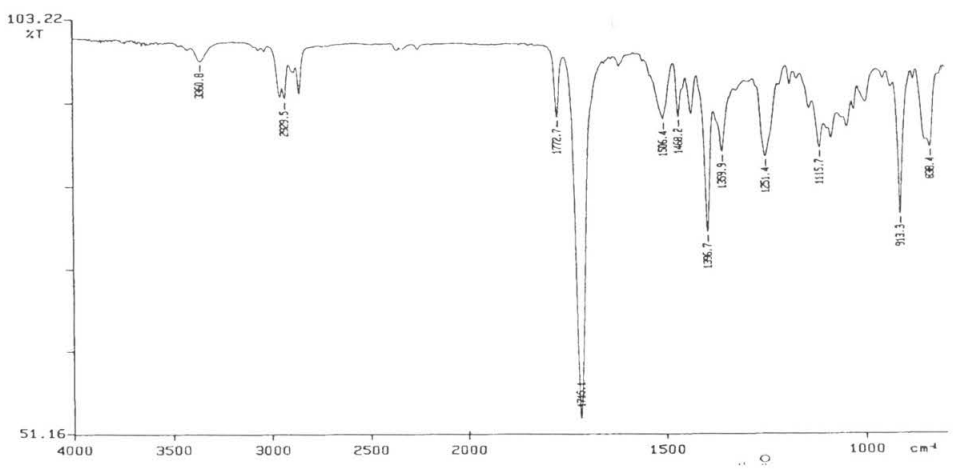
^{1}H NMR
300 MHz
$CDCl_3$

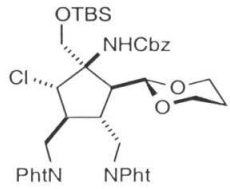


^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film





153. To a solution of **149** (0.060g, 0.075 mmol) in 2 mL ^{t}BuOH at 23 °C was added $KMnO_4$ (0.016g, 0.10 mmol) dissolved in 1.5 mL pH=7 buffer (1.25 M phosphate). After 45 min the reaction was poured onto 10 mL ice-cold 1 N $NaHSO_4$ and extracted 2 x 5 mL EtOAc. The combined organic layers were dried over Na_2SO_4. Solvent removal *in vacuo* gave 0.064g (quant.) of unpurified carboxylic acid **151**.

A solution of **151** (0.021g, 0.0259 mmol), thiopyridine-*N*-oxide (0.0044g, 0.035 mmol), and DMAP (0.001g, 0.008 mmol) in 1.0 mL CCl_4 in a sealed tube was subjected to 4 cycles of freeze-pump-thaw then transferred then EDC (0.010g, 0.052 mmol) was added and the bright yellow reaction stirred at 23 °C until it became colorless (~12 h). The reaction was directly purified by silica gel chromatography (grad. 2:1 → 1:1 hexanes/EtOAc) to give 0.016g (76%) of **153** as a colorless resin.

Optical rotation: $[\alpha]_{Na}$ +30.4 (c = 0.650, $CDCl_3$).

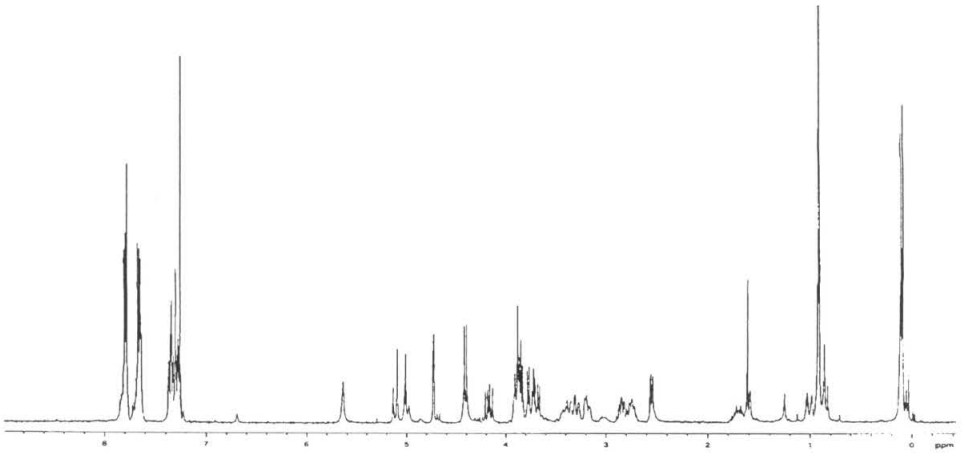
^{1}H-NMR ($CDCl_3$, 300 MHz, an inseparable contaminant was present, <10%, and is believed to be the minor diastereomeric chloride) δ 7.84 (m, 4H), 7.77 (m, 4H), 7.05-7.25 (m, 5H), 5.64 (bs, 1H), 5.10 (d, 1H, *J*=12.1), 4.97 (bd, 1H, *J*=12.1), 4.73 (d, 1H, *J*=1.6), 4.41 (d, 1H, *J*=6.2), 4.18 (dd, 1H, *J*=5.0, 8.7), 3.95-3.65 (m, 5H), 3.45-3.15 (bm, 4H), 2.82 (m, 1H), 2.74 (m, 1H), 2.56 (dd, 1H, *J*=6.5, 1.6), 1.60-1.80 (m, 2H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ 168.63, 168.17, 155.05, 133.76, 133.44, 132.53, 132.08, 128.42, 127.99, 123.26, 122.86, 100.08, 66.96, 66.59, 66.47, 66.41, 64.92, 51.67, 48.58, 42.11, 41.38, 38.84, 26.03, 25.35, 18.46, -5.49, -5.59.

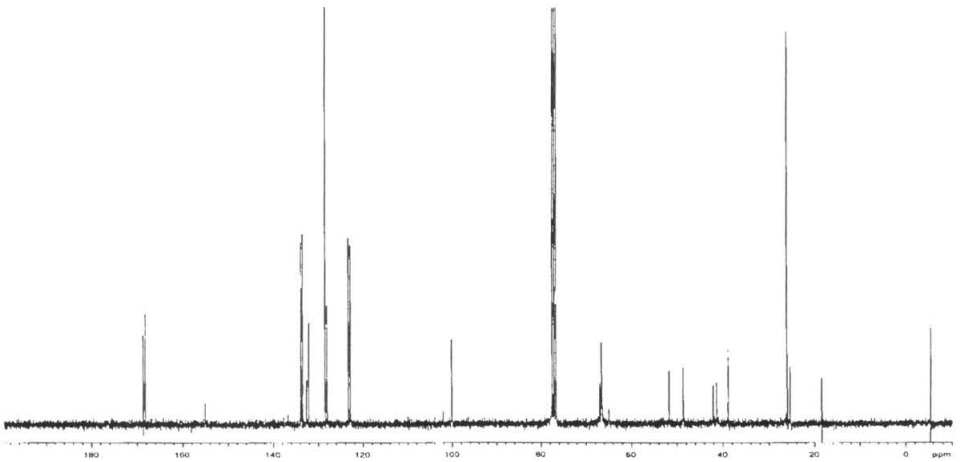
IR (thin film) ν 3360, 2929, 1772, 1715, 1506, 1468, 1396, 1359, 1251, 1115, 913, 838.

HRMS(MALDI) calc'd for $(C_{42}H_{48}ClO_9N_3SiNa)^+$, 824.2746; found, 824.2727.

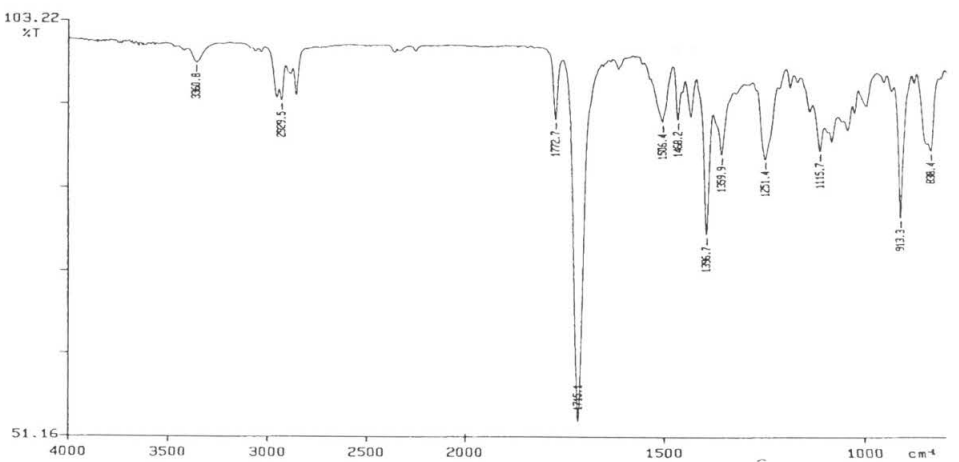
^{1}H NMR
300 MHz
$CDCl_3$



^{13}C NMR
75 MHz
$CDCl_3$



FTIR
thin film



Appendix A. X-ray Crystallographic Data for (+)-**127.**

Table 1. Crystal data and structure refinement for 1.

Empirical formula	$C_{19}H_{30}O_5Si$
Formula weight	366.52 g/mol
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 21.184(11) Å $\alpha = 90°$
	b = 8.806(4) Å $\beta = 97.10(4)°$
	c = 11.295(6) Å $\gamma = 90°$
Volume	2091(2) $Å^3$
Z	4
Density (calculated)	1.164 g/cm^3
Absorption coefficient	1.189 mm^{-1}
F(000)	792
Crystal size	0.3 x 0.1 x 0.1 mm
Theta range for data collection	3.94 to 49.98°
Index ranges	$-20 \leq h \leq 20, 0 \leq k \leq 8, 0 \leq l \leq 11$
Reflections collected	1158
Independent reflections	1158 [R(int) = 0.0000]
Absorption correction	None

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1158 / 1 / 227
Goodness-of-fit on F^2	1.038
Final R indices [$I>2\sigma_I$]	$R_1 = 0.0823$, $wR_2 = 0.2254$
R indices (all data)	$R_1 = 0.0837$, $wR_2 = 0.2285$
Absolute structure parameter	0.26(13)
Extinction coefficient	0.005(2)
Largest diff. peak and hole	0.418 and -0.324 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for (+)-**127**. U(eq) is defined as one-third of the trace of the orthogonalized U(ij) tensor.

	x	y	z	U(eq)
Si(1)	3768(1)	2872(4)	7741(3)	82(1)
O(1)	3011(3)	2689(9)	7243(5)	74(2)
O(2)	2073(4)	6003(9)	7782(6)	81(2)
O(3)	2242(3)	4724(8)	9488(6)	79(2)
O(4)	510(5)	3578(12)	9442(10)	130(4)
O(5)	506(4)	1134(10)	9419(9)	106(3)
C(1)	1587(4)	3158(11)	6656(7)	57(2)
C(2)	1469(4)	3808(12)	7910(8)	58(2)
C(3)	1346(4)	2402(12)	8612(7)	57(2)

C(4)	1375(4)	1065(12)	7669(9)	65(3)
C(5)	818(4)	1342(14)	6735(8)	70(3)
C(6)	943(4)	2562(15)	6135(8)	71(3)
C(7)	1933(4)	1644(11)	7011(7)	54(2)
C(8)	2021(5)	672(15)	5937(9)	75(3)
C(9)	2182(7)	1052(22)	4967(13)	118(5)
C(10)	2576(4)	1753(12)	7773(8)	61(2)
C(11)	1964(4)	4853(12)	8509(9)	62(2)
C(12)	730(5)	2327(14)	9171(8)	64(3)
C(13)	2534(8)	7113(15)	8241(11)	108(5)
C(14)	3926(6)	2505(19)	9350(9)	102(4)
C(15)	4063(8)	4749(18)	7381(14)	118(5)
C(16)	4099(13)	1509(19)	6872(10)	168(10)
C(17)	4936(5)	1729(30)	7344(15)	160(9)
C(18)	4084(6)	1837(26)	5535(11)	127(6)
C(19)	3954(10)	-218(21)	7139(16)	143(6)

Table 3. Bond lengths [Å] and angles [°] for (+)-**127**.

Bond Lengths		C(7)-C(8)	1.515(14)
Si(1)-O(1)	1.641(7)	C(7)-C(10)	1.520(12)
Si(1)-C(16)	1.75(2)	C(8)-C(9)	1.23(2)
Si(1)-C(15)	1.83(2)	C(16)-C(18)	1.53(2)
Si(1)-C(14)	1.836(11)	C(16)-C(19)	1.59(3)
O(1)-C(10)	1.423(11)	C(16)-C(17)	1.80(3)
O(2)-C(11)	1.341(12)	Bond Angles	
O(2)-C(13)	1.432(14)	O(1)-Si(1)-C(16)	100.5(8)
O(3)-C(11)	1.192(11)	O(1)-Si(1)-C(15)	111.0(6)
O(4)-C(12)	1.248(14)	C(16)-Si(1)-C(15)	108.8(8)
O(5)-C(12)	1.201(14)	O(1)-Si(1)-C(14)	111.9(5)
C(1)-C(6)	1.511(13)	C(16)-Si(1)-C(14)	113.4(8)
C(1)-C(7)	1.551(13)	C(15)-Si(1)-C(14)	110.7(7)
C(1)-C(2)	1.576(13)	C(10)-O(1)-Si(1)	124.7(6)
C(2)-C(11)	1.49(2)	C(11)-O(2)-C(13)	117.0(8)
C(2)-C(3)	1.510(14)	C(6)-C(1)-C(7)	100.3(8)
C(3)-C(12)	1.520(13)	C(6)-C(1)-C(2)	103.9(7)
C(3)-C(4)	1.594(14)	C(7)-C(1)-C(2)	101.6(6)
C(4)-C(5)	1.503(13)	C(11)-C(2)-C(3)	115.1(7)
C(4)-C(7)	1.557(13)	C(11)-C(2)-C(1)	116.8(8)
C(5)-C(6)	1.31(2)	C(3)-C(2)-C(1)	103.3(8)

C(2)-C(3)-C(12)	117.7(8)	C(9)-C(8)-C(7)	129.3(14)
C(2)-C(3)-C(4)	103.4(6)	O(1)-C(10)-C(7)	112.3(7)
C(12)-C(3)-C(4)	110.6(8)	O(3)-C(11)-O(2)	122.5(9)
C(5)-C(4)-C(7)	100.9(8)	O(3)-C(11)-C(2)	126.9(9)
C(5)-C(4)-C(3)	104.9(8)	O(2)-C(11)-C(2)	110.6(8)
C(7)-C(4)-C(3)	99.9(7)	O(5)-C(12)-O(4)	123.0(8)
C(6)-C(5)-C(4)	107.7(9)	O(5)-C(12)-C(3)	121.3(9)
C(5)-C(6)-C(1)	108.2(8)	O(4)-C(12)-C(3)	115.5(10)
C(8)-C(7)-C(10)	107.4(7)	C(18)-C(16)-C(19)	112.7(13)
C(8)-C(7)-C(1)	112.3(7)	C(18)-C(16)-Si(1)	118(2)
C(10)-C(7)-C(1)	117.0(8)	C(19)-C(16)-Si(1)	116.7(13)
C(8)-C(7)-C(4)	111.9(8)	C(18)-C(16)-C(17)	100(2)
C(10)-C(7)-C(4)	115.5(7)	C(19)-C(16)-C(17)	105(2)
C(1)-C(7)-C(4)	92.4(6)	Si(1)-C(16)-C(17)	102.1(10)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for (+)-**127**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U(11)+ ... + 2hka^*b^*U(12)]$

	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
Si(1)	62(2)	102(3)	84(2)	3(2)	15(1)	-6(2)
O(1)	46(3)	105(6)	72(4)	19(4)	16(3)	-12(4)
O(2)	107(5)	70(5)	65(4)	2(4)	9(3)	-21(4)
O(3)	98(5)	75(5)	62(4)	1(4)	1(4)	-10(4)
O(4)	151(9)	88(7)	176(9)	13(6)	124(8)	10(6)
O(5)	104(6)	72(6)	159(8)	15(5)	89(6)	-1(5)
C(1)	45(5)	73(6)	53(5)	8(5)	10(4)	0(5)
C(2)	50(5)	60(5)	63(5)	3(5)	7(4)	9(5)
C(3)	43(4)	73(6)	59(5)	-4(5)	14(4)	1(5)
C(4)	60(6)	68(6)	71(6)	1(5)	23(5)	4(5)
C(5)	39(5)	100(9)	71(6)	-11(6)	11(4)	0(5)
C(6)	58(5)	92(8)	62(5)	0(6)	7(4)	6(6)
C(7)	36(4)	72(6)	58(5)	-4(5)	17(4)	-6(4)
C(8)	71(6)	98(8)	61(6)	-12(6)	22(5)	-5(6)
C(9)	109(9)	139(12)	109(9)	-47(10)	33(8)	-12(10)
C(10)	54(5)	67(6)	66(5)	6(5)	18(4)	-3(5)
C(11)	65(6)	67(6)	57(6)	2(6)	21(5)	5(5)
C(12)	63(6)	69(7)	62(5)	6(5)	19(4)	15(6)
C(13)	162(13)	73(8)	93(8)	-8(7)	24(8)	-38(9)

C(14)	109(9)	119(10)	78(7)	3(8)	7(6)	-22(9)
C(15)	116(11)	101(10)	131(11)	16(9)	-6(9)	-37(9)
C(16)	368(32)	88(10)	52(6)	-11(7)	45(11)	-74(15)
C(17)	40(6)	260(27)	180(14)	44(18)	11(7)	24(11)
C(18)	96(9)	191(18)	105(8)	6(11)	51(7)	10(10)
C(19)	181(17)	108(12)	147(13)	-13(11)	49(13)	38(13)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for (+)-**127**.

	x	y	z	U(eq)
H(4)	0(5)	3579(12)	10000(10)	195
H(5)	0(4)	988(10)	10000(9)	159
H(1A)	1796(4)	3825(11)	6156(7)	85
H(2A)	1078(4)	4370(12)	7789(8)	87
H(3A)	1698(4)	2269(12)	9226(7)	86
H(4A)	1415(4)	55(12)	7988(9)	98
H(5A)	433(4)	754(14)	6618(8)	105
H(6A)	675(4)	2985(15)	5468(8)	106
H(8A)	1918(5)	-380(15)	6025(9)	113
H(9B)	2303(7)	2049(22)	4735(13)	176
H(9A)	2181(7)	157(22)	4482(13)	176
H(10A)	2521(4)	2153(12)	8544(8)	92

H(10B)	2751(4)	750(12)	7884(8)	92
H(13A)	2570(8)	7873(15)	7644(11)	163
H(13B)	2401(8)	7581(15)	8938(11)	163
H(13C)	2938(8)	6629(15)	8449(11)	163
H(14A)	3720(6)	3262(19)	9777(9)	153
H(14B)	3765(6)	1519(19)	9518(9)	153
H(14C)	4376(6)	2535(19)	9596(9)	153
H(15A)	3976(8)	4922(18)	6537(14)	176
H(15B)	3852(8)	5510(18)	7798(14)	176
H(15C)	4513(8)	4803(18)	7620(14)	176
H(17A)	5183(5)	1023(30)	6945(15)	241
H(17B)	5056(5)	2747(30)	7166(15)	241
H(17D)	5014(5)	1564(30)	8190(15)	241
H(18A)	4288(6)	1082(26)	5102(11)	191
H(18D)	3638(6)	1864(26)	5249(11)	191
H(18B)	4269(6)	2813(26)	5421(11)	191
H(19D)	4175(10)	-897(21)	6667(16)	215
H(19A)	4062(10)	-454(21)	7969(16)	215
H(19B)	3504(10)	-330(21)	6925(16)	215