

## CHAPTER FOUR

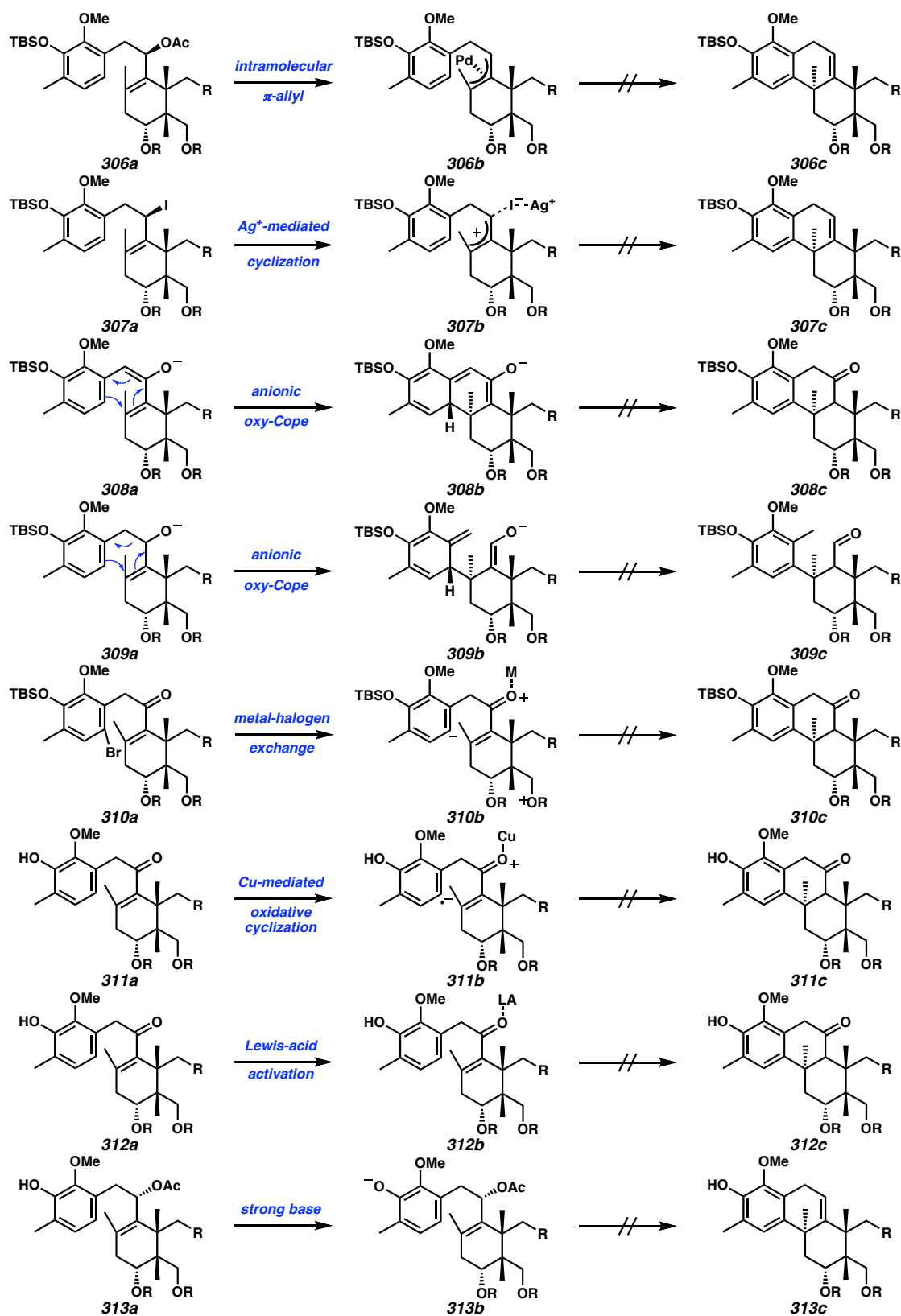
Radical Cyclization Approaches Toward  
the Tricyclic Core of Zoanthanol<sup>†</sup>

## 4.1.1 Introduction

The acid-mediated cyclization chemistry detailed in Chapter 3 is a powerful method for the formation of the carbocyclic core of zoanthanol. Unfortunately, the utility of these cyclizations is limited by the sensitivity of the system to the substrate, the harsh conditions required, and the loss of functionality during cyclization. With these issues in mind, other strategies were explored to form the B ring from the available tethered A–C ring systems. Among these, several methods displayed no reactivity for the tested substrates (Scheme 4.1.1). Such cyclization methods included intramolecular  $\pi$ -allyl reactions<sup>1</sup> of allylic acetates (**306a**  $\rightarrow$  **306b**  $\rightarrow$  **306c**), reductive Heck reactions of enones, silver-mediated cyclizations of allylic iodides (**307a**  $\rightarrow$  **307b**  $\rightarrow$  **307c**), anionic oxy-Cope electrocyclizations<sup>2</sup> of enones (**308a**  $\rightarrow$  **308b**  $\rightarrow$  **308c**) or allylic alcohols (**309a**  $\rightarrow$  **309b**  $\rightarrow$  **309c**), aryl anion additions (**310a**  $\rightarrow$  **310b**  $\rightarrow$  **310c**), Lewis-acid enone activation (**311a**  $\rightarrow$  **311b**  $\rightarrow$  **311c**), copper-mediated arene/enone oxidative cyclizations<sup>3</sup> (**312a**  $\rightarrow$  **312b**  $\rightarrow$  **312c**), and strong base-mediated cyclization of allylic acetates (**313a**  $\rightarrow$  **313b**  $\rightarrow$  **313c**).

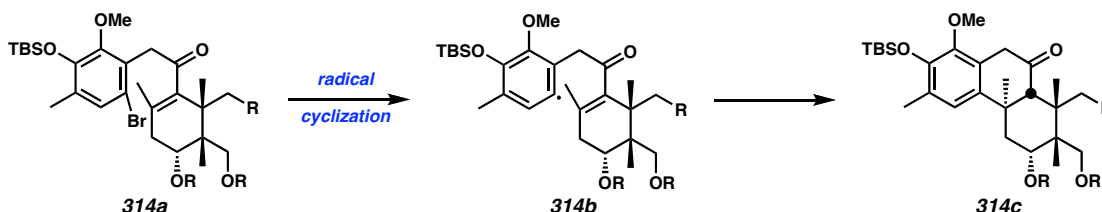
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<sup>†</sup> This work was conducted in close collaboration with Dr. Douglas C. Behenna, a former graduate student in the Stoltz Group.



**Scheme 4.1.1** Failed methods for cyclization of tethered A–C ring systems.

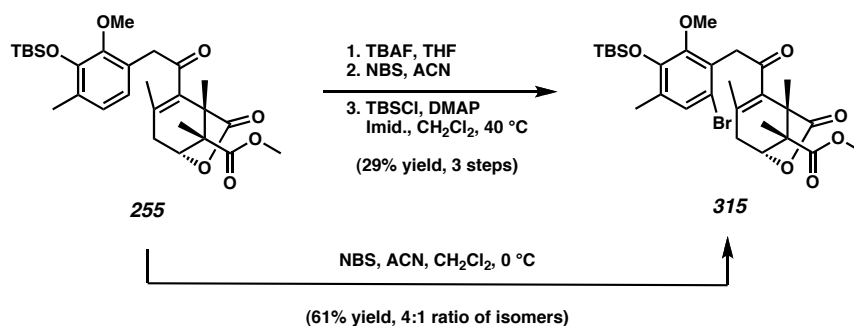
However, one cyclization method held some promise: the conjugate radical addition of an aryl radical to our enone substrates (Scheme 4.1.2). Although this type of reaction has substantial precedence, *endo* radical conjugate addition cyclization reactions are much less common than *exo* reactions.<sup>4</sup> However, we were inspired by a report of an arene radical conjugate addition that built a quaternary center while closing a six-membered ring.<sup>5</sup> In this chapter, we detail efforts toward the application of radical conjugate additions for the synthesis of zoanthanol's tricyclic core.



**Scheme 4.1.2** Radical-induced cyclization of a tethered A–C ring system.

#### 4.2.1 Synthesis and Cyclization of a Lactone-Derived Precursor

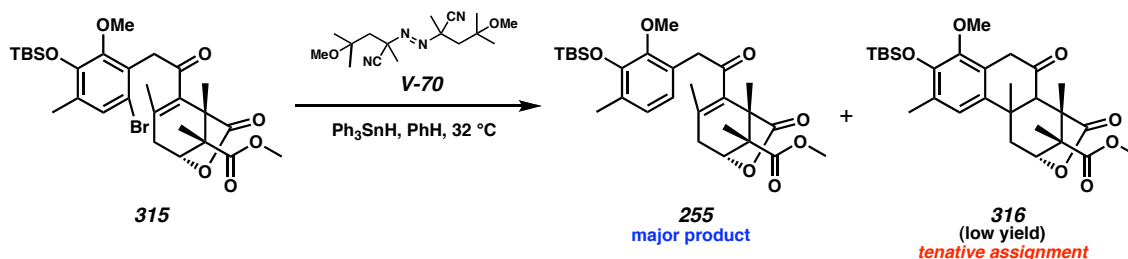
The radical cyclization substrate required a selective bromination of the A ring *para* to the silyl ether. While bromination with *N*-bromosuccinimide (NBS) was well known to occur *para* to electron releasing groups,<sup>6</sup> there was little precedent for *para*-directing preference of silyl ethers versus methyl ethers. There was significant evidence that phenols were superior to methyl ethers in their directing ability.<sup>7</sup> Thus, we began by executing a selective synthesis of the desired aryl bromide over three steps (Scheme 4.2.1). Desilylation of **255** provided a phenol, which was treated with NBS in acetonitrile to afford a single bromide isomer. Resilylation provided **315** in 29% yield over the three steps.<sup>8</sup> Subsequently, direct bromination of enone **255** led to a 4:1 mixture of bromide positional isomers favoring the desired aryl bromide.



**Scheme 4.2.1** Synthesis of lactone-derived radical cyclization precursor

We initially tested a number of conditions for cyclization. The most effective conditions employed V-70 initiator in benzene at 32 °C with triphenyltin hydride. The V-70 initiator decomposes more readily ( $t_{1/2} = \sim 10$  h at 30 °C) than AIBN ( $t_{1/2} = \sim 10$  h at 80 °C), and it enables initiation of the radical reaction at lower temperatures. Additionally, the lower temperature reduces the amount of debrominated enone recovered. For all substrates tested, these are the conditions used.

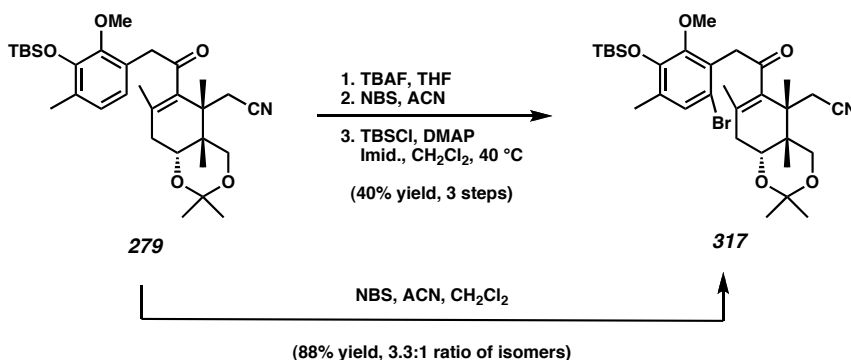
Treatment of aryl bromide **315** led to the formation of a 1:1 mixture of two diastereomers of cyclized product **316** as well as reisolation of debrominated precursor **255**. This result was very promising, but we were only able to isolate small amounts of the cyclized material, which was produced as a 1:1 ratio of diastereomers. Thus, we ventured forward to explore cyclizations of more synthetically advanced A–C ring systems.



**Scheme 4.2.2** Attempted cyclization of lactone-derived A–C ring system

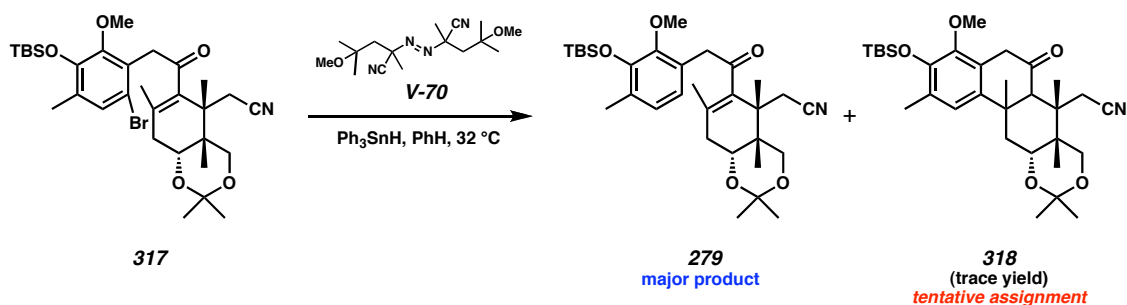
#### 4.3.1 Synthesis and Cyclization of a Homologated Nitrile-Derived Cyclization Precursor

Having established the selectivity of the bromination for arene **313**, it was anticipated that similar bromination selectivity would allow preparation of the desired bromide isomer. Nevertheless, an independent synthesis of **317** was conducted as confirmation for the product assignments. Accordingly, enone **279** was desilylated with TBAF, treated with NBS in acetonitrile and methylene chloride, and finally resilylated to afford a cyclization precursor **317** in 40% yield over the three steps (Scheme 4.3.1). The one-step procedure was accomplished by treating enone **279** with NBS in acetonitrile at ambient temperature and led to the formation of a favorable 3.3:1 mixture of bromide isomers in 88% combined yield.



**Scheme 4.3.1** Synthesis of homologated nitrile-derived radical cyclization precursor.

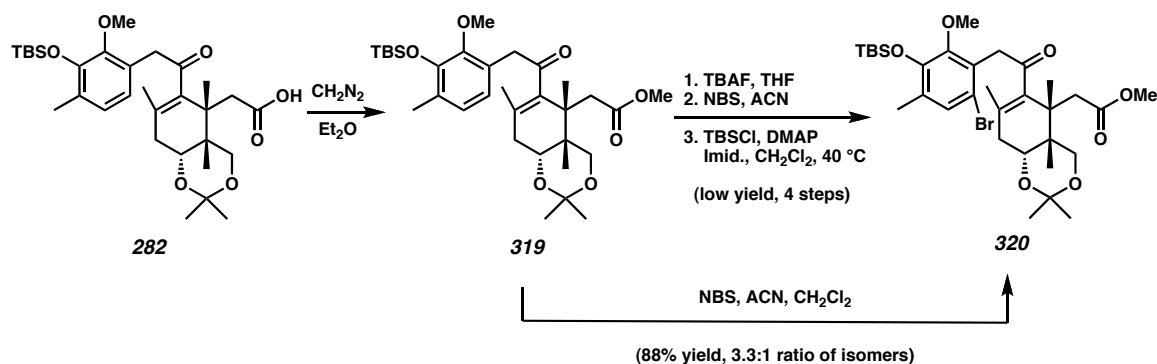
Treatment of cyclization precursor **317** with the standard cyclization conditions once again yielded mainly reductive debromination product **279** (Scheme 4.3.2). However, we were also able to obtain spectra for what appeared to be two diastereomers of cyclized products, tentatively assigned as a 1:1 mixture of diastereomers of **318**.



**Scheme 4.3.2** Attempted cyclization of nitrile-derived A–C ring system.

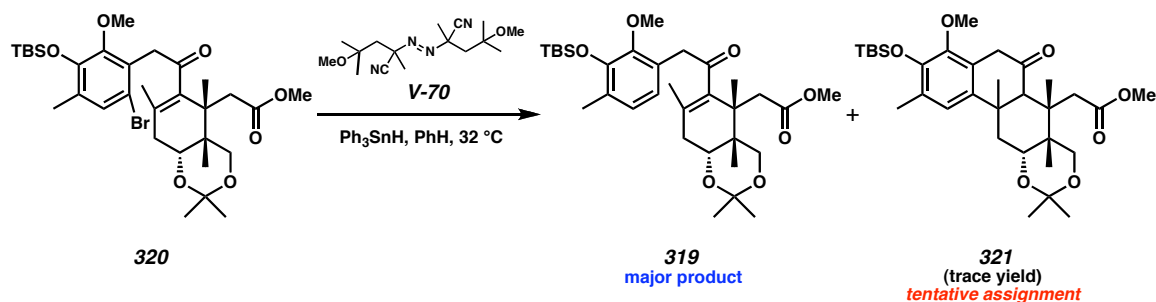
#### 4.4.1 Synthesis and Cyclization of a Homologated Ester-Derived Cyclization Precursor

Owing to concerns that the nitrile moiety was interfering with the cyclization, the corresponding methyl ester-derived substrate was targeted. Thus, carboxylic acid **282**<sup>9</sup> was treated with diazomethane to afford the corresponding ester, **319** (Scheme 4.4.1). Desilylation, bromination, and resilylation afforded aryl bromide **320** in < 20% overall yield.<sup>10</sup> In the one-step procedure, bromination of methyl ester **319** led directly to 88% yield of radical cyclization precursor **320** in a 3.3:1 dr.



**Scheme 4.4.1** Synthesis of homologated ester-derived radical cyclization precursor.

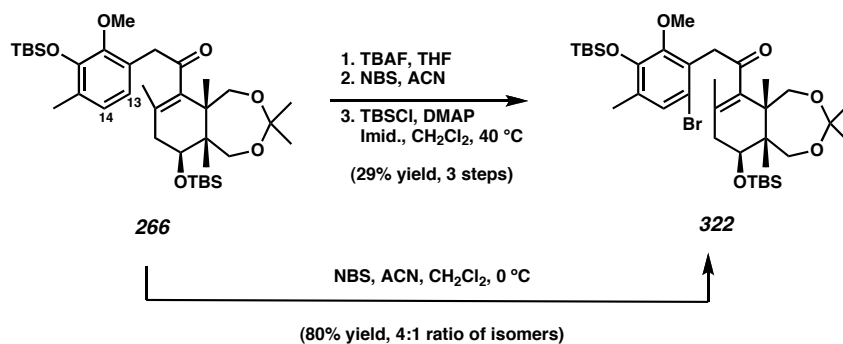
Aryl bromide **320** was subjected to the radical cyclization conditions to afford trace amounts of a mixture of diastereomeric cyclized products as well as a substantial amount of enone **319** (Scheme 4.4.2).



**Scheme 4.4.2** Attempted cyclization of ester-derived A–C ring system.

#### 4.5.1 Synthesis and Cyclization of a 7-Membered Acetal-Derived Cyclization Precursor

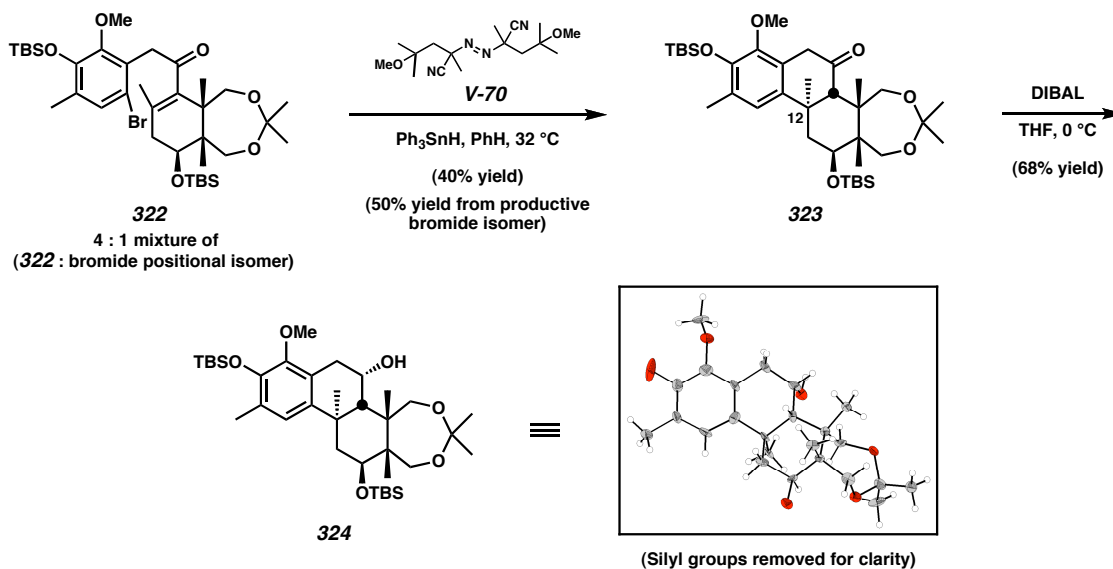
To this point, the C(10) oxygen functionality of all substrates tested was  $\alpha$ -disposed. These substrates were initially targeted due to their bicyclic nature, with the expectation that this would bias the formation of the desired stereochemistry at the new quaternary center. To explore the impact of the C(10) stereocenter, we assembled the aryl bromide derivative of enone **266**. Direct bromination afforded a 4:1 mixture of isomers in 80% yield, while the three-step procedure confirmed the identity of the major product with a 29% yield of **322** over the 3 steps (Scheme 4.5.1).<sup>8</sup>



**Scheme 4.5.1** Synthesis of 7-membered acetal-derived radical cyclization precursor.

Aryl bromide **322** was treated under the standard cyclization conditions. Much to our delight, significant amounts of cyclization product **323** were observed (Scheme 4.5.2). As in other cyclization attempts, debrominated enone **266** was also obtained. The relative stereochemistry at the newly formed stereocenter was confirmed by X-ray

structure analysis of alcohol **324**, obtained by DIBAL reduction of **323**.<sup>11</sup> While the yield of ketone **323** was modest, many reaction parameters remain to be optimized, such as amounts of reagents, temperature, and rate of triphenyltin hydride addition, as well as the possibility of activating the system further by employing Lewis acids.<sup>12</sup>

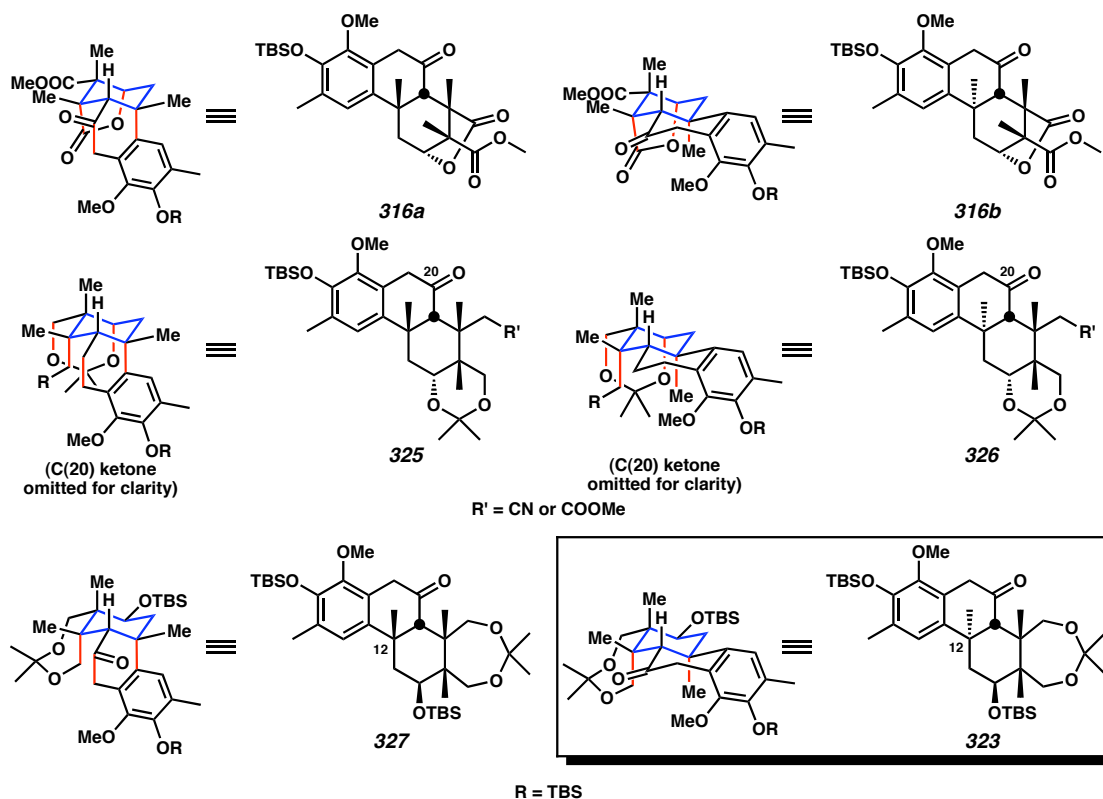


**Scheme 4.5.2** Cyclization of 7-membered acetal-derived A–C ring system.

#### 4.6.1 Substrate Requirements and Limits of System

Radical cyclizations of aryl bromides **315**, **317**, and **320** lead primarily to reductive debromination as well as trace yields of cyclized products as mixtures of diastereomers at C(12). However, in the case of aryl bromide **322**, the desired diastereomer was isolated as the exclusive cyclized product. Although all of the substrates tested possess a bicyclic framework, the facial bias provided by the 6-7 bicycle in aryl bromide **324** is expected to be the least substantial. Additionally, this system is the most structurally flexible. Thus, the observed selectivity must be derived from a different feature of the 7-membered acetal substrate. Analysis of the two most likely product structures for each case provided insight into the selectivity of the transformation. Scheme 4.6.1 outlines the key 1,3-diaxial interactions experienced by each product. In accessing the desired

diastereomer, a minimal number of destabilizing interactions are formed. In all cases, the desired diastereomer (**316b**, **326**, and **323**) exhibits one fewer diaxial interaction than the alternative diastereomer. Additionally, **316b** and **326** possess one and two additional diaxial interactions, respectively, when compared with **323**. It is reasonable to assume that, at the reaction temperature (32 °C), the additional destabilizing energy imparted by an extra diaxial interaction is sufficient to guide selectivity toward the desired case for **323** versus **327** or to almost completely prevent reactivity in the more hindered cases (**316a**, **316b**, **325**, and **326**). All of these arguments are dependent on the 6-membered ring depicted in blue occupying the chair conformation shown. For the lactone and 6-membered acetonide substrates, this conformation is locked by the bicycle. However, in the 7-membered acetal substrate, there is more conformational flexibility, and it is the equatorial disposition of the C(10) alcohol that favors the chair conformation illustrated below.

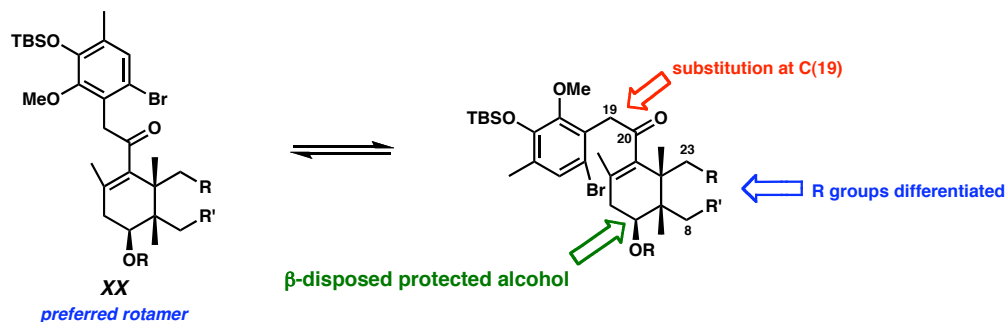


**Scheme 4.6.1** 3D representations of cyclization products. (1,3-Diaxial interactions are depicted in red.)

In addition to these considerations, it is important to note that the major non-productive pathway in these cyclizations is reductive debromination. We hypothesize that this by-product is observed in such high quantities because of the slow rotation about the C(19)-C(20) bond (Figure 4.6.2), combined with a strong conformational preference for the substrate to orient itself in a more linear arrangement to reduce steric interactions. One possibility to improve the outcome of the reaction is to functionalize the molecule at C(19) with the goal of decreasing the energetic advantage of occupying the linear conformation relative to the reactive conformation.<sup>13,14</sup>

Any future substrates should possess substitution at C(19) to increase the reactivity. Owing to the harsh conditions required in other systems for the differentiation and homologation of C(23) and C(8), these groups should be differentiated and, ideally, homologated. Finally, the alcohol functionality at C(10) should be  $\beta$ -disposed. This

substituent will occupy the equatorial position, thus setting the preferred chair conformation and enabling the selectivity arguments presented above to occur as expected.



**Scheme 4.6.2** Structural requirements for future radical cyclization products.

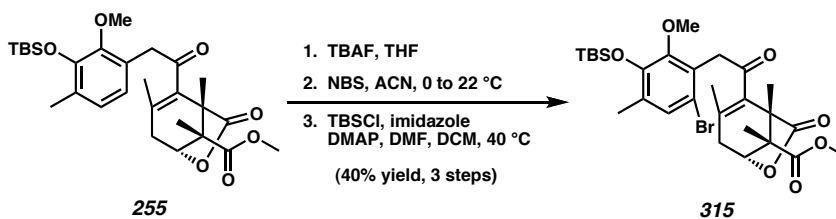
#### 4.7.1 Summary

In summary, we believe that this radical cyclization strategy provides a novel, functional group tolerant method to form the key C(12) quaternary stereocenter and to close the B ring. Although cyclization products are observed in all cases, substantial amounts of the product are only isolable in the case of the 7-membered acetal-derived substrate (**322**  $\rightarrow$  **323**). Additionally, this substrate is the only one to display selectivity for the desired relative stereochemistry of the product. Unique to this substrate is a  $\beta$ -disposed silyl ether at C(10), which is thought to be instrumental in the stereochemical outcome of the reaction.

#### 4.8.1 Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 19–24 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. *N*-Bromosuccinimide was recrystallized before use. TBSCl was purchased from Gelest. V-70 was purchased from Waco Chemicals. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, KMnO<sub>4</sub>, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to Me<sub>4</sub>Si (δ 0.0). Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm<sup>-1</sup>). High-resolution mass spectra were obtained from the Caltech Mass Spectroscopy Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix C for deposition numbers).

## 4.8.2 Preparation of Compounds



**Aryl bromide 315.** Enone **255** (58.8 mg, 0.114 mmol, 1.0 equiv) was treated with a 1.0 M solution of TBAF in THF (314  $\mu$ L, 0.341 mmol, 3.0 equiv) for 40 min at ambient temperature. The reaction mixture was then diluted with H<sub>2</sub>O (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL), dried over MgSO<sub>4</sub>, and concentrated to an oil, which was purified by flash chromatography (20 to 50% EtOAc in Hexanes) to provide phenol **255a** (28 mg, 0.070 mmol, 61% yield). *R<sub>f</sub>* 0.25 (50% EtOAc in hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.85 (d, *J* = 7.8 Hz, 1H) 6.59 (d, *J* = 7.9 Hz, 1H), 5.53 (s, 1H), 4.62 (t, *J* = 2.7 Hz, 1H), 3.98 (d, *J* = 17.8, 1H), 3.77 (s, 3H), 3.77 (d, *J* = 17.6 Hz, 1H), 3.76 (s, 3H), 2.45 (dd, *J* = 19.0, 2.2 Hz, 1H), 2.36 (ddd, *J* = 19.0, 2.2, 0.98 Hz, 1H), 2.23 (s, 3H), 1.63 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  203.0, 176.3, 173.1, 147.2, 145.4, 135.5, 130.9, 126.4, 124.6, 123.5, 122.0, 77.9, 61.2, 53.6, 52.8, 47.9, 45.6, 34.4, 19.0, 15.5, 12.6, 11.9; IR (Neat film NaCl) 3446, 2951, 1779, 1731, 1706, 1465, 1425, 1333, 1272, 1239, 1200, 1150, 1063, 732 cm<sup>-1</sup>; HRMS (FAB+) [M+H]<sup>+</sup> calc'd for [C<sub>22</sub>H<sub>26</sub>O<sub>7</sub>+H]<sup>+</sup>: *m/z* 403.1757, found 403.1766.

To a solution of the above phenol (**255a**, 27.8 mg, 0.691 mmol, 1.0 equiv) in ACN (1.4 mL, 0.05 M) was added *N*-Bromosuccinimide (13.5 mg, 0.0760 mmol, 1.1 equiv). The solution was stirred at ambient temperature for 6 h then quenched with H<sub>2</sub>O (10 mL) and diluted with EtOAc (20 mL) and H<sub>2</sub>O (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO<sub>4</sub>, and concentrated to an oil, which was

purified by flash chromatography (20 to 60% EtOAc in hexanes) to provide aryl bromide **255b** (20.1 mg, 0.042 mmol, 61% yield) as an oil.  $R_f$  0.33 (50% EtOAc in hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.15 (s, 1H), 5.47 (s, 1H), 4.63 (t,  $J = 2.2$  Hz, 1H), 4.26 (d,  $J = 19.0$  Hz, 1H), 3.91 (d,  $J = 19.0$  Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.49 (dd,  $J = 19.0, 2.2$  Hz, 1H), 2.39 (app. d,  $J = 18.8$  Hz, 1H), 2.22 (s, 3H), 1.82 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.2, 176.4, 173.2, 146.6, 146.2, 135.3, 131.3, 129.9, 126.4, 124.2, 114.8, 78.0, 61.3, 53.6, 52.8, 48.1, 46.4, 34.5, 19.2, 15.4, 12.6, 11.6; IR (Neat film NaCl) 3441, 2951, 2255, 1780, 1730, 1708, 1141, 1271, 1240, 1150, 1073, 912, 731  $\text{cm}^{-1}$ ; HRMS (FAB+)  $[\text{M}+\text{H}]^+$  calc'd for  $[\text{C}_{22}\text{H}_{25}\text{O}_7\text{Br}+\text{H}]^+$ :  $m/z$  481.0862, found 481.0869.

To a solution of aryl bromide **255b** (19.0 mg, 0.039 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1 mL, 0.04 M) were added TBSCl (11.9 mg, 0.079 mmol, 2.0 equiv), DMAP (4.8 mg, 0.039 mmol, 1.0 equiv), and imidazole (8.1 mg, 0.118 mmol, 3.0 equiv). Stirred at 40 °C for 1.5 d before adding TBSCl (11.9 mg, 0.079 mmol, 2.0 equiv), DMAP (4.8 mg, 0.039 mmol, 1.0 equiv), and imidazole (8.1 mg, 0.118 mmol, 3.0 equiv). Upon completion, the reaction was quenched with  $\text{NH}_4\text{Cl}$  (5 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 5 mL), dried over  $\text{MgSO}_4$ , concentrated to an oil, and purified by flash chromatography (10 to 50% EtOAc in Hexanes) to provide isomerically pure aryl bromide **315** (18.6 mg, mmol, 79% yield, 29% yield over 3 steps) as an oil.  $R_f$  0.63 (50% EtOAc in Hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (s, 1H), 4.618 (t,  $J = 2.4$  Hz, 1H), 4.25 (d,  $J = 19.0$  Hz, 1H), 3.90 (d,  $J = 19.0$  Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 2.48 (dd,  $J = 19.0, 2.4$  Hz, 1H), 2.38 (dd,  $J = 18.8, 1.2$  Hz, 1H), 2.19 (s, 3H), 1.81 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.00 (s, 9H), 1.40 (app. d,  $J = 3.9$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.7, 176.4, 173.3, 150.8, 146.5, 135.5, 131.5, 131.1, 129.4, 125.3, 116.3, 77.9, 60.1, 53.7, 52.8, 48.1, 46.9, 34.6, 26.0, 19.1, 18.5, 16.9, 12.7, 11.6, -4.26, -4.28; IR (Neat film NaCl) 2954, 2932, 2859, 1784, 1732, 1710, 1470, 1405, 1237, 1149, 1084, 1017, 841, 784, 733  $\text{cm}^{-1}$ ; HRMS (FAB+)  $[\text{M}+\text{H}]^+$  calc'd for  $[\text{C}_{28}\text{H}_{39}\text{O}_7\text{BrSi}+\text{H}]^+$ :  $m/z$  595.1727, found 595.1719.

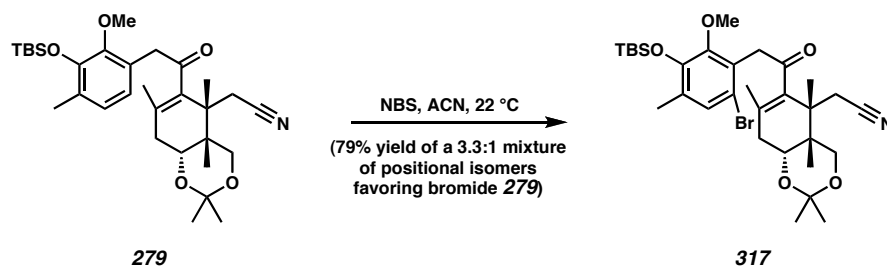
1. TBAF, THF  
 2. NBS, ACN, 0 to 22 °C  
 3. TBSCl, imidazole, DMAP, DMF, DCM, 40 °C  
 (40% yield, 3 steps)

279 317

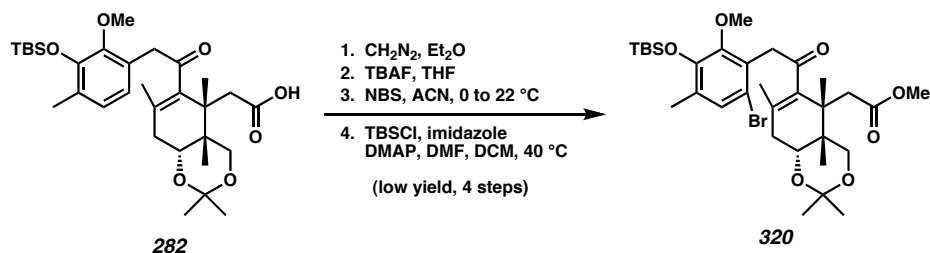
To a cooled (0 °C) solution of intermediate phenol (33.7 mg, 78.8 μmol, 1.00 equiv) in ACN (1.6 mL) was added NBS (15.4 mg, 86.7 μmol, 1.10 equiv) and the reaction

mixture was allowed to come to ambient temperature. After 5 h, the reaction was diluted with H<sub>2</sub>O (10 mL) and EtOAc (20 mL), and extracted with EtOAc (5 x 10 mL). The combined organics were dried (MgSO<sub>4</sub>), concentrated and used without further purification in the next step.

To a solution of the above crude material (theory: 78.8  $\mu$ mol, 1.00 equiv), imidazole (16.1 mg, 0.236 mmol, 3.00 equiv), TBSCl (17.8 mg, 0.118 mmol, 1.50 equiv) in DMF (200  $\mu$ L) and CH<sub>2</sub>Cl<sub>2</sub> (200  $\mu$ L) was added DMAP (9.6 mg, 78.8  $\mu$ mol, 1.00 equiv) and the reaction was stirred at ambient temperature for 24 h and then at 30 °C for 18 h. An additional portion of DMAP (10.0 mg, 81.9  $\mu$ mol, 1.04 equiv) and TBSCl (20.0 mg, 132.7  $\mu$ mol, 1.69 equiv) were added and the reaction mixture was heated at 40 °C for 4 h. The reaction was diluted with EtOAc (10 mL), washed with saturated aqueous NH<sub>4</sub>Cl (3 x 5 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were concentrated and purified by flash chromatography on silica gel (5 to 15% Et<sub>2</sub>O in hexanes) to give isomerically pure bromide **317** (23.0 mg, 47% yield, 40% yield for three steps) as an amorphous white solid: *R<sub>f</sub>* 0.43 (20% EtOAc in hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (s, 1H), 4.29 (d, *J* = 8.5 Hz, 1H), 4.10 (d, *J* = 7.0 Hz, 1H), 4.07 (d, *J* = 7.0 Hz, 1H), 4.06 (d, *J* = 4.0 Hz, 1H), 3.88 (dd, *J* = 6.3, 8.8 Hz, 1H), 3.62 (s, 3H), 3.54 (app. t, *J* = 9.3 Hz, 1H), 2.55 (dd, *J* = 6.3, 17.8 Hz, 1H), 2.32 (dd, *J* = 8.5, 18.0 Hz, 1H), 2.18 (s, 3H), 1.87 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.01 (s, 9H), 0.14 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  205.4, 150.9, 146.4, 138.3, 131.4, 129.3, 128.7, 126.0, 121.5, 116.3, 75.5, 75.3, 75.2, 70.5, 60.0, 49.7, 47.7, 47.2, 35.7, 28.7, 27.6, 26.0, 21.0, 20.8, 18.1, 16.8, -4.3; IR (Neat film NaCl) 2932, 2860, 2252, 1699, 1470, 1404, 1234, 1171, 1083, 1047, 853, 842, 734 cm<sup>-1</sup>; HRMS (FAB+) [M+H]<sup>+</sup> calc'd for [C<sub>31</sub>H<sub>46</sub> O<sub>5</sub>NSiBr+H]<sup>+</sup>: *m/z* 620.2407, found 620.2394.



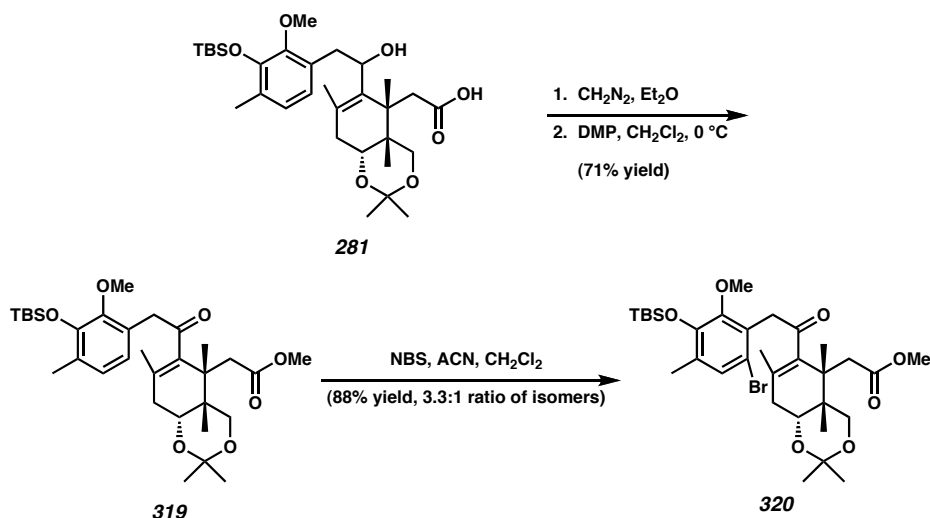
**Aryl bromide 317** directly from enone **279**. To a solution of enone **279** (74.7 mg, 0.138 mmol, 1.00 equiv) in ACN (1.4 mL, 0.1 M) was added NBS (27.0 mg, 0.1517 mmol, 1.1 equiv). After 2 h, the reaction was diluted with H<sub>2</sub>O (10 mL) and EtOAc (10 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were washed with brine (10 mL), dried over MgSO<sub>4</sub>, concentrated, and purified by flash chromatography on silica gel (5 to 30% Et<sub>2</sub>O in hexanes) to give aryl bromide **317** (67.5 mg, 79% yield) as a 3.3:1 mixture of bromide isomers favoring the desired aryl bromide **317**.



**Aryl bromide 320**. To a solution of enone **282** (27.1 mg, 0.048 mmol, 1.0 equiv) in Et<sub>2</sub>O (1 mL, 0.05 M) was added CH<sub>2</sub>N<sub>2</sub> (2 mL, 1–2 M in Et<sub>2</sub>O). The reaction was stirred uncovered until no further yellow color was observed, and then it was concentrated to an oil and redissolved in THF (1.6 mL, 0.03 M). A 1.0 M solution of TBAF (72.5  $\mu$ L, 0.073 mmol, 1.5 equiv) in THF was added, and the reaction was stirred at ambient temperature 25 min, quenched with H<sub>2</sub>O (5 mL) and brine (5 mL), and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL), and the combined organics were dried over MgSO<sub>4</sub> and concentrated to an oil, which was carried on without further purification.

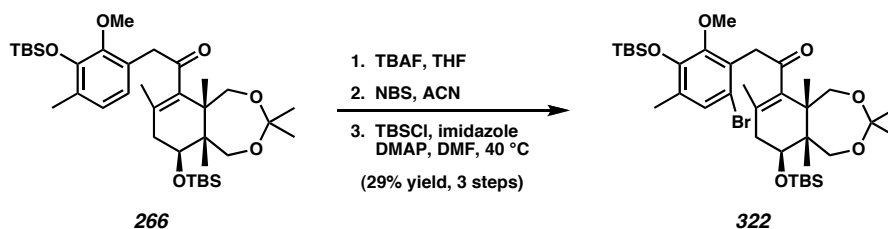
To a solution of the intermediate phenol **282a** in ACN (1 mL, 0.05 M) at 0 °C was added *N*-bromosuccinimide (9.4 mg, 0.053 mmol, 1.1 equiv). The reaction was then stirred at ambient temperature 10 h, diluted with H<sub>2</sub>O (15 mL) and EtOAc (10 mL), and extracted with EtOAc (5 x 10 mL). The combined organics were dried over MgSO<sub>4</sub> and concentrated to an oil.

The intermediate aryl bromide **282b** was redissolved in DMF (0.2 mL, 0.25 M) and CH<sub>2</sub>Cl<sub>2</sub> (0.2 mL, 0.25 M) and TBSCl (11.0 mg, mmol, equiv), DMAP (5.9 mg, mmol, equiv), and imidazole (9.9 mg, mmol, equiv) were added. The reaction was stirred at 40 °C for 24 h then diluted with sat. NH<sub>4</sub>Cl (5 mL), H<sub>2</sub>O (5 mL), and EtOAc (5 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried over MgSO<sub>4</sub>, concentrated, and purified by flash chromatography (5 to 10% EtOAc in hexanes) to provide a small amount of aryl bromide **320** as a single positional isomer (plus impurities unrelated to the product). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.13 (d, *J* = 0.6 Hz, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 4.11 (d, *J* = 8.5 Hz, 1H), 4.06 (s, 2H), 3.77 (m, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.55 (d, *J* = 8.8 Hz, 1H), 3.53 (d, *J* = 9.1 Hz, 1H), 2.19 (s, 3H), 1.83 (s, 3H), 1.55 (s, 9H), 1.44 (s, 6H), 1.16 (s, 3H), 1.11 (s, 3H), 1.01 (s, 3H), 0.14 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 205.8, 174.8, 150.9, 146.4, 138.2, 131.4, 129.4, 129.1, 126.1, 116.4, 75.2, 74.9, 72.3, 60.0, 51.9, 49.8, 47.8, 35.9, 29.7, 26.4, 26.0, 24.2, 21.1, 20.8, 18.5, 17.9, 16.9, -4.3; IR (Neat film NaCl) 2928, 2857, 1733, 1670, 1470, 1404, 1290, 1234, 1142, 1083, 1048, 936, 841, 783, 735 cm<sup>-1</sup>; HRMS (FAB+) [M+H]<sup>+</sup> calc'd for [C<sub>32</sub>H<sub>49</sub>O<sub>7</sub>SiBr+H]<sup>+</sup>: *m/z* 653.2509, found 653.2510.



**Aryl bromide 320** directly from enone **319**. To a solution of allylic alcohol **281a** (24.3 mg, 0.043 mmol, 1.0 equiv) in Et<sub>2</sub>O (2 mL) was added CH<sub>2</sub>N<sub>2</sub> (1 mL, 1–2 M in Et<sub>2</sub>O). The reaction was stirred uncovered until no yellow color remained. The solvents were removed by rotary evaporation, and the intermediate methyl ester was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 0.03 M). The solution was cooled to 0 °C, and DMP (27.9 mg, 0.065 mmol 1.5 equiv) was added. The reaction was stirred at 0 °C for 4 h then diluted with Et<sub>2</sub>O (20 mL). The solids were removed by filtration thru #2 Whatman paper, the solution was concentrated to an oil then purified by flash chromatography (5 to 15% EtOAc in hexanes) to provide enone **319** (17.5 mg, 0.030 mmol, 71% yield).

To a solution of enone **319** (50.9 mg, 0.089 mmol, 1.00 equiv) in ACN (1.8 mL, 0.05 M) and CH<sub>2</sub>Cl<sub>2</sub> (0.68 mL, 0.13 M) was added NBS (15.9 mg, 0.089 mmol, 1.01 equiv). After 3 h, the reaction was diluted with H<sub>2</sub>O (25 mL) and EtOAc (25 mL), and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organics were washed with brine (25 mL), dried over MgSO<sub>4</sub>, concentrated, and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give aryl bromide **320** (51.2 mg, 88% yield) as a 3.3:1 mixture of bromide isomers favoring the desired aryl bromide **320**.

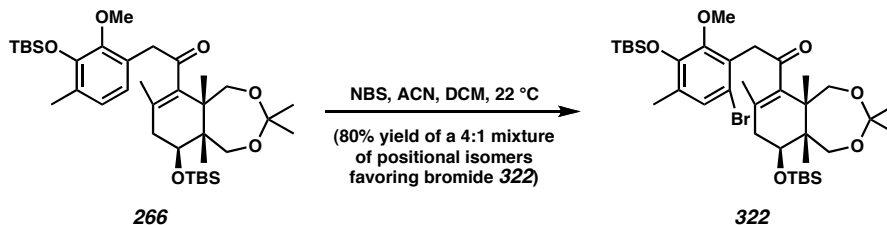


**Aryl bromide 322.** To a solution of enone **266** (114 mg, 0.176 mmol, 1.00 equiv) in THF (8.0 mL) was added a 1.0 M solution of TBAF (176  $\mu$ L, 0.176 mmol, 1.00 equiv) in THF. After 5 min, the reaction mixture was diluted with H<sub>2</sub>O (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 25 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to give the intermediate phenol (91 mg, 97% yield).

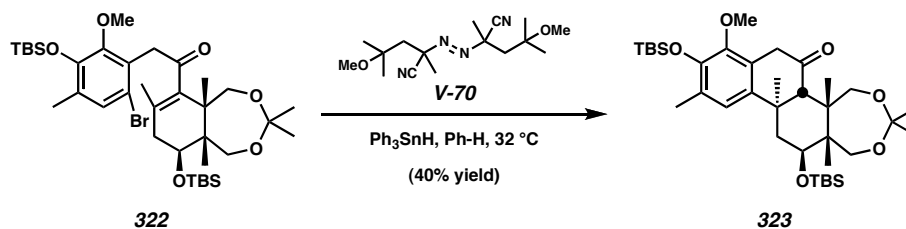
To a solution of intermediate phenol (36.0 mg, 67.6  $\mu$ mol, 1.00 equiv) in ACN (2.0 mL) was added NBS (18.0 mg, 101  $\mu$ mol, 1.50 equiv). After 2.5 h, the reaction was diluted with H<sub>2</sub>O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give the intermediate bromide (14.4 mg, 35% yield).

To a solution of intermediate bromide (14.4 mg, 23.5  $\mu$ mol, 1.00 equiv), imidazole (36.0 mg, 0.530 mmol, 22.5 equiv), and TBSCl (26.6 mg, 0.177 mmol, 7.50 equiv) in DMF (2.5 mL) was added DMAP (21.5 mg, 0.176 mmol, 7.50 equiv) and the reaction was warmed to 40  $^\circ$ C. After 36 h, the reaction was diluted with H<sub>2</sub>O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et<sub>2</sub>O in hexanes) to give isomerically pure bromide **322** (14.5 mg, 85% yield, 29% yield for three steps) as a white foam: *R<sub>f</sub>* 0.76, 0.79 (10% Et<sub>2</sub>O in hexanes, 25% Et<sub>2</sub>O in hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (s, 1H), 4.29 (dd, *J* = 7.1, 9.5 Hz, 1H), 4.11 (d, *J* = 18.6 Hz, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.62 (s, 3H), 3.55 (d, *J* = 12.9 Hz,

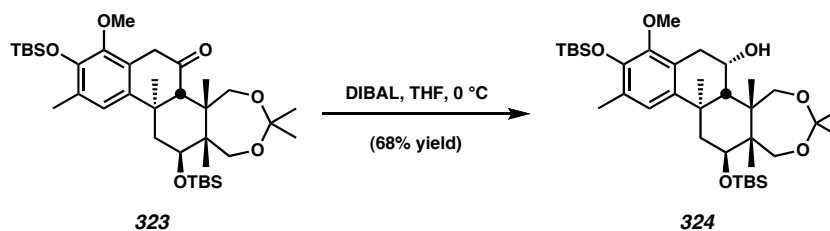
1H), 3.54 (d,  $J = 12.6$  Hz, 1H), 3.39 (d,  $J = 12.3$  Hz, 1H), 2.19 (s, 3H), 2.14–2.04 (m, 2H), 1.82 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.01 (s, 9H), 0.90 (s, 9H), 0.67 (s, 3H), 0.15 (s, 6H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  206.1, 151.0, 146.4, 137.8, 131.4, 130.9, 129.4, 126.0, 116.4, 101.1, 66.0, 65.5, 61.5, 60.0, 48.0, 45.5, 43.0, 38.1, 26.0, 25.9, 24.7 (2C), 20.7, 18.5, 18.2, 18.1, 16.9, 11.1, -4.2, -4.3, -4.4, -5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1700, 1471, 1404, 1233, 1220, 1099, 1075, 855, 837, 779  $\text{cm}^{-1}$ ; HRMS (FAB+)  $[\text{M}-\text{H}_2+\text{H}]^+$  calc'd for  $[\text{C}_{36}\text{H}_{60}\text{Si}_2\text{O}_6\text{Br}]^+$ :  $m/z$  723.3112, found 723.3128.



**Aryl bromide 322** directly from enone **266**. To a solution of enone **266** (200 mg, 0.309 mmol, 1.00 equiv) in ACN (8.0 mL) and  $\text{CH}_2\text{Cl}_2$  (1.2 mL) was added NBS (66.0 mg, 0.371 mmol, 1.20 equiv). After 2.5 h, the reaction was diluted with  $\text{H}_2\text{O}$  (30 mL) and EtOAc (15 mL), and extracted with EtOAc (5 x 15 mL). The combined organics were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and purified by flash chromatography on silica gel (1 to 5%  $\text{Et}_2\text{O}$  in hexanes) to give aryl bromide **322** (179 mg, 80% yield) as a 4:1 mixture of bromide isomers favoring the desired aryl bromide **322**.



**Cyclized ketone 323.** To a solution of aryl bromide **322** (25.0 mg, 34.4  $\mu\text{mol}$ , 1.00 equiv of a 4:1 mixture of isomers) and initiator **V-70** (15.9 mg, 51.7  $\mu\text{mol}$ , 1.50 equiv) in benzene (2.0 mL) at  $32\text{ }^\circ\text{C}$  was added a solution of  $\text{Ph}_3\text{SnH}$  (24.2 mg, 68.8  $\mu\text{mol}$ , 2.00 equiv) in benzene (0.5 mL) by syringe pump over 5 h. At the end of the addition, the reaction was cooled to ambient temperature, concentrated, and purified by flash chromatography on silica gel (2 to 7.5%  $\text{Et}_2\text{O}$  in hexanes) to give ketone **323** (8.9 mg, 40% yield, 50% yield based on the correct isomer of the starting material) as an oil:  $R_f$  0.52 (25%  $\text{Et}_2\text{O}$  in hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.77 (s, 1H), 4.53 (d,  $J = 12.0$  Hz, 1H), 4.43 (dd,  $J = 4.5, 12.5$  Hz, 1H), 3.97 (d,  $J = 12.5$  Hz, 1H), 3.66 (d,  $J = 22.0$  Hz, 1H), 3.64 (s, 3H), 3.55 (d,  $J = 12.5$  Hz, 1H), 3.39 (d,  $J = 22.0$  Hz, 1H), 3.33 (d,  $J = 12.5$  Hz, 1H), 2.84 (s, 1H), 2.22 (s, 3H), 2.18 (dd,  $J = 4.5, 12.5$  Hz, 1H), 1.92 (app. t,  $J = 12.5$  Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.03 (s, 9H), 0.94 (s, 9H), 0.57 (s, 3H), 0.19 (s, 6H), 0.18 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  209.3, 147.8, 145.1, 141.5, 129.0, 123.8, 120.8, 100.9, 65.8, 62.2, 62.1, 59.3, 58.8, 44.7, 43.5, 42.5, 41.2, 41.0, 27.4, 26.0 (2C), 24.8, 24.6, 20.0, 18.6, 18.2, 17.6, 10.1,  $-4.0$ ,  $-4.2$  (2C),  $-4.9$ ; IR (Neat film NaCl) 2954, 2929, 2857, 1715, 1472, 1462, 1254, 1221, 1088, 1071, 838  $\text{cm}^{-1}$ ; HRMS (FAB+)  $[\text{M}-\text{H}_2+\text{H}]^+$  calc'd for  $[\text{C}_{36}\text{H}_{61}\text{Si}_2\text{O}_6]^+$ :  $m/z$  645.4007, found 645.4007.



**Alcohol 324.** To a cooled (0 °C) solution of ketone **323** (19.9 mg, 30.8 μmol, 1.00 equiv) in THF (5.0 mL) was added a 1.0 M solution of DIBAL-H (250 μL, 0.250 mmol, 8.12 equiv) in toluene. After 4 h, an additional portion of DIBAL-H (100 μL, 0.100 mmol, 3.25 equiv) in toluene was added. After an additional 1 h at 0 °C, the reaction mixture was quenched with Na<sub>2</sub>SO<sub>4</sub>•10H<sub>2</sub>O (300 mg) in a portionwise manner, filtered, washed (CH<sub>2</sub>Cl<sub>2</sub>), concentrated, and purified by flash chromatography on silica gel (10 to 40% Et<sub>2</sub>O in hexanes) to give alcohol **324** (13.6 mg, 68% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature: mp 185–190 °C decomp. (CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* 0.21 (25% Et<sub>2</sub>O in hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.78 (s, 1H), 4.68 (s, 1H), 4.47 (dd, *J* = 3.8, 12.3 Hz, 1H), 4.28 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.65 (s, 3H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 2.95 (s, 1H), 2.94 (s, 1H), 2.20 (s, 3H), 2.07 (dd, *J* = 4.0, 12.5 Hz, 1H), 1.66 (s, 1H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.58 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.20 (bs, 1H), 1.11 (s, 3H), 1.03 (s, 9H), 0.92 (s, 9H), 0.57 (s, 3H), 0.19 (s, 3H), 0.17 (s, 6H), 0.14 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 148.6, 144.4, 141.8, 128.3, 122.8, 122.1, 100.9, 66.4, 65.4, 65.3, 63.0, 59.2, 48.6, 45.7, 45.4, 44.6, 37.5, 36.7, 29.6, 26.1, 26.0, 25.0, 24.6, 22.2, 18.6, 18.1, 17.5, 10.4, –4.0 (2C), –4.1, –4.9; IR (Neat film NaCl) 3454, 2954, 2930, 2858, 1473, 1252, 1220, 1089, 1061, 836 cm<sup>–1</sup>; HRMS (FAB+) [M–H<sub>2</sub>+H]<sup>+</sup> calc'd for [C<sub>36</sub>H<sub>63</sub>Si<sub>2</sub>O<sub>6</sub>]<sup>+</sup>: *m/z* 647.4163, found 647.4162.

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8. The yields for this sequence were low for several substrates. Depending on the substrate, the desilylation and bromination steps led to significant decomposition if stirred for too long or at too high of a temperature. Generally, we found the mixture of bromide isomers sufficient for investigation of cyclizations. Thus, the three-step procedure was not optimized in most cases.
9. See Chapter 3 for details.
10. The exact yield for this sequence was not calculated owing to impurity of the product. An analytically pure sample was ultimately obtained by repetitive preparative methods.
11. TBS groups removed from the figure for clarity.
12. Lewis acids have been used numerous times to promote radical conjugate additions, see: a) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, 121, 7517–7526; b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, 10, 2417–2428; c) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, 3, 299–302. d) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, 4, 2929–2932.
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