CHAPTER 2

The Variecolin Family of Sesterterpenoids

2.1 INTRODUCTION AND BACKGROUND

The variecolin family of sesterterpenoids has emerged as an intriguing class of biologically relevant natural products. Members of this family possess an array of biological activities including anti-HIV, antihypertensive, and immunosuppressant properties. Structurally, the variecolin-type sesterterpenoids are defined by their complex molecular architecture including a central eight-membered ring, a high degree of stereocomplexity, and a low degree of oxidation. Thus, this important class of natural products constitutes a formidable challenge for chemical synthesis.

2.1.1 ISOLATION AND STRUCTURAL ELUCIDATION

Hensens and co-workers at Merck first isolated variecolin (**95**) in 1991 as a bioactive component of the fungi imperfecti *Aspergillus variecolor*.[1] Extensive structural elucidation via 2D NMR spectroscopy and ^1H–^1H coupling constant analysis revealed a sesterterpenoid with a novel tetracyclic ring skeleton possessing the relative stereochemistry as shown in Figure 2.1.1. The absolute stereochemistry was proposed as *ent*-**95** due to biosynthetic considerations and structural similarity to the ceriferene class of sesterterpenoids (e.g., Flocerol (**96**)), which contains an analogous CD ring system.[2]

Figure 2.1.1. Proposed structure of variecolin.[†]

Variecolin (ent-95)
initially proposed

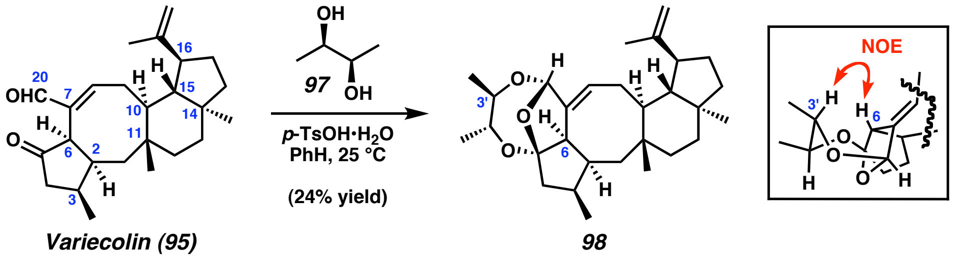
Asperigillus variecolor

Flocerol (96)
Ceriferene Sesterterpenoid

Variecolin (**95**) was later identified from the fungus *Emericella aurantiobrunnea* nine years after its first isolation.[3,4] Although direct confirmation of the absolute configuration was not feasible, Fujimoto and co-workers obtained structural verification through derivatization. Functionalization of **95** with (2*R*,3*R*)-(–)-butane-2,3-diol (**97**) generated chiral polycyclic acetal **98**, which, upon structural analysis, revealed four possible conformations—two derived from each enantiomer of **95**—that could be distinguished by NOESY correlation (Scheme 2.1.1). In a key NOE experiment a sole interaction of 6–9% was observed between H6 and H3', indicating that variecolin possesses a C(6) R-configuration, opposite to that of the biosynthetic proposal by Hensens. Butler provided further validation of the relative stereochemistry by X-ray crystal analysis of **95**, although the absolute configuration could not be determined.[5]

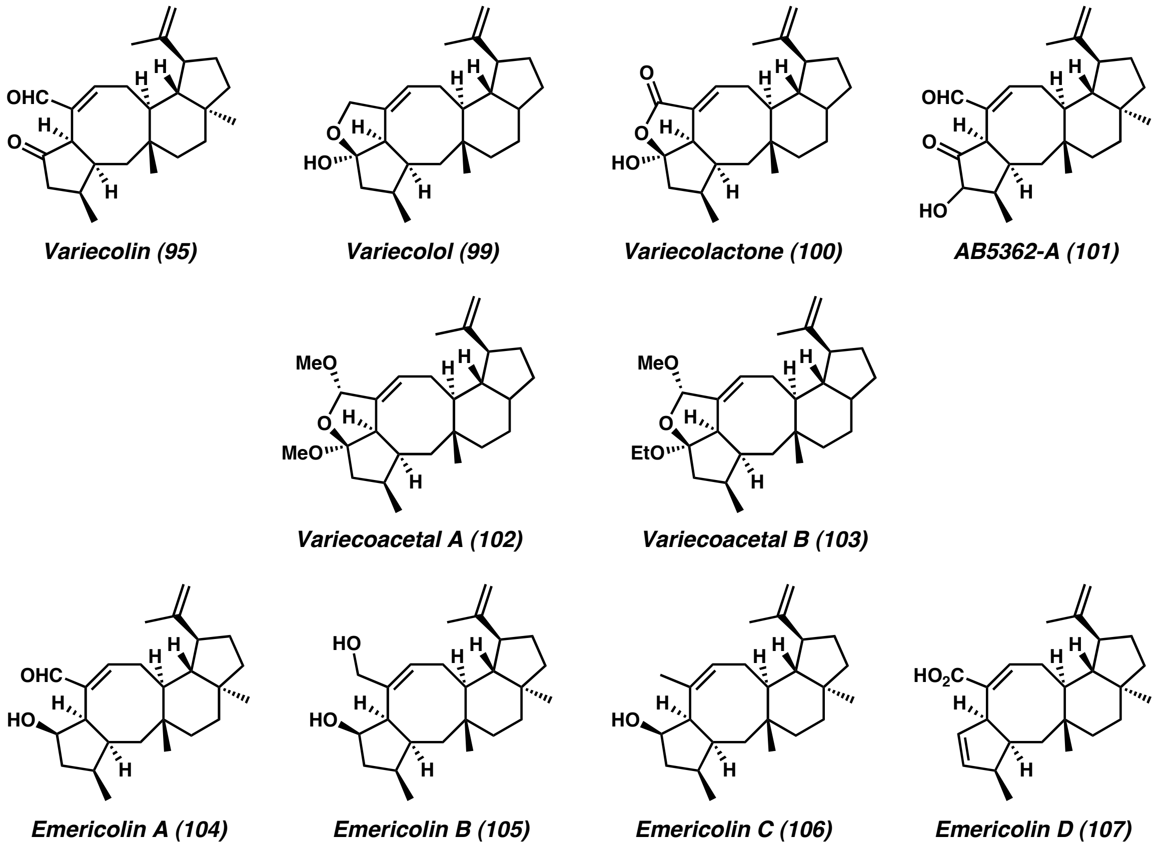
[†] http://www.ibioo.com/picture/microorganism/2009/6888.html

Scheme 2.1.1. Assignment of the absolute configuration of variecolin



In subsequent reports, variecolin (**95**) has been isolated from the related fungi *Emericella purpurea*[6] and *Phoma* sp.[7] Several variecolin congeners (**99–107**, Figure 2.1.2) have also been identified from the aforementioned fungi extracts[3,5–8] and share a common ABCD ring system with identical CD rings and subtle oxidation state variations in the A and B rings. In addition to the structural data of **95**, the absolute stereochemistry of variecolol (**99**) has been confirmed by semisynthesis[3,6b] and the relative stereochemistry of variecolactone (**100**) has been verified by X-ray crystal analysis.[6b] The structural information and origin of isolation for the members of this family suggests the absolute stereochemistry of all related members is that depicted in Figure 2.1.2, and thus based on the revised assignment of variecolin.

Figure 2.1.2. Variecolin family of sesterterpenoids.



Variecolin (95) *Variecolol (99)* *Variecolactone (100)* *AB5362-A (101)*

Variecoacetal A (102) *Variecoacetal B (103)*

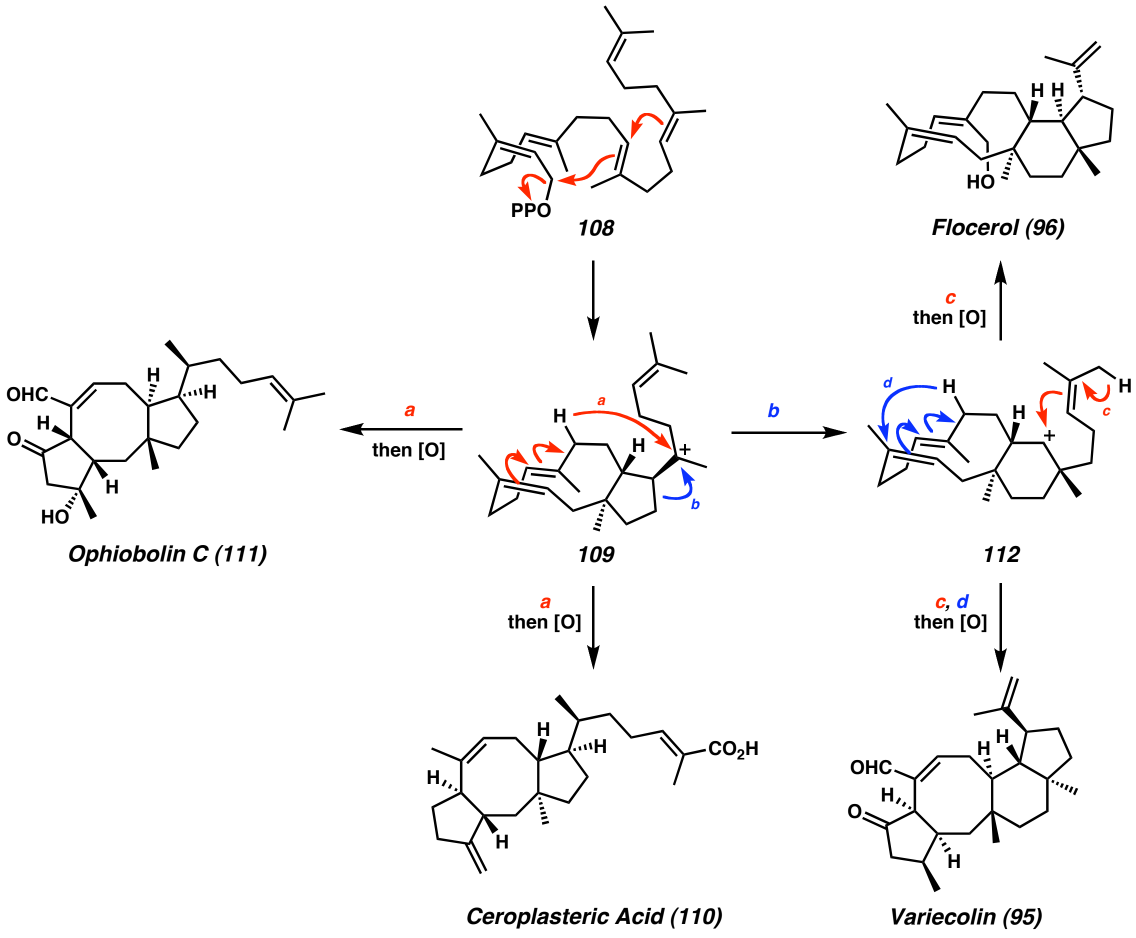
Emericolin A (104) *Emericolin B (105)* *Emericolin C (106)* *Emericolin D (107)*

2.1.2 BIOSYNTHETIC PROPOSAL

A detailed study of the variecolin family sesterterpenoid[2] biosynthesis has not been reported. The authors from the original isolation work surmised that a potential biogenetic link existed between the ophiobolin and ceriferene class of sesterterpenoids, of which variecolin is thought to be descended.[1] Utilizing the reported biosynthetic studies of the ophiobolins[2a] and triterpenoids[9] as a premise, Hensens proposed that the variecolin sesterterpenoids arise from geranylfarnesyl diphosphate (**108**) of the mevalonate biosynthetic pathway. An initial cyclization cascade with displacement of pyrophosphate generates intermediate **109**, which is perceived as a divergent intermediate (Scheme

2.1.2). One potential fate of this intermediate is cyclization concomitant with a hydride shift (path a) and oxidation to generate the ring system of the ophiobolanes ceroplasteric acid (**110**) or ophiobolin C (**111**). Alternatively, a ring-expanding C–C migration (path b) affords ceriferene intermediate **112** that can undergo a cyclization (path c) to afford the flocerol (**96**), or cyclization followed by a H-shift cyclization (paths c and d) to give variecolin (**95**). This unified scheme effectively links all three classes to this divergent intermediate (**109**).[10]

Scheme 2.1.2. Hensens' biosynthetic proposal for variecolin



2.2 BIOLOGICAL ACTIVITY

Variecolin and related sesterterpenes exhibit diverse biological activities. Numerous studies describe the general activity of this family toward a distinct biological target; however, details regarding specificity and mode of action are nonexistent at this time.

2.2.1 ANTIHYPERTENSIVE PROPERTIES

The initial isolation by Hensens indicated variecolin (**95**) as an angiotensin II antagonist that was shown to inhibit ^{125}I-labeled angiotensin II binding in rabbit aortic or bovine adrenal cortical membranes (IC_{50} = 3.6 ±1 μM).[1] Angiotensin II is a blood hormone that acts as a vasoconstrictor that contributes to the pathogenesis of hypertension, cardiovascular disease, and affects water and ion homeostasis in the kidneys.[11] Angiotensin II antagonists have been shown to be effective toward treating hypertension as well as for the prevention of congestive heart failure. Although variecolin has shown modest antagonist activity, inhibition of carbachol-induced inositol phosphate accumulation indicates a possible nonspecific inhibition of the angiotensin response.[1]

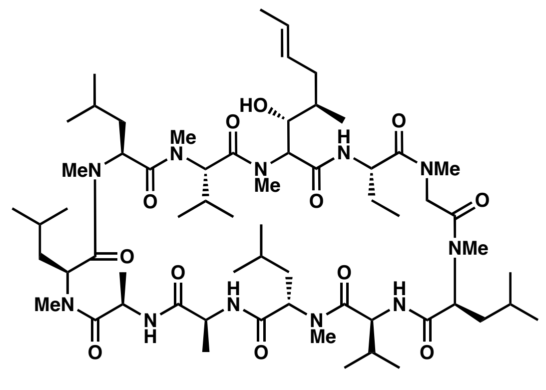
Several years later, a Japanese patent claimed variecolactone (**100**) to be an effective endothelin antagonist that inhibits binding to endothelin A (ET_A, IC_{50} = 0.765 μM) and endothelin B (ET_B, IC_{50} = 0.683 μM) receptors.[8] Endothelin is a potent vasoconstrictor peptide that has similar physiological effects as the angiotensin II peptide.[12] This finding suggests **100** as a potential therapy for hypertension, cardiovascular diseases, cerebrovascular diseases, renal disease, asthma, and pulmonary hypertension.

2.2.2 IMMUNOMODULATORY PROPERTIES

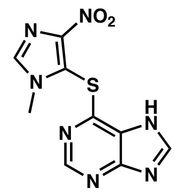
Variecolin and related sesterterpenes have been shown to possess immunosuppressive properties against both humoral (B-cell, LPS-induced) and cell-mediated (T-cell, Con A-induced) proliferations of splenic lymphocytes (Table 2.2.1).[3] Of those examined, variecolin was the most active at suppressing the immune responses, suggesting an important role of the ketone and aldehyde functionalities. The activity compared to other classic immunosuppressants shows comparable data up to the strong binder FK506 (**115**).

Table 2.2.1. Immunosuppressant activity of the variecolin sesterterpenes

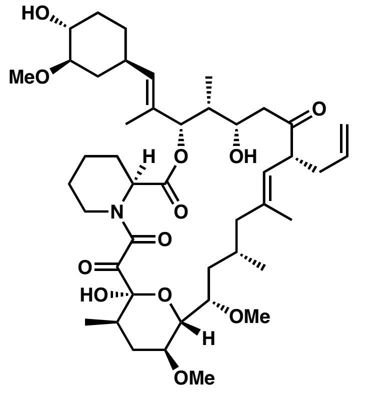
compound	Con A-induced IC_{50} (μg/mL)	LPS-induced IC_{50} (μg/mL)
Variecolin (***95***)	0.4	0.1
Variecolactone (***100***)	8.0	2.5
Variecoacetal A (***102***)	4.5	1.5
Variecoacetal B (***103***)	6.5	2.2
Variecolol (***99***)	1.7	0.6
Azathioprine (***114***)	2.7	2.7
Cyclosporin A (***113***)	0.04	0.07
FK506 (***115***)	1.5×10^{-5}	1.6×10^{-3}



Cyclosporin A (113)



Azathioprine (114)



FK506 (115)

2.2.3 CCR5 ANTAGONIST

Butler and co-workers showed in 2004 that variecolin (**95**) and variecolol (**99**) both compete with macrophage inflammatory protein (MIP)-1α for binding to human CCR5 receptor (IC_{50} = 9 and 32 μM, respectively).[5] Chemokine receptor CCR5 is a key co-receptor involved in the uptake of HIV-1 into target cells.[13] As a result, CCR5 plays a major role in the early transmission of HIV-1, the major cause of AIDS. Observation that the inhibition of CCR5 retards viral uptake while maintaining immune competence suggests this receptor as an emerging target for anti-HIV therapeutics. It should be noted that emericolins A–D (**104–107**) showed no activity toward CCR5, further indicating an important role for the ketone and aldehyde functionalities present in **95**.

2.2.4 ANTIBIOTIC AND ANTIFUNGAL PROPERTIES

A 1998 Japanese patent disclosed the potential antibacterial and antifungal properties of variecolin (**95**), variecolactone (**100**), and AB5362-A (**101**).[7] It was observed that **100** displays 100% antifungal activity at 10 ppm against *Pseudoperonospora cubensis* without damaging a cucumber, highlighting its potential as a herbicide.

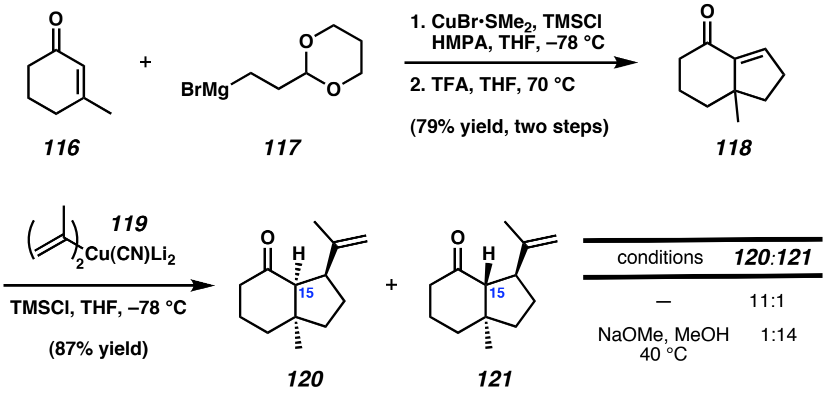
2.3 SYNTHETIC STUDIES TOWARD VARIECOLIN

The variecolin family of sesterterpenes has received only modest attention from the synthetic community in the 18 years since the first discovery of variecolin despite their intriguing structure and biological relevance. At the onset of our studies toward variecolin (**95**), two laboratories have disclosed synthetic efforts en route to this sesterterpenoid. Despite significant progress is this area, these distinct approaches have not yet culminated in the completion of variecolin or any member of this class (Figure 2.1.2).

2.3.1 PIERS' APPROACH TO THE CD RING SYSTEM

In the first report of a synthetic approach toward variecolin, Piers and Boulet demonstrated their key method for the stereoselective generation of the CD ring system.[14] Starting racemic enone **118** was prepared in two steps from 3-methylcyclohexenone (**116**), followed by a diastereoselective conjugate addition of a higher-order 2-propenyl cuprate to afford a mixture of C(15)[15] epimers **120** and **121** (11:1) in 86% yield (Scheme 2.3.1). An important feature of this transformation is the generation of the relative anti stereochemistry of the all-carbon quaternary stereocenter and the newly installed 2-propenyl group. However, the cis stereochemistry of the ring juncture is opposite to that required for variecolin. Thus, a thermodynamic equilibration with NaOMe in methanol facilitated a C(15) epimerization to favor the desired *trans*-fused isomer, **121** (14:1 of **121**:**120**), the bicyclic CD system of which maps on to **95** as well as several other diterpenoids.[14]

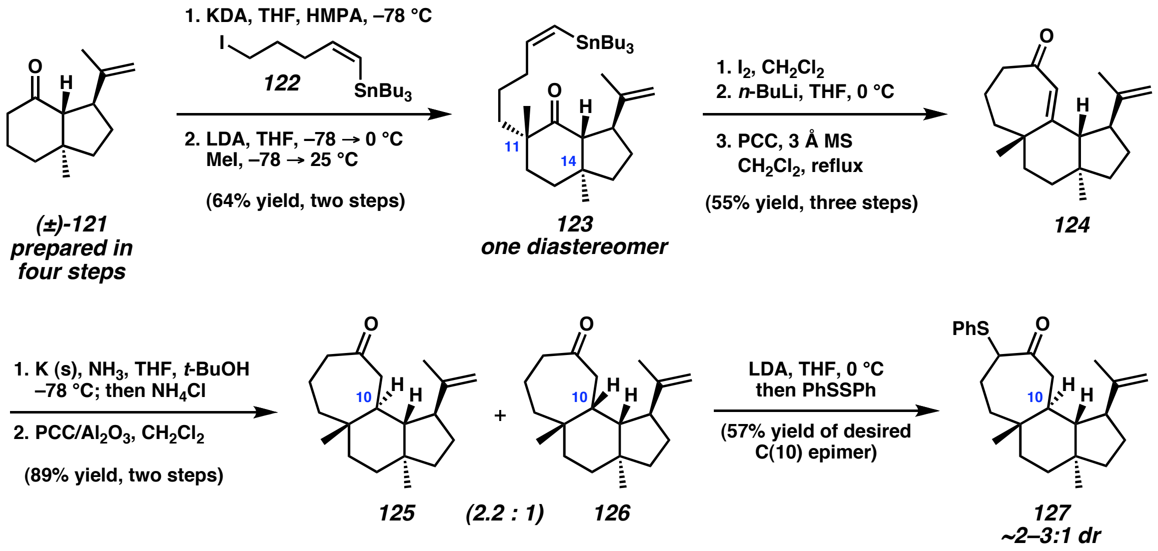
Scheme 2.3.1. Piers' stereoselective CD ring preparation



conditions	**120**:**121**
–	11:1
NaOMe, MeOH 40 °C	1:14

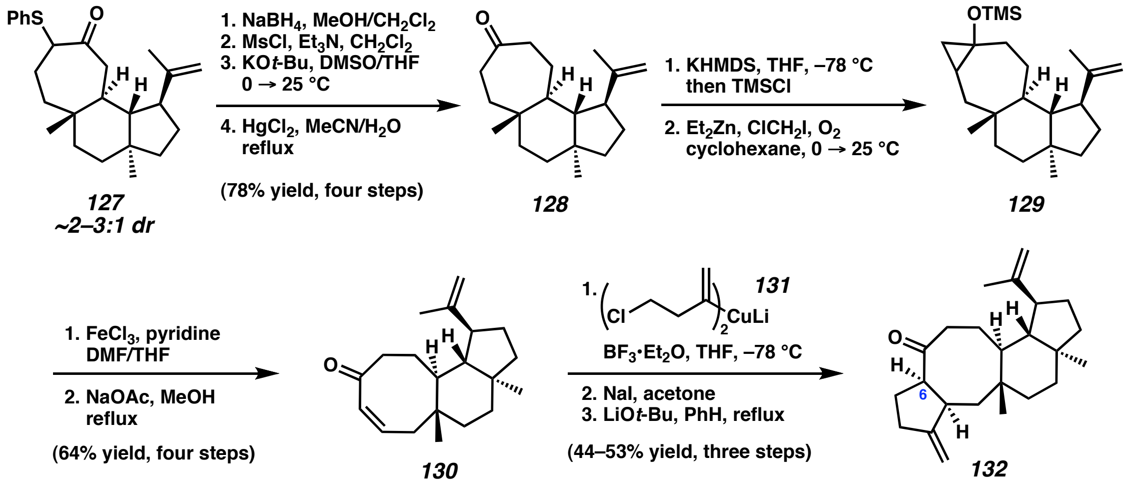
With an effective preparation of this key bicyclic intermediate (**121**), graduate student Shawn Walker explored its utility toward the total synthesis of variecolin.[16] Their devised synthetic strategy employing this intermediate involved the linear, stepwise annulation of the B and A rings on to this key CD ring fragment. Accordingly, sequential alkylation of intermediate (±)-**121** provided ketone **123** as a single diastereomer, possessing the correct relative quaternary stereochemistry at C(11) (Scheme 2.3.2). Functional group interconversion to a vinyl iodide, followed by lithium–halogen exchange with carbonyl addition, then a PCC-mediated allylic alcohol transposition with oxidation afforded the annulated tricycle **124**. The stereochemistry at C(10) was achieved via Birch reduction of this cycloheptenone (**124**) using potassium in ammonia, moderately favoring the desired C(10) epimer **125** as a 2.2:1 mixture of inseparable isomers (**125**:**126**). Further transformation via α-functionalization of the carbonyl with diphenyldisulfide afforded separable compounds at the C(10) stereocenter to provide **127** in modest yield.

Scheme 2.3.2. Piers' annulation of the B ring



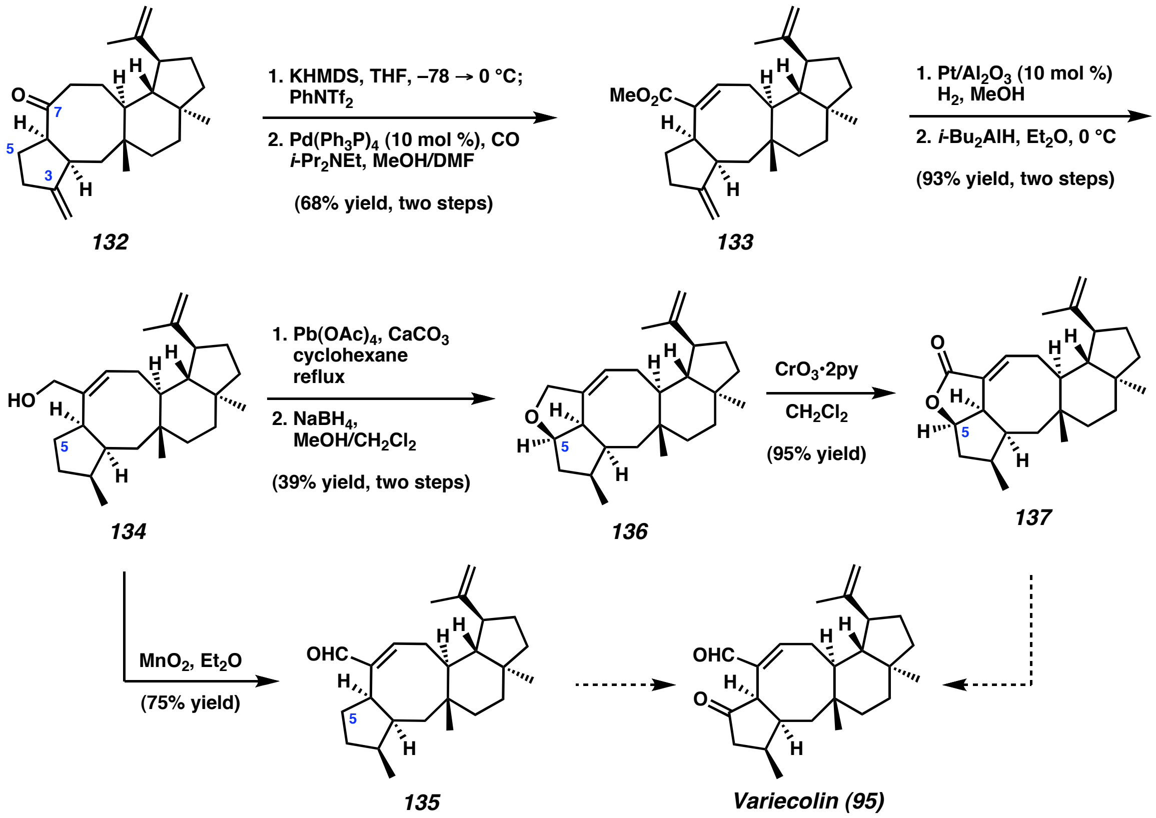
Carbonyl transposition of **127** over four steps provided ketone **128** which was then utilized for a one-carbon ring expansion via a cyclopropanation–cleavage sequence (Scheme 2.3.3). Ketone enolization and cyclopropanation afforded **129**, which upon $FeCl_3$-mediated radical cleavage followed by β-chloro elimination completed the B-ring expansion to generate cyclooctenone **130** in 64% yield over four steps. With the BCD carbocyclic skeleton in place, annulation of the final A ring was accomplished utilizing a bifunctional cuprate reagent (**131**), first to achieve the conjugate 1,4-addition, succeeded by an alkylation event (i.e., **130** → **132**). The C(6) stereocenter readily epimerized during the final alkylation event and, consequently, modest conversions employing LiO*t*-Bu were necessary to overcome this difficulty. Importantly, the preparation of tetracycle **132** comprised the complete ABCD ring structure of variecolin.

Scheme 2.3.3. Completion of the ABCD tetracycle via A-ring annulation



The remaining transformations toward completion of variecolin involved the functionalization of the A and B rings. Accordingly, conversion of ketone **132** to an enol triflate and palladium-catalyzed carbonylation generated ester **133** (Scheme 2.3.4). This trisolefin intermediate was then chemo- and stereoselectively hydrogenated at C(3), followed by ester reduction to form (±)-5-deoxyemericolin B (**134**). Allylic oxidation using MnO_2 provided (±)-deoxyemericolin A (**135**), whereas oxidation using $Pb(OAc)_4$ afforded (±)-5-deoxyvariecolol (**136**). Further oxidation using Collins reagent gave (±)-5-deoxyvariecolactone (**137**).

Scheme 2.3.4. Piers' end game progress toward completion of variecolin

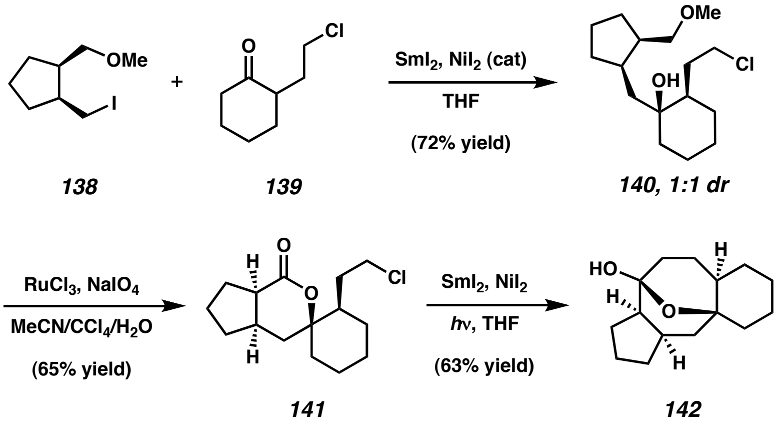


The preparation of highly advanced deoxy analogues of variecolin and related sesterterpenes set the stage for further C(5) oxidation and completion of the targets, although "material constraints" have hindered this progress. Indeed, this synthetic sequence is highly linear, requiring 28 steps for the longest linear sequence. The incorporation of the central eight-membered B ring is tedious, requiring 12 steps to achieve a one-carbon ring expansion. An issue yet to be addressed is the incorporation of asymmetry, which would have to occur at the beginning of the synthesis due to linearity.[17] Nonetheless, Piers' impressive synthetic effort has highlighted various reactivity and selectivity features of this system and enabled the preparation of highly advanced intermediates.

2.3.2 MOLANDER'S APPROACH TO THE B RING

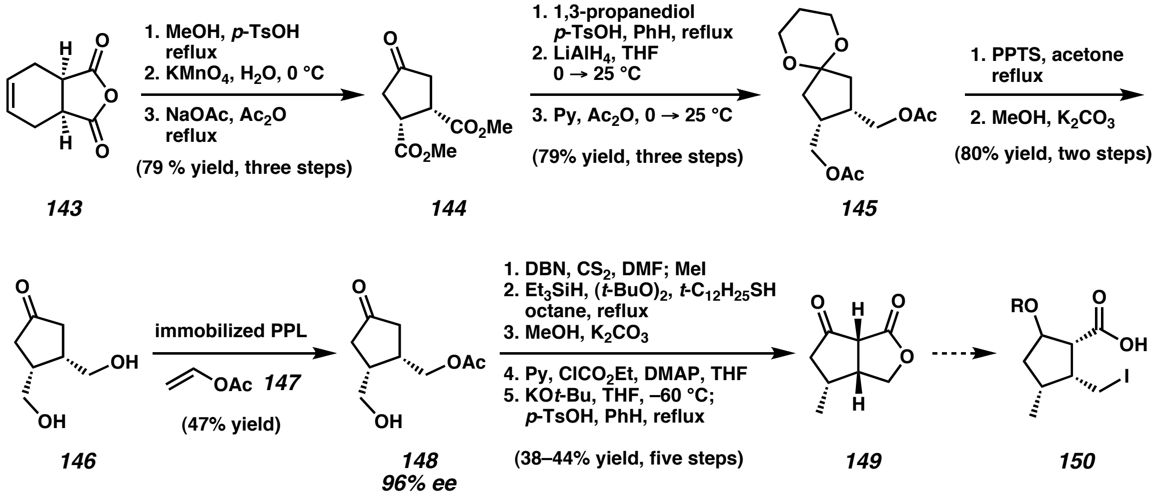
The Molander laboratory disclosed a samarium(II) iodide-promoted annulative approach toward variecolin in 2001.[18] This strategy was derived from previous work in their laboratory delineating SmI_2-promoted sequential reactions for the rapid and stereoselective construction of medium-sized carbocycles.[19] A model system was devised to rapidly explore a carbonyl addition–nucleophilic acyl substitution reaction en route to the carbocyclic core of variecolin. The samarium(II) iodide-promoted intermolecular Barbier reaction of ketochloride **139** and alkyl iodide **138** furnished chloroalcohol **140** (Scheme 2.3.5). Oxidation of the methyl ether moiety with concomitant lactonization gave spirocyclic lactone **141**, a substrate for the intramolecular nucleophilic acyl substitution reaction studies. The samarium(II) iodide-promoted reductive cyclization occurred under photochemical conditions to generate **142**, which possesses the ABC carbocyclic core of variecolin.

Scheme 2.3.5. Samarium(II) iodide-promoted medium ring synthesis



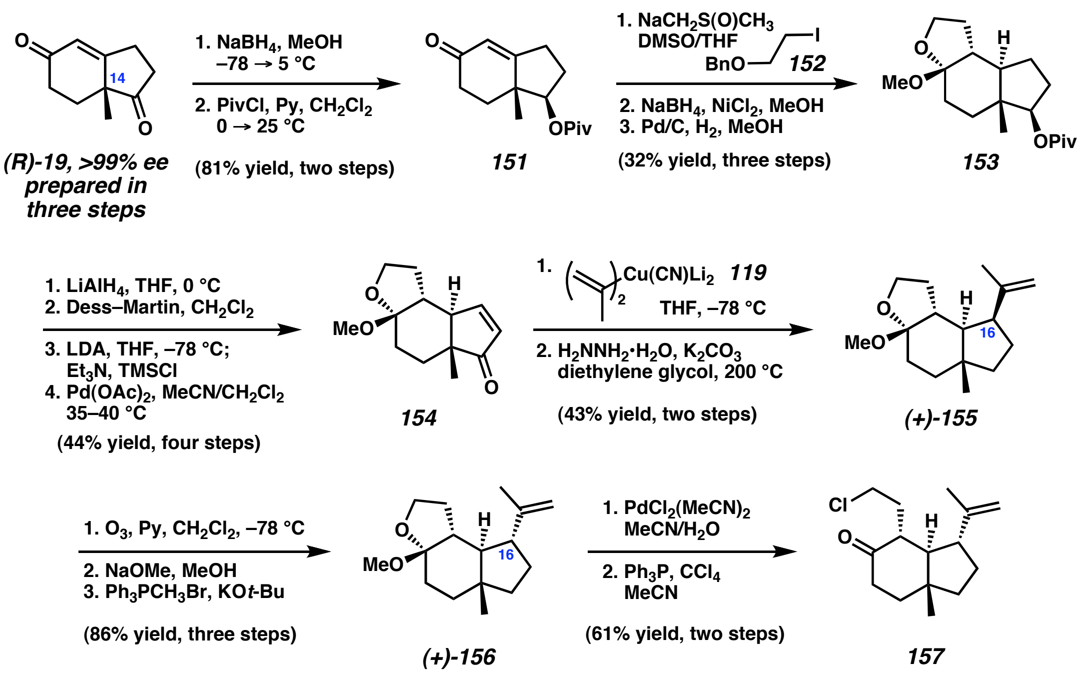
With a viable strategy in hand, Molander and co-workers pursued enantioselective syntheses of suitable A- and CD ring fragments to explore their key sequential samarium-promoted coupling toward *ent*-**95**.[20] Accordingly, the A-ring fragment was asymmetrically synthesized from *meso*-diol **146**, which was prepared in eight steps from tetrahydrophthalic anhydride (**143**, Scheme 2.3.6). Acidic methanolysis of **143**, oxidative olefin cleavage and intramolecular Dieckmann cyclization with decarboxylation generated *meso*-cyclopentanone **144**. Ketone protection, ester reduction and exposure to Ac_2O afforded protected *meso*-bisacetate **145**, upon which all protecting groups were cleaved to form *meso*-diol **146** (50% yield over eight steps). Enzymatic desymmetrization via acylation produced monoacetate **148** in 47% yield and 96% ee, which was elaborated to β-ketolactone **149** over five steps. Advancement of this material toward an intermediate analogous to **150**, what would be suitable for the key samarium coupling, was not described.

Scheme 2.3.6. Molander's first-generation synthesis of A-ring fragment



The targeted CD ring fragment was prepared from Hajos–Parrish ketone (*R*)-**19**, which is readily available in >99% ee (Scheme 2.3.7). Stereoselective ketone reduction and protection as a pivalate ester generated **151**. α-Alkylation of this intermediate with iodide **152** was achieved from the thermodynamic enolate of enone **151** using sodium dimsylate, and subsequent stereoselective 1,4-reduction and benzyl cleavage steps provided acetal **153**. This material was advanced to enone **155** in four steps to set the stage for a diastereoselective 2-propenyl cuprate (**119**) addition followed a Wolff–Kishner reduction to afford acetal (+)-**155**, albeit in modest yield with the undesired C(16) stereochemistry.[15] This was rectified with a three-step ozonolysis, epimerization, and Wittig olefination sequence to provide thermodynamic product (+)-**156**. Acetal cleavage and conversion to an alkyl chloride gave desired intermediate **157**. These efforts have demonstrated enantioselective approaches to A-ring fragment **149** and CD ring fragment **157**, although details of the potential samarium-promoted coupling and further functionalization toward variecolin were not described.

Scheme 2.3.7. Molander's first-generation synthesis of a CD ring fragment



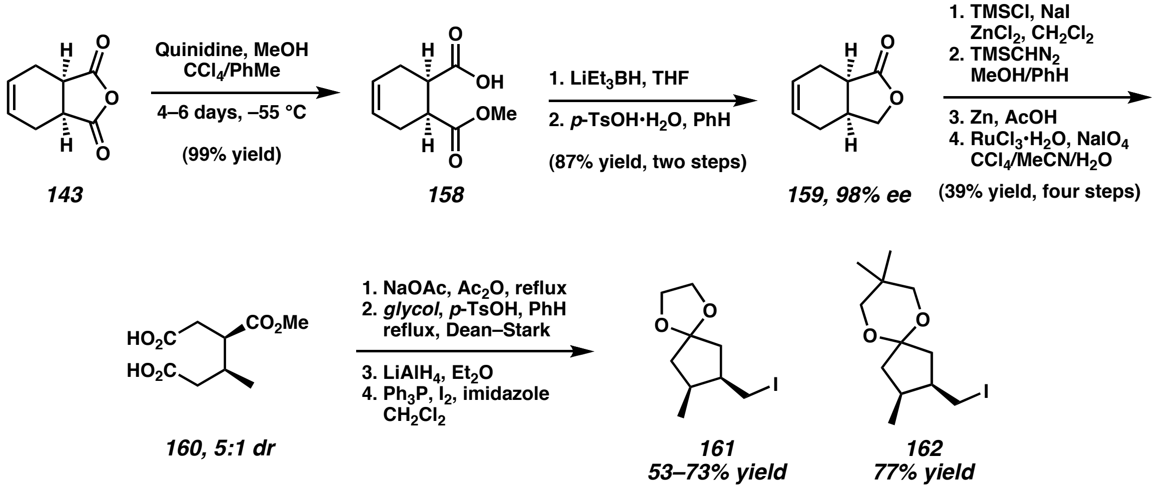
2.3.3 MOLANDER'S SECOND-GENERATION APPROACH

Graduate student Kelly George of the Molander laboratory disclosed a second-generation approach to variecolin in 2005.[21] The overall synthetic strategy incorporating the key sequential samarium coupling remained the same. However, the synthetic sequences to the A- and CD ring fragments were improved and coupling studies were explored.

The revised stereoselective synthesis of a viable A-ring fragment began with the asymmetric desymmetrization of *meso*-anhydride **143** with quinidine to produce monoacid **158** in 99% yield (Scheme 2.3.8). Chemoselective ester reduction and cyclization provided γ-lactone **159** in 98% ee and 87% yield over two steps. Lactone functionalization and olefin oxidative cleavage over four steps afforded acyclic diacid

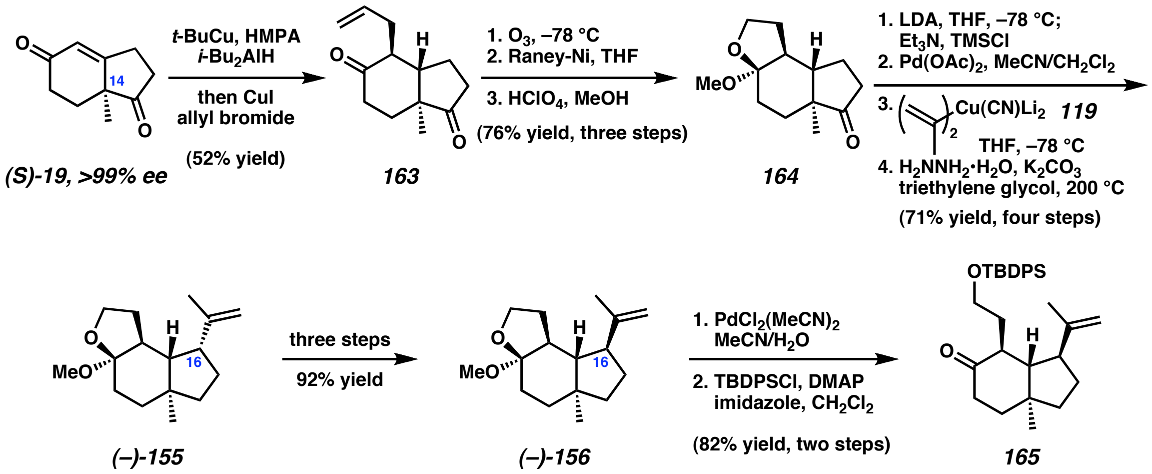
160 which was transformed into iodides **161** and **162** in good overall yield (four steps). This reaction sequence provided the A-ring intermediates in 11 steps, a marked improvement over the previous generation synthesis (>14 steps).[22]

Scheme 2.3.8. Molander's revised A-ring synthesis



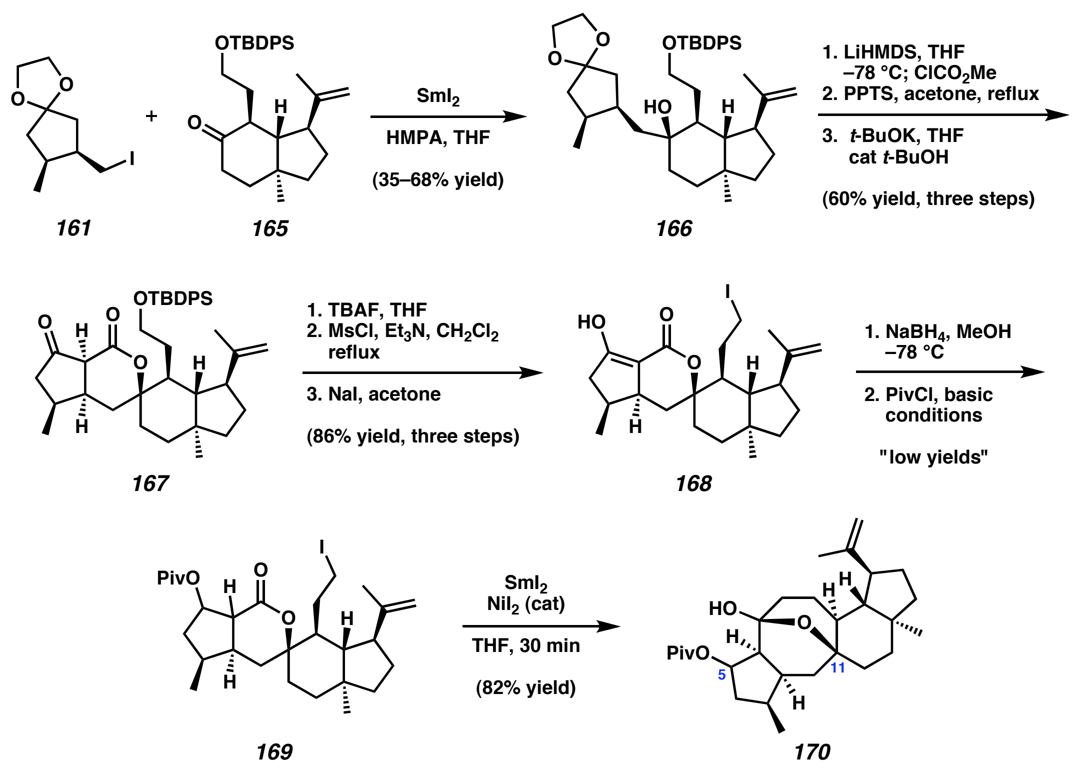
Molander's revised approach to the CD ring proceeded from the correct enantiomer of the Hajos–Parrish ketone ((*S*)-**19**) (Scheme 2.3.9). Enone reduction with copper hydride and diastereoselective allylation of the resulting enolate furnished allyl ketone **163**. Oxidative cleavage of the allyl group, aldehyde reduction and acetylization gave acetal **164**. Typical D-ring functionalization installed the C(16) 2-propenyl moiety in the wrong configuration ((–)-**155**). This was advanced to acetal (–)-**156** by a similar three-step sequence as above (cf. Scheme 2.3.7) to achieve the correct C(16) stereochemistry, and acetal cleavage with alcohol protection provided a suitable coupling partner (**165**). The revised CD ring fragment synthesis was accomplished in 14 steps, a modest improvement over the previous 16-step sequence.

Scheme 2.3.9. Molander's revised CD ring synthesis



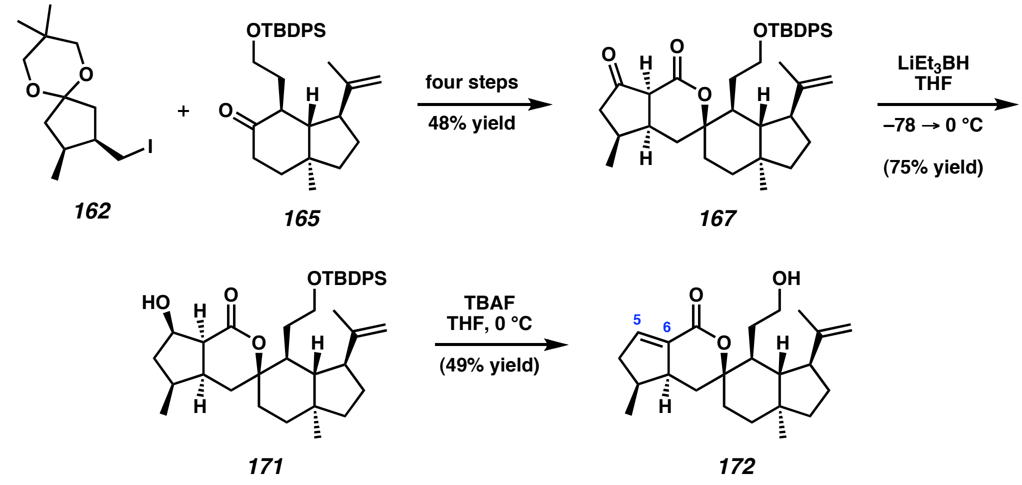
The development of scalable asymmetric syntheses of both the A- and CD ring fragments enabled the exploration of the samarium-promoted coupling strategy. In the event, the intermolecular samarium-promoted Barbier coupling of iodide **161** and chloroketone **165** generated intermediate **166** in variable yields (Scheme 2.3.10). This material was advanced to β-ketolactone **167** over three steps. Silyl cleavage and alcohol conversion to an alkyl iodide afforded **168**; however, the β-ketoester moiety existed in the enolized form removing the C(6) stereochemistry. Ketone reduction and protection as a pivalate under various conditions provided iodolactone **169** in low yields. In the key reaction, it was found that the samarium-promoted intramolecular nucleophilic acyl substitution of this iodolactone proceeded efficiently, constructing **170** in 82% yield. While this method successfully generated the ABCD carbocyclic core of variecolin, low and variable yields as well as C(5) stereochemical issues hampered further progress.

Scheme 2.3.10. Molander's Sm(II)-promoted fragment coupling studies



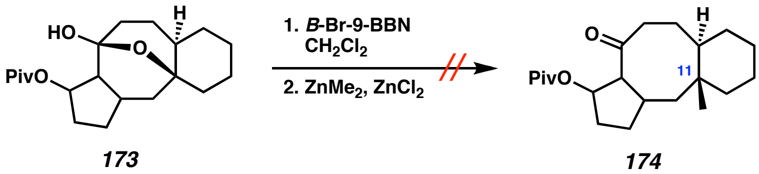
To overcome these difficulties, Molander and co-workers investigated a revised reaction sequence altering the order of operations. The new route involved the samarium-promoted coupling of iodide **162** and ketone **165** over four steps to produce β-ketoester **167** in 48% yield (Scheme 2.3.11). Importantly, the revised A-ring ketone protecting group and modified reaction conditions improved yields and minimized the troublesome C(6) enolization. Diastereoselective ketone reduction with super hydride produced β-hydroxyketone **171** and subsequent fluoride-mediated silyl cleavage resulted in β-hydroxy elimination to form α,β-unsaturated lactone **172**, removing the C(5) and C(6) stereocenters. Efforts to circumvent this problem have not been described.

Scheme 2.3.11. Alternate Sm(II)-promoted fragment coupling studies



The progress of Molander and co-workers toward variecolin appears to have stalled at this intermediate (**172**). The apparent difficulties observed with this sequential samarium-promoted coupling strategy seem to be involved with the order of chemical operations on sensitive intermediates as well as lengthy preparations of these intermediates. In addition to these issues, the strategy necessitates the late installation of the C(11) all-carbon quaternary stereocenter after the final intramolecular nucleophilic acyl substitution reaction. However, model system studies to forge this bond by reported methods[23] resulted with intractable mixtures and no quaternary stereocenter formation (Scheme 2.3.12). Thus, the strategy must be further revised to incorporate this stereocenter at an earlier intermediate via a separate method, which would obviate the designed sequential samarium couplings.

Scheme 2.3.12. Molander's attempted installation of the C(11) quaternary stereocenter



2.4 CONCLUSION

The variecolin sesterterpenes are a structurally complex and biologically active class of natural products isolated from various fungal sources. Biological investigations of this family have indicated anti-HIV, antihypertension, immunomodulatory, and antibacterial properties. The extraordinary tetracyclic core defined by a central eight-membered ring with a high degree of stereocomplexity has inspired valiant synthetic efforts from the Piers and Molander laboratories. These unique approaches to variecolin highlight various stereochemical and functional group attributes for this unusual system. Despite significant progress in this area, completion of variecolin or any of its congeners has yet to be reported.

2.5 NOTES AND REFERENCES

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(2) For reviews of sesterterpenoids, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123–132. (b) Hanson, J. R. *Nat. Prod. Rep.* **1992**, *9*, 481–489. (c) Hanson, J. R. *Nat. Prod. Rep.* **1996**, *13*, 529–535. (d) Liu, Y.; Wang, L.; Jung, J. H.; Zhang, S. *Nat. Prod. Rep.* **2007**, *24*, 1401–1429.

(3) Fujimoto, H.; Nakamura, E.; Okuyama, E.; Ishibashi, M. *Chem. Pharm. Bull.* **2000**, *48*, 1436–1441.

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