Published in final edited form as:
Tetrahedron. 2011 December 30; 67(52): 10249–10260. doi:10.1016/j.tet.2011.10.026.

Synthetic studies toward (+)-cortistatin A

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Abstract

We describe herein the synthesis of a late-stage intermediate *en route* to cortistatin A. Key transformations included a Snieckus-like cascade sequence culminating in a 6π-electrocyclization, an alkylative dearomatization, and the stereoselective functionalization of the cortistatin A-ring. While the total synthesis we sought was not accomplished, the work sets the stage for several approaches to the preparation of novel analogs via diverted total synthesis.

Keywords

total synthesis; angiogenesis inhibitor; nitrone–aryne cycloaddition; 6π-electrocyclization

Introduction

Our laboratory devotes much of its effort to the discovery and development of small molecule natural product (SMNP)–derived agents of potential therapeutic value. [i] Under our paradigm of diverted total synthesis (DTS),[1] we identify SMNPs with compelling biological activity and challenging structural features. We first undertake the total synthesis of the natural product itself and subsequently seek to adapt the synthetic route to allow access to rationally designed analogs for further investigation and SAR analysis. Through recourse to the strategy of DTS, we have discovered a range of promising SMNP–derived lead agents – including those based on the epothilone,[ii] migrastatin,[iii] and panaxytriol[iv] natural product frameworks – which are under development in preclinical and clinical settings.

In our ongoing pursuit of new lead structure types, we took note of a recent report by Kobayashi and co-workers, [v] on the isolation of a novel class of steroidal alkaloids, the cortistatins, from the marine sponge *Corticium simplex* (Scheme 1). Notably, members of the cortistatin family appear to exhibit potent *in vitro* anti-angiogenesis activity. Angiogenesis, the formation of new blood vessels in tissues, is an essential biological process, involved in embryonic development, reproduction, and wound healing.[vi] The process of angiogenesis is regulated by a series of stimulators and inhibitors – including vascular endothelial growth factor (VEGF) and angiopoietin 1 (ANGPT1), respectively – and is therefore typically focal and self-limited in time in regular tissues.[vii] Pathological angiogenesis, however, is implicated in a variety of diseases, including atherosclerotic plaques, diabetic retinopathy, and – of particular interest to our laboratory – the growth and metastasis of malignant tumors. Selective small molecule angiogenesis inhibitors, perhaps of the cortistatin genre, seemed to represent a promising avenue of research directed toward the

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treatment of angiogenesis-dependent diseases. Cortistatin A, in particular, has been reported to exhibit potent growth-inhibitory activity against human umbilical vein endothelial cells (HUVECs), with an IC_{50} of 1.8 nM and selectivity indices of above 3000 compared to normal human dermal fibroblast (NHDF) and other tumor cell lines.[viii] Cortistatin A also exhibits inhibitory effects against the migration of HUVECs, and against VEGF- and bFGF-induced tubular formation at a concentration of 2 nM, with comprehensive activity against neovascularization. [ix] Thus, cortistatin A, which exhibits strong and selective anti-angiogenesis activity, could potentially serve as an exciting lead agent in the development of anti-angiogenic therapeutics via chemical synthesis.

In contemplating a total synthesis, one soon comes to focus on the unique 9(10-19)-*abeo*-androstane-type steroidal core, incorporating an oxabicyclo[3.2.1]octene motif, shared by the cortistatins. Among the various members of this class, three different types of C_{17} side chains (isoquinoline, 3-methylpyridine, and methylpiperidine) and various levels of A-ring oxidation are represented. Following the initial structure-activity relationship (SAR) study reported by the Kobayashi group,[ix] Nicolaou and co-workers reported the results of a binding assay screening, which indicated strong binding affinity of cortistatin A toward a series of biologically essential kinases with extended C-termini, including cyclin-dependent kinases (CDK8 and CDK11) and Rho-associated coiled-coil containing protein kinases (ROCK I and ROCK II). [x] Docking simulations suggest that the isoquinoline moiety of cortistatin A projects inside the kinase hinge, while the steroidal skeleton blocks the ATP-binding cleft and the polar A-ring is exposed to solvent. The extended C-termini of these kinases apparently place an aromatic side chain proximal to cortistatin A, thereby encapsulating the ATP–binding site. Thus, the cytostatic activity of the cortistatins against HUVECs is proposed to arise from inhibition of HUVEC kinase activity, resulting in diminished HUVEC proliferation and migration.

Not surprisingly, the potent biological activity and unique structures of the cortistatins have prompted many laboratories to undertake their synthesis. To date, total syntheses have been reported from the Baran,[xi] Nicolaou,[xii] Shair,[xiii] Myers,[xiv] Hirama,[xv] and Funk groups,[xvi] and formal syntheses have been achieved by the Sarpong[xvii] and Yang groups.[xviii] Numerous synthetic studies toward the steroidal core of the cortistatins have been published.[xix] In the aggregate, these synthetic studies represent a wide range of strategies, each of which might be adapted to provide access to different types of analogs for further investigation. Indeed, a variety of synthetic cortistatin analogs have been prepared and evaluated in preclinical settings.[xx]

Preliminary SAR studies on the cortistatins and synthetic analogs have revealed important information with respect to the structural features required for biological activity. As shown in Scheme 2, in order to exhibit inhibitory activity, the A-ring must incorporate at least one –OH or $–NMe_2$ group and stereointegrity at C_{17} must be preserved. Moreover, there is some evidence to the effect that the A–B–C ‘skeleton angle’ and core ring planarity are important factors in mediating biological activity.[xxa]

Synthetic Plan

In designing our synthetic strategy toward cortistatin A, of course, we took note of its rearranged steroidal skeleton. Seeking to capitalize on the wisdom accumulated over years of research in the field of steroid synthesis,[xxi] we considered both B–ring[xxii] and C– ring[xxiii] disconnection strategies toward cortistatin A. In the case at hand, disconnection along the B–ring would reduce the challenge to the syntheses of the A–ring fragment, from an aromatic precursor, and the more complex C–D ring system. Pattern recognition analysis suggests that the C–D ring system could be derived from the optically enriched Hajos-Parrish ketone.[xxiv,xxv] As shown in Scheme 3, following some early experimentation, [xxvi] a

convergent strategy which envisioned 1,3-dipolar cycloaddition between an aryne (**2**, A-ring) and an α,β-unsaturated nitrone (**3**, C-D ring) presented itself. The resultant benzoisoxazoline, **4**, could well be converted to benzopyran intermediate **7** through a sequence involving reductive N-O bond cleavage, followed by 1,4-elimination and, finally, 6π-electrocyclization. [xxvii] Finally, alkylative dearomatization of **7** would deliver intermediate **8** *en route* to cortistatin A.[xxviii]

Results and Discussion

Nitrone-Aryne [3+2] Cycloaddition–Based Route to the Cortistatin Core

At the outset of our studies, few examples of nitrone-aryne [3+2] cycloadditions, such as **2**+**3**→**4**, had been reported. Model studies, performed with simple nitrone substrates (**11**), revealed that high levels of regioselectivity could be achieved when the aryne dipolarophiles were equipped with *ortho*-substituents (Scheme 4). [xxix] Interestingly, *ortho*-TMS aryne, **10a**, underwent cycloaddition to yield adduct **12a** as a single regioisomer. By contrast, *ortho*-OMe aryne **10b** generated adduct **12b**, with completely inverted regioselectivity. These findings seem to reflect the interplay of competing steric and electronic factors. It was also observed that *meta*- and *para*- substituted aryne substrates (cf. **13**) generally underwent cycloaddition to afford mixtures of products with poor levels of regiocontrol (Scheme 4). Similar regioselectivity trends have been reported previously.[xxx]

Having probed the nature of the nitrone-aryne [3+2] cycloaddition, we now sought to prepare a more sophisticated model system, through which we would explore the viability of the proposed alkylative dearomatization sequence. In order to achieve the requisite sense of regioselectivity in the cycloaddition step, we elected to install an inductively operating electron-withdrawing group, –OMe, at the *ortho* position of the aryne substrate. This functionality would ultimately become the C_1 hydroxyl group of cortistatin A. In the event, 1,3-dipolar cycloaddition between nitrone **15** and the aryne generated from **16** afforded benzoisoxazoline **17**. Treatment under mild N–O cleavage conditions followed by 1,4-elimination served to generate the intermediate *o*-quinomethide, which readily underwent 6π–electrocyclization to deliver adduct **18**, as planned, in high yield. Deprotection and subsequent bromination afforded **19**, which, upon exposure to TBAF, smoothly underwent alkylative dearomatization to provide the key model system, **20** (Scheme 5). Given this encouraging demonstration of “reduction to practice”, we hoped to build in to our scheme a sufficient functionality to enable progression, hopefully to cortistatin A itself.

Snieckus Cascade–Based Route to the Cortistatin Core

An alternative route toward a more highly functionalized version of the quinomethide system was also pursued. Based on the elegant precedent of Snieckus, [xxxi] with a later adaptation by Alvarez-Manzaneda, [xxxii] we envisioned a cascade sequence commencing with an aryllithium substrate, **21**, and a bicyclic aldehyde of the type **22**[xvc] (Scheme 6). According to our plan, 1,2-addition of **21** to **22** would generate an alkoxide intermediate (**23**), which would undergo carbamate migration to afford **24**. A facile 1,4-elimination would give rise to quinomethide **25**, which was expected to undergo 6π-electrocyclization. Subsequent alkylative dearomatization would generate an advanced intermediate of the type **27**. At the outset of our studies, there was uncertainty regarding the stereochemistry at C_8 following electrocyclization (see asterisk, **26**). We postulated that the isomer required for cortistatin would be the thermodynamic product, as it encompasses *trans/anti* stereoconnectivity between the angular methyl (C_{18}), the C_{14} hydrogen, and the angular two-carbon chain.

We first set out to synthesize the A ring precursor fragments. In order to preserve maximum synthetic flexibility in the later stages of the synthesis, we prepared both the substrate bearing a MOM protecting group at the eventual C_1 (**31a**) and the fragment possessing a C_1 methoxy group (**31b**). As outlined in Scheme 7, the route commenced with commercially available **28**. Bromination,[xxxiii] followed by selective acylation, afforded carbamate **29**. The remaining free hydroxyl was protected as a TBS group, and Baeyer-Villiger oxidation with subsequent saponification delivered **30**. This intermediate was converted to both **31a** and **31b** under the conditions shown.

With fragments **31** and **32**[xvc] in hand, we were able to reduce the proposed Snieckus-type cascade sequence to practice (Scheme 8). Interestingly, isomers bearing the undesired C_8 stereochemistry (*epi*-**33a** and *epi*-**33b**) were preferentially formed (10:1 dr), presumably due to unfavorable 1,3-diaxial interactions between C_{18} and C_6-C_7 in the 6π-electrocyclization event. Fortunately, however, the electrocyclization step (cf. **25**→**26**, Scheme 6) proved to be reversible, and thermally induced epimerization of isolated *epi*-**33a** and *epi*-**33b** afforded isomeric mixtures, of which the thermodynamic products, **33a** and **33b**, were predominant (>2:1 dr).

The diastereomeric product mixtures, which were not readily separable, were subjected to I_2-mediated TBS deprotection (Scheme 9).[xxxiv] Chromatographic separation was achieved at this stage, to afford diastereomerically pure adducts **34a** and **34b**. The primary alcohol functionality of **34a** was subjected to tosylation conditions to provide **35a**, which, upon exposure to TBAF, underwent the hoped-for alkylative dearomatization to generate pentacyclic adduct **36a** in excellent overall yield. A similar sequence was employed for the conversion of **34b** to adduct **36b** (Scheme 9).

Functionalization of the A ring *en route* to cortistatin A

With the cortistatin core framework in place, we now turned our attention to the functionalization of the A-ring. In the natural product, the C_1, C_2, and C_3 functionalities (OH, OH, and NMe_2, respectively) all occupy equatorial orientations, thus raising the possibility that they might be stereoselectively installed through reduction of iminium and ketone precursors, for instance, with sodium borohydride.[xxxv]

We first explored methods for the introduction of the C_3 amine functionality. This turned out to be a surprisingly challenging task. Methods based on electrophilic amination,[xxxvi] Neber reaction,[xxxvii] silyl enol ether aziridination,[xxxviii] and dimethylamine displacement of a C_3 bromide derived from a 3,4-dihydro version of **36b** (vide infra) were all unsuccessful. Finally, following extensive experimentation, an α-azido ketone fragmentation method [xxxix] was found to successfully enable emplacement of the C_3 amine. As shown, compound **36a** was advanced to the C_3-bromo intermediate **38a** through exposure to L-selectride, followed by the electrophilic brominating agent, **37** (Scheme 10). Upon treatment with Bu_4NN_3 in THF, intermediate **38a** was susceptible to displacement by azide. Subsequent fragmentation of **39a** yielded enamine **40a**, as shown. The stereoselective reduction of **40a** was accomplished through treatment with $NaBH_3(CN)$ in CH_2Cl_2. The air-sensitive intermediate **41a** was rapidly reduced under Luche conditions,[xl] to provide intermediate **42a**. The latter was then protected in the form of either Boc or Fmoc carbamates. A similar sequence (unoptimized) served to advance intermediate **36b**, bearing the C_1 methoxy group, to compound **43b**, as shown.

With the A-ring C_2 and C_3 stereocenters in place, the task would now involve deprotection of the C_1 MOM (**43a**) or Me (**43b**) protecting group. Unfortunately, all efforts to achieve nucleophilic deprotection of the methoxy functionality of **43b** (and its precursor **40b**) were

unsuccessful. Accordingly, we focused our efforts on the removal of the MOM protecting group. Extensive experimentation in the context of model systems revealed surprising complexities associated with this apparently straightforward proposed transformation. In summary, perhaps due to the destabilizing presence of the conjugated trienyl system, standard acid-catalyzed methods for the removal of the MOM group were not productive.

We sought to exploit the reactivity of the triene as a means to achieve the hoped-for MOM deprotection. We postulated that, if an appropriate electrophile were to attack the triene at its C_{12} terminus, then C_1 might be rendered more susceptible to hydrolysis. In fact, in model systems, mild bromine-induced removal of the MOM enol ether could, in fact, be achieved (Scheme 11, **45**→**46**).[xli] Interestingly, the ω-bromodienone adducts were unstable, and under standard work-up and purification conditions (evaporation of EtOAc solution, silica gel), these products underwent apparently rapid HBr elimination to generate trienones of the type **47**. Though unexpected, we postulated that these HBr elimination products might offer a new avenue for the installation of the C_1 and C_2 stereocenters. We envisioned a sequence involving reduction of the C_2 ketone, trienol–dienone tautomerization, and C_1 ketone reduction to stereoselectively generate the C_1 and C_2 *trans*-diol system. We reasoned that protonic solvents might serve to effectively facilitate proton transfer, and Luche conditions would ensure selective 1,2 reduction.

In the context of our target system, intermediate **43a** underwent MOM deprotection followed by rapid HBr elimination to generate adduct **48**, as shown. To our surprise, however, exposure of either intermediate **48** or its C_1 TBS ether derivative to Luche conditions gave rise to intermediate **49**, incorporating an extra hydroxyl on C_{12}. At the time, the mechanism of this transformation was unclear; however, subsequent studies provided a plausible explanation (*vide infra*).

We now refocused our efforts on derivatizing the C_{12} brominated system arising from Br_2-induced MOM deprotection (cf. **46**). Based on the Hirama precedent, we were optimistic that we could achieve C_{12} debromination through recourse to radical methods.[15a,c] Surprisingly, however, in a model system, exposure of compound **50** to radical conditions yielded an isomeric mixture,[xlii] of which the diene **52** was the major product (Scheme 13). Moreover, when the reaction mixture was subjected to prep-TLC in air, **52** was partially converted to **53**. The structural assignment of **53** was supported by ^{1}H NMR and LR-MS analysis. The facile formation of **53** under these conditions was quite unexpected. We postulate that, considering the ease with which **52** isomerizes to its trienol form (**54**) under acidic conditions, it may well be that **54** is the reactive intermediate *en route* to **53**. Similar systems are known to react with O_2 in a similar manner,[xliii,xliv] and electron paramagnetic resonance (EPR)/ spin trapping studies support a stepwise radical pathway involving triplet oxygen. [xlv] Small scale attempts to prevent peroxidation through freeze-pump-thaw degassing were unsuccessful.

The mechanistic analysis advanced above might also serve to explain the unexpected and remarkable C_{12} *formal oxidation* observed in the context of the Luche reduction, described above (Scheme 12, **48**→**49**). According to this reasoning, compound **48** did, perhaps, indeed undergo Luche reduction at the C_2 ketone, to generate intermediate **56** (Scheme 14). Presumably, C_{12} peroxidation would be more rapid than enol-ketone tautomerization, and intermediate **57** would be formed. Further reduction would deliver the observed adduct, **49**. It should be noted that **56** might exist in its enolate form during the reaction.[xlvi] Enolate peroxidation by O_2 has also been suggested to proceed through a chain-reaction-based radical pathway.[xlvii]

Having realized a two-step sequence for the deprotection of the C_1 MOM functionality in a model setting, we sought to accomplish the transformation in the context of the cortistatin core system. First, the C_2 hydroxyl of compound **43b** was acylated to generate **58** (Scheme 15). In the event, exposure to mild bromination conditions afforded intermediate **59**, which subsequently underwent radical debromination to furnish the target compound **60**, albeit in disappointingly low yield (ca. 10% from **58**). In this more complex setting, the debromination reaction was quite sensitive, and signficant levels of decomposition were observed. Thorough degassing through repeated freeze-pump-thaw was required. Finally, compound **60** was advanced to **61** through Luche reduction followed by acylation of the resultant C_1 hydroxyl. In principle, this compound could be advanced to **62**, a late-stage intermediate in the Shair synthesis, upon Fmoc removal followed by reductive methylation. However, at this stage, we no longer had adequate levels of material on hand to pursue even a formal relay total synthesis. What was clear is that this route, which began on a very promising note, would not lead to cortistatin A in a useful way.

Conclusion

In summary, the synthesis of a late-stage intermediate *en route* to cortistatin A has been accomplished. Key transformations include a Snieckus-like cascade sequence and the development of methods for the functionalization of the challenging cortistatin A-ring. In this context, our attempts to manipulate A-ring functionalities led to surprising findings, which served to deepen our understanding of the reactivities of the complex cortistatin core system. While even a formal total synthesis of the natural product was not achieved, the ability to generate serious amounts of look-alike structures (cf. inter alia: **38**, **40**, **42**) might well be exploitable to what is now the important problem of producing an accessible and therapeutically useful agent based on cortistatin A.

Experimental Section

General Methods

Unless mentioned otherwise, all non-aqueous reactions were carried out in vacuum-flame-dried glassware under a balloon-pressure of argon; commercially available reagents were used as received; anhydrous solvents were purchased as the highest grade from Sigma-Aldrich, or passed through a solvent-purification system, or purified as follows: THF was distilled from Na-benzophenone, CH_2Cl_2 was distilled from CaH_2. Reactions were monitored by thin-layer chromatography on Merck silica gel 60-F254 coated 0.25 mm plates. Flash column chromatography was performed using RediSep® pre-packed disposable silica gel columns (normal phase, 230-400 mesh) from Teledyne Isco. Prep-TLC was performed on Merck silica gel 60-F254 coated 0.50 or 1 mm plates. Yields are reported for isolated, spectroscopically pure compounds. NMR spectra were obtained on Bruker DRX 300 or 400 MHz, or Bruker DMX 500 MHz spectrometers. $CDCl_3$, dried by standing over K_2CO_3, was used for NMR samples and chemical shifts were referenced on residual solvent peaks (δ = 7.26 for ^{1}H NMR and 77.0 for ^{13}C NMR). Abbreviations for ^{1}H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or br = broad. IR spectra were obtained on a Perkin-Elmer Paragon 1000 FTIR spectrometer. High resolution mass spectra were acquired at the Columbia University Mass Spectral Core facility on a JEOL HX110 spectrometer. Optical rotations were measured on a JASCO DIP-1000 spectrometer.

Synthesis of compound 29

To a mixture of 2-bromo-3,6-dihydroxybenzaldehyde[xlviii] (9.25 g, 42.6 mmol) and DMAP (98.6 mg, 0.81 mmol) in 35 mL pyridine was added diethyl carbamyl chloride (5.40 mL, 44 mmol) at room temperature. The reaction mixture was stirred at reflux for 13 h under argon atmosphere. Then the reaction mixture was poured into ice water and extracted with ether 3

times. The combined organic phases were washed with 1N HCl, brine and dried with anhydrous $MgSO_4$ and then filtrated. The residue was purified by flash chromatography (hexane / EtOAc: 92 / 8) to give 6.42 g desired product **29** in 48% yield (the synthesis of 2-bromo-3,6-dihydroxybenzaldehyde from **28** was quantitative).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 1H), 10.33 (s, 1H), 7.32 (d, J = 9.2 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 3.50 (q, J = 7.2 Hz, 2H), 3.38 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 160.6, 152.4, 141.1, 131.9, 120.4, 117.3, 116.8, 41.9, 41.5, 13.7, 12.7. IR (NaCl, cm^{-1}): 2976, 2935, 1725, 1652, 1607, 1580, 1462, 1420, 1380, 1294, 1265, 1240, 1220, 1176, 1152. HR-MS (FAB+) calcd for $C_{12}H_{15}O_4N^{79}Br$ (M + 1): 316.0184, found 316.0176.

Synthesis of 2-bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-formylphenyl diethylcarbamate

To a solution of **29** (1.37 g, 4.34 mmol) and 2,6-lutidine (1.15 mL, 13.0 mmol) in 20 mL of CH_2Cl_2 was added TBSOTf (1.19 mL, 5.16 mmol) slowly at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with ether 3 times. The combined organic layers were washed with 1N HCl, saturated aqueous sodium bicarbonate, water and brine, sequentially. The combined organic layer was dried over anhydrous $MgSO_4$, concentrated and then purified by flash chromatography (hexane / EtOAc: 92 / 8) to give 1.88 g desired product in 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 3.47 (q, J = 7.2 Hz, 2H), 3.35 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 0.96 (s, 9H), 0.21 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 155.7, 153.0, 143.4, 128.6, 126.2, 119.6, 118.0, 42.3, 41.9, 25.5, 18.1, 14.1, 13.1, −4.5. IR (NaCl, cm^{-1}): 2932, 2859, 1727, 1702, 1591, 1562, 1462, 1420, 1393, 1243, 1221, 1153. HR-MS (FAB+) calcd for $C_{18}H_{27}O_4N^{79}BrSi$ (M − 1): 428.0893, found 428.0899.

Synthesis of compounds 31a and 31b

To a stirred solution of 2-bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-formylphenyl diethylcarbamate (1.89g, 4.40 mmol) in 50 mL dichloromethane was added mCPBA (3.79g, 77% max.) at 0 °C, and the solution was slowly warmed to room temperature and stirred for 1 day. The reaction was quenched by NH_4Cl (sat.) solution at 0 °C, and after separation, the aqueous phase was re-extracted by EtOAc three times, the combined EtOAc solution was to added hexanes, and then washed with $NaHCO_3$ (sat.) and brine sequentially and dried over $MgSO_4$. The filtrate was evaporated and the desired crude 2-bromo-6-((*tert*-butyldimethylsilyl)oxy)-3-((diethylcarbamoyl)oxy)phenyl formate was directly used in the next step.

The crude 2-bromo-6-((*tert*-butyldimethylsilyl)oxy)-3-((diethylcarbamoyl)oxy)phenyl formate from the last step was dissolved in 50 mL methanol and K_2CO_3 (1.50 g) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 0.5 hr. The reaction was quenched by NH_4Cl (sat.) at 0 °C, and the aqueous phase was extracted with Et_2O three times. The organic phase was evaporated and then re-dissolved in Et_2O, and hexanes were added, then washed with NH_4Cl (sat.) and brine. After drying over $MgSO_4$, the filtrate was evaporated and the crude **30** was directly used in the next step.

The crude **30** was dissolved in 50 mL dichloromethane and cooled to 0 °C, then diisopropylamine (6.17 mL, 35.2 mmol) was added, followed by MOMCl (1.34 mL, 17.6 mmol). The reaction mixture was evaporated 1 h later and the residue was chromatographed

(hexanes:EtOAc = 9:1 to 7:1) to give the desired product **31a** (1.17 g, 2.53 mmol, 58% yield for 3 steps).

In another batch, the crude phenol **30** (prepared from 1.11 g 2-bromo-4-((*tert*-butyldimethylsilyl)oxy)-3-formylphenyl diethylcarbamate) in 10 mL of MeOH and 10 mL of PhH was added $TMSCHN_2$ (1.94 mL, 1.5 equiv.) dropwise. The reaction mixture was stirred at room temperature for 2 h. After removal of the solvents, the residue was purified by flash chromatography (hexane / EtOAc : 90 / 10) to give 0.75 g desired product **31b** in 65% yield over three operations.

31a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.16 (s, 2H), 3.63 (s, 3H), 3.48 (q, J = 7.2 Hz, 2H), 3.38 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 0.98 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 146.4, 146.3, 143.6, 119.4, 118.7, 113.3, 98.7, 58.2 42.3, 41.9, 25.6, 18.1, 14.2, 13.3, −4.5. IR (NaCl, cm^{-1}): 2955, 2931, 2857, 1727, 1483, 1469, 1416, 1388, 1241, 1221, 1154. HR-MS (FAB+) calcd for $C_{19}H_{31}O_4N^{79}BrSi$ (M − 1): 460.1155, found 460.1161.

31b

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.82 (s, 3H), 3.49 (q, J = 6.8 Hz, 2H), 3.39 (q, J = 6.8 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 6.8 Hz, 3H), 1.01 (s, 9H), 0.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 149.2, 146.9, 143.4, 119.5, 118.6, 112.8, 60.0, 42.2, 41.8, 25.4, 18.0, 14.0, 13.1, −4.9. HR-MS (FAB+) calcd for $C_{18}H_{31}O_4N^{79}$ BrSi (M + 1): 432.1206, found 432.1185.

Synthesis of *epi*-33a

(Caution: the sealed tube must be thick and strong enough, and a blast shield is needed) In a flame-dried sealed tube was charged bromide **31a** (37 mg, 0.080 mmol) in 1 mL Et_2O, and the mixture was cooled to −78 °C. Next, *t*-BuLi (1.7 M in pentane, 0.160 mmol) was added dropwise and stirring continued for 10 min. Then aldehyde **32**[xv] (32.8 mg, 0.073 mmol) in 2 mL Et_2O was added dropwise, and the stirring continued for another 10 min. The reaction mixture was warmed to room temperature and then heated at 130 °C in an oil bath for 4 hrs before being quenched by brine at room temperature. The two phases were separated and the aqueous phase was re-extracted by Et_2O twice. The combined organic phase was dried over $MgSO_4$, and after filtration and evaporation, the residue was chromatographed by prep-TLC (hexanes:EtOAc = 50:1) and gave desired product *epi*-**33a** (10:1 d.r. at C8, 31.1 mg, 60% yield).

In a large scale reaction, 11.27 g bromide **31a** and 9.98 g aldehyde **32** (both divided into two identical batches for the reaction and then combined during work-up) gave 8.14 g (51% yield) of the desired product *epi*-**33a**, and only 20 min was needed for heating at 130 °C.

Synthesis of 34a and *epi*-34a

(Caution: the sealed tube must be thick and strong enough, and a blast shield is needed) In a sealed tube was charged *epi*-**33a** (446 mg, 0.623 mmol) in 10 mL THF, and the vessel was placed in a 192 °C oil bath and heated for 11 hrs. The sealed tube was cooled to room temperature and 10 mL MeOH and I_2 (14.7 mg, 0.058 mmol) were added. 3 hrs later, the reaction was quenched by 10% $Na_2S_2O_3$ solution until the color faded. The mixture was evaporated and then partitioned by Et_2O and brine and separated. The aqueous phase was re-extracted by Et_2O twice and the combined organic phase was dried over $MgSO_4$, and the

filtrate was evaporated and chromatographed, providing **34a** (204.4 mg, 0.339 mmol, 54% yield) and *epi*-**34a** (81.4 mg, 0.135 mmol, 22% yield).

Synthesis of *epi*-33a from *epi*-34a

epi-**34a** (20.4 mg, 0.034 mmol) was dissolved in 1 mL dichloromethane, and imidazole (31.8 mg, 0.467 mmol) and TBSCl (43.9 mg, 0.291 mmol) were added sequentially. The reaction mixture was stirred overnight before being quenched by NH_4Cl (sat.). Et_2O and brine were added, and the separated aqueous phase was re-extracted with Et_2O twice. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was evaporated and prep-TLC (hexanes:EtOAc = 10:1) gave the desired product *epi*-**33a** (22.0 mg, 0.031 mmol, 91% yield). This product can be used for the thermal C8 epimerization reaction.

epi-33a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.25 (d, J = 9.6 Hz, 1H), 6.17 (d, J = 9.2 Hz, 1H), 5.16 (d, J = 6.0 Hz, 1H), 5.10 (d, J = 6.0 Hz, 1H), 3.83 (t, J = 8.4 Hz, 1H), 3.53 (s, 3H), 3.65 – 3.50 (m, 2H), 2.15 – 1.91 (m, 4H), 1.86 – 1.78 (m, 1H), 1.75 – 1.67 (m, 1H), 1.61 – 1.51 (m, 1H), 1.00 (s, 9H), 0.903 (s, 9H), 0.896 (s, 3H), 0.83 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), −0.05 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 144.1, 141.5, 139.1, 134.7, 126.7, 120.2, 119.5, 114.4, 111.9, 98.8, 76.8, 76.8, 59.1, 57.6, 47.8, 46.3, 39.5, 30.7, 25.8, 25.8, 19.2, 18.2, 18.0, 12.8, −4.4, −4.4, −4.5, −4.8. $[\alpha]_D^{20}$: +41.44 (c = 0.93, CH_2Cl_2). IR (NaCl, cm^{-1}): 2955, 2929, 2893, 2857, 1570, 1471, 1387, 1251, 1176, 1162, 1094, 1000. HR-MS (FAB+) calcd for $C_{39}H_{68}O_6Si_3$ (M^+): 716.4324, found 716.4312.

33a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 6.46 (d, J = 8.8 Hz, 1H), 6.01 (d, J = 9.6 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H), 5.13 (d, J = 6.0 Hz, 1H), 5.10 (d, J = 6.0 Hz, 1H), 3.82 – 3.63 (m, 3H), 3.52 (s, 3H), 2.25 (dd, J = 13.2, 6.4 Hz, 1H), 2.21 – 1.87 (m, 4H), 1.85 – 1.72 (m, 1H), 1.55 – 1.45 (m, 1H), 1.07 (s, 3H), 0.98 (s, 9H), 0.91 (s, 9H), 0.80 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), −0.08 (s, 3H), −0.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 144.0, 141.7, 137.0, 136.5, 125.4, 120.3, 118.6, 115.0, 111.4, 98.9, 78.8, 78.0, 59.4, 57.7, 50.6, 47.1, 38.4, 30.6, 25.9, 25.8, 25.8, 20.9, 18.3, 18.2, 18.1, 14.0, −4.4, −4.5, −4.5, −4.9, −5.3, −5.3. $[\alpha]_D^{19}$: −1.19 (c = 2.20, CH_2Cl_2). IR (NaCl, cm^{-1}): 2953, 2928, 2887, 2857, 1571, 1471, 1384, 1295, 1252, 1161, 1121, 1088. HR-MS (FAB+) calcd for $C_{39}H_{68}O_6Si_3$ (M^+): 716.4324, found 716.4319.

epi-34a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (d, J = 8.8 Hz, 1H), 6.58 (s, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.24 (d, J = 9.6 Hz, 1H), 6.19 (d, J = 9.2 Hz, 1H), 5.16 (d, J = 6.0 Hz, 1H), 5.09 (d, J = 6.0 Hz, 1H), 3.86 (t, J = 8.4 Hz, 1H), 3.75 – 3.66 (m, 1H), 3.64 – 3.57 (m, 1H), 3.53 (s, 3H), 2.21 – 2.01 (m, 3H), 1.91 (dd, J = 12.4, 7.2 Hz, 1H), 1.78 – 1.53 (m, 4H), 1.00 (s, 9H), 0.91 (s, 3H), 0.90 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 144.1, 141.8, 139.4, 134.6, 126.4, 120.4, 119.4, 114.6, 111.8, 98.8, 77.1, 76.7, 59.3, 57.6, 48.3, 46.6, 39.6, 30.7, 25.8, 25.7, 19.6, 18.1, 18.0, 12.8, −4.3, −4.4, −4.8. $[\alpha]_D^{21}$: +31.43 (c = 0.81, CH_2Cl_2). IR (NaCl, cm^{-1}): 3417, 2954, 2929, 2886, 2857, 1471, 1361, 1295, 1250, 1159, 1116, 1046, 998. HR-MS (FAB+) calcd for $C_{33}H_{54}O_6Si_2$ (M^+): 602.3459, found 602.3461.

34a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H), 6.46 (d, J = 8.4 Hz, 1H), 6.02 (d, J = 9.6 Hz, 1H), 5.93 (d, J = 9.2 Hz, 1H), 5.14 (d, J = 6.0 Hz, 1H), 5.07 (d, J =

6.0 Hz, 1H), 3.82 – 3.65 (m, 3H), 3.52 (s, 3H), 2.30 (dd, J = 13.6, 6.4 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.11 – 1.91 (m, 3H), 1.90 – 1.78 (m, 1H), 1.73 (s, br, 1H), 1.57 – 1.47 (m, 1H), 1.06 (s, 3H), 0.98 (s, 9H), 0.91 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 144.0, 141.9, 137.2, 136.3, 125.4, 120.4, 118.5, 115.0, 111.2, 98.8, 79.3, 78.0, 59.4, 57.6, 50.7, 47.1, 37.5, 30.6, 25.8, 25.7, 20.6, 18.1, 18.0, 14.0, −4.5, −4.9. $[\alpha]_D^{20}$: +4.75 (c = 2.04, CH_2Cl_2). IR (NaCl, cm^{-1}): 3413, 2955, 2929, 2892, 2857, 1472, 1386, 1296, 1252, 1159, 1120. HR-MS (FAB+) calcd for $C_{33}H_{54}O_6Si_2$ (M^+): 602.3459, found 602.3476.

Synthesis of *epi*-33b

(Caution: the sealed tube must be thick and strong enough, and a blast shield is needed) To a solution of bromide **31b** (72 mg, 0.166 mmol) in Et_2O (3 mL) was added *t*-BuLi (0.215 mL, 0.366 mmol, 1.7 M in pentane) at −78 °C. The reaction mixture was stirred for 30 min, then a solution of aldehyde **32** (68 mg, 0.151 mmol) in Et_2O (3 mL) was added slowly. After 30 min at −78 °C, the reaction was warmed to room temperature for 1 h, then heated at 130 °C for 5 h. After cooling to 0 °C, it was quenched with aqueous saturated NH_4Cl. The mixture was extracted with ether 3 times and the combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexane / EtOAc : 98 / 2 to 97 / 3) to give 52 mg of **33b** in 50% yield (10:1 dr).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 6.47 (s, 1H), 6.24 (d, J = 9.2 Hz, 1H), 6.17 (d, J = 9.2 Hz, 1H), 3.83 (t, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.53-3.62 (m, 2H), 1.92-2.12 (m, 4H), 1.78-1.85 (m, 1H), 1.67-1.71 (m, 1H), 1.54-1.59 (m, 1H), 1.01 (s, 9H), 0.90 (s, 9H), 0.89 (s, 3H), 0.82 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), −0.06 (s, 3H), −0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 146.9, 142.1, 139.1, 134.9, 126.7, 120.5, 118.9, 113.9, 111.7, one overlaps with $CDCl_3$, 76.9, 60.8, 59.2, 48.0, 46.4, 39.8, 30.7, 25.84, 25.76, 19.3, 18.2, 18.1, 12.8, −4.3, −4.58, −4.63, −4.8, −5.37, −5.43. HR-MS (FAB+) calcd for $C_{38}H_{66}O_5Si_3$: 686.4218. found 686.4204.

Synthesis of 34b and *epi*-34b

(Caution: the sealed tube must be thick and strong enough, and a blast shield is needed) The solution of *epi*-**33b** (420 mg, 0.611 mmol) in 20 mL THF in a sealed tube was heated at 198 °C for 36 h. After the reaction mixture was cooled to room temperature, 20 mL of MeOH and 7.8 mg of I_2 (0.05 equiv., 0.031 mmol) were added. After 8 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and 20% aqueous $Na_2S_2O_3$. The mixture was extracted twice with ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$, 20% aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$. Concentration and flash column chromatography (hexane / EtOAc : 96 / 4) gave **34b** (215 mg) in 62% yield as well as *epi*-**34b** (87 mg) in 25% yield.

34b

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 8.4 Hz, 1H), 6.46 (s, 1H), 6.45 (d, J = 8.8 Hz, 1H), 6.02 (d, J = 10.0 Hz, 1H), 5.94 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 3.71-3.81 (m, 3H), 2.10-2.33 (m, 2H), 1.78-2.09 (m, 4H), 1.48-1.56 (m, 1H), 1.07 (s, 3H), 1.01 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 146.8, 142.6, 137.1, 136.5, 125.3, 120.6, 117.8, 114.5, 111.1, 79.3, 78.0, 60.8, 59.4, 50.7, 47.1, 37.5, 30.6, 25.8, 25.7, 20.7, 18.2, 18.0, 14.0, −4.5, −4.6, −4.7, −4.9. HR-MS (FAB+) calcd for $C_{32}H_{52}O_5Si_2$: 572.3353, found: compound is not stable under various mass conditions.

Synthesis of 35a

To a stirred solution of **34a** (338.4 mg, 0.56 mmol) in 2 mL dichloromethane was added pyridine (0.20 mL), 4-dimethylaminopyridine (10.5 mg), and *p*-toluenesulfonyl chloride (300.2 mg, 1.57 mmol). The reaction mixture was stirred overnight before being quenched by NH_4Cl (sat.), then Et_2O and brine were added, and the separated aqueous phase was re-extracted with Et_2O twice. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was evaporated and flash column chromatography (hexanes:EtOAc = 1:0 to 9:1) gave the desired product **35a** (403.8 mg, 0.533 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 6.32 (d, J = 8.8 Hz, 1H), 5.98 (d, J = 9.6 Hz, 1H), 5.90 (d, J = 9.6 Hz, 1H), 5.11 (d, J = 6.0 Hz, 1H), 5.06 (d, J = 6.0 Hz, 1H), 4.20 – 4.11 (m, 1H), 4.11 – 4.03 (m, 1H), 3.72 (t, J = 8.0 Hz, 1H), 3.50 (s, 3H), 2.43 (s, 3H), 2.28 – 2.10 (m, 3H), 2.05 – 1.94 (m, 1H), 1.91 – 1.82 (m, 1H), 1.68 – 1.55 (m, 1H), 1.52 – 1.41 (m, 1H), 1.00 (s, 9H), 0.94 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 144.4, 144.0, 142.1, 137.0, 135.2, 132.9, 129.7, 127.8, 125.2, 120.6, 118.4, 115.5, 111.2, 98.7, 77.8, 77.7, 67.0, 57.6, 50.2, 46.9, 34.1, 30.4, 25.7, 25.7, 21.5, 20.5, 18.1, 18.0, 13.8, −4.5, −4.9. $[\alpha]_D^{19}$: +24.37 (c = 2.39, $C_1H_2Cl_2$). IR (NaCl, cm^{-}): 2954, 2929, 2887, 2857, 1472, 1386, 1363, 1252, 1178, 1124. HR-MS (FAB+) calcd for $C_{40}H_{60}O_8Si_2S$ (M^+): 756.3547, found 756.3535.

Synthesis of 35b

To a solution of **34b** (215 mg, 0.376 mmol) and pyridine (304 μL, 3.76 mmol) in 15 mL CH_2Cl_2 was added MsCl (146 μL, 1.88 mmol) slowly at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours before it was quenched with aqueous saturated NH_4Cl. The mixture was extracted with ether and washed with 1N HCl, water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane / EtOAc : 92 / 8) to give the desired product (220 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (d, J = 8.8 Hz, 1H), 6.50 (s, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.03 (d, J = 9.6 Hz, 1H), 5.95 (d, J = 9.2 Hz, 1H), 4.35-4.41 (m, 1H), 4.23-4.29 (m, 1H), 3.79 (s, 3H), 3.76 (t, J = 8.4 Hz, 1H), 2.83 (s, 3H), 2.27-2.38 (m, 3H), 1.94-2.06 (m, 2H), 1.69-1.75 (m, 1H), 1.49-1.56 (m, 1H), 1.07 (s, 3H), 1.00 (s, 9H), 0.91 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 146.7, 142.8, 137.2, 135.5, 125.2, 120.9, 117.7, 115.0, 111.2, 77.9, 77.8, 66.3, 60.9, 50.3, 47.0, 37.2, 34.4, 30.5, 25.8, 25.7, 20.8, 18.2, 18.0, 14.0, −4.5, −4.6, −4.7, −4.9. FT-IR (NaCl, cm^{-1}): 2955, 2926, 2858, 1475, 1361, 1254. HR-MS (FAB+) calcd for $C_{33}H_{54}O_7Si_2S$: 650.3129, found 650.3131.

Synthesis of 36a

To a vial with 2 mL THF solution of **35a** (46.6 mg, 0.062 mmol) was added TBAF (1.0 M in THF, 0.065 mL). After stirring for 5 min, the reaction mixture was heated at 70 °C for 30 min. The vial was cooled to r.t. and all the volatiles were evaporated. Flash column chromatography (hexanes:EtOAc = 9:1) gave the desired product **36a** (27.3 mg) in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (d, J = 10.0 Hz, 1H), 6.53 (s, 1H), 6.25 (d, J = 9.6 Hz, 1H), 6.22 (d, J = 10.0 Hz, 1H), 6.05 (d, J = 9.6 Hz, 1H), 5.15 (d, J = 6.0 Hz, 1H), 5.10 (d, J = 6.0 Hz, 1H), 3.85 (t, J = 8.4 Hz, 1H), 3.51 (s, 3H), 2.31 – 1.96 (m, 5H), 1.93 – 1.86 (m, 1H), 1.80 – 1.65 (m, 2H), 1.60 – 1.50 (m, 1H), 0.95 (s, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 150.5, 147.1, 144.2, 142.4, 140.7, 129.1, 125.5, 115.5, 97.7, 85.2, 77.3, 77.1, 57.5, 47.5, 46.1, 37.7, 30.3, 29.4, 25.8, 19.2, 18.0, 15.0, −4.4,

−4.9. $[\alpha]_D^{20}$: +109 (c = 2.20, CH_2Cl_2). IR (NaCl, cm^{-1}): 2954, 2928, 2896, 2855, 1659, 1633, 1583, 1149, 1119, 1018. HR-MS (FAB+) calcd for $C_{27}H_{39}O_5Si$ (M + 1): 471.2567, found 471.2576.

Synthesis of 36b

To a solution of mesylate **35b** (300.8 mg, 0.462 mmol) in 18 mL THF was added TBAF (1.0 M in THF, 508 μL, 0.508 mmol). The reaction mixture was stirred for 15 min at room temperature, and then heated to 130 °C for 1 h (oil bath). After it was cooled to room temperature, it was quenched with aqueous saturated NH_4Cl. The mixture was extracted with EtOAc three times. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (hexane / EtOAc : 90 / 10) to give the desired product **36b** (194 mg, 95%).

^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, J = 10.0 Hz, 1H), 6.45 (s, 1H), 6.22 (d, J = 9.6 Hz, 1H), 6.19 (d, J = 10.0 Hz, 1H), 6.03 (d, J = 9.6 Hz, 1H), 3.83 (t, J = 8.4 Hz, 1H), 3.78 (s, 3H), 1.94-2.27 (m, 5H), 1.84-1.89 (s, 1H), 1.67-1.74 (m, 2H), 1.52-1.58 (m, 1H), 0.93 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 150.2, 146.9, 143.7, 143.4, 142.2, 129.2, 125.4, 115.3, 85.1, 77.15, 77.09, 60.6, 47.4, 46.1, 37.6, 30.3, 29.4, 25.7, 19.1, 17.9, 14.9, −4.5, −4.9. FT-IR (NaCl, cm^{-1}): 2955, 2858, 1775, 1731, 1659, 1631, 1582, 1462, 1441, 1399. $[\alpha]_D^{19}$: −126.47 (c 0.45, $CHCl_3$). HR-MS (FAB+) calcd for $C_{26}H_{37}O_4Si$: 441.2461; found 441.2471.

Synthesis of 38a

To a stirred solution of **36a** (51 mg, 0.11 mmol) in 2 mL THF was added L-Selectride (1.0 M, 0.12 mL) at −78 °C. 20 min later, 5,5-dibromo-Meldrum's acid **37** (39.5 mg, 0.13 mmol) was added in one portion. 0.5 hr later, the reaction was quenched by adding NH_4Cl (sat.), then EtOAc and brine were added, and the separated aqueous phase was re-extracted with EtOAc twice. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was evaporated and flash column chromatography (hexanes:EtOAc = 9:1) gave the desired product **38a** (38 mg, 0.069 mmol, 62% yield). It is recommended that the product be used in the next step as soon as possible.

Selected characterization of **38a**: ^1H NMR (400 MHz, $CDCl_3$) key peaks: δ 6.46 (s, 1H, *a*-Br-**38a**), 6.41 (s, 1H, *e*-Br-**38a**), 4.80 (dd, J = 14.0, 5.2 Hz, 1H, *e*-Br-**38a**), 4.68 (dd, J = 4.8, 2.0 Hz, 1H, *a*-Br-**38a**). HR-MS (FAB+) calcd for $C_{27}H_{40}O\,^{79}{}_5BrSi$ (M + 1): 551.1828, found 551.1854.

Synthesis of 3,4-dihydro-36b

To a cooled (−78 °C) solution of **36b** (37.1 mg, 84.2μmol; azeotroped twice with benzene) in THF (4 mL) was added L-Selectride (1.0 M in THF, 92μL, 92μmol) dropwise. The clear, yellow solution was stirred for 22 min at −78 °C, then quenched by successive addition of MeOH (0.10 mL), NaOH (1.0 M in H_2O, 0.50 mL), and H_2O_2 (30 wt % in H_2O, 80μL). The mixture was allowed to warm to room temperature with vigorous stirring. The resulting clear, dull yellow solution was then diluted with EtOAc (12 mL) and brine (6 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a cloudy yellow oil. Purification by flash chromatography (10% EtOAc/hexanes) afforded the desired trienone product 3,4-dihydro-**36b** as a clear, yellow oil in 80% yield (30.0 mg, 67.8 μmol).

^1H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 1H), 6.25 (d, J = 9.4 Hz, 1H), 6.04 (d, J = 9.4 Hz, 1H), 3.83 (t, J = 8.2 Hz, 1H), 3.71 (s, 3H), 2.67 – 2.58 (m, 1H), 2.52 (td, J = 14.3, 4.4 Hz, 1H), 2.43 (td, J = 14.3, 4.8 Hz, 1H), 2.24 – 2.11 (m, 3H), 2.10 – 1.99 (m, 3H), 1.96 – 1.87

(m, 1H), 1.79 – 1.63 (m, 2H), 1.59 – 1.48 (m, 1H), 0.93 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 152.4, 145.7, 143.2, 142.7, 125.4, 115.4, 82.4, 79.2, 77.2, 60.6, 47.4, 46.2, 36.4, 35.1, 33.2, 31.5, 30.3, 25.8, 19.3, 18.0, 14.6, −4.4, −4.9. $[\alpha]_D^{19}$: −70.28 (c = 0.88, $CHCl_3$). IR (NaCl, cm^{-1}): 2955, 2887, 2857, 1672, 1585, 1464, 1440, 1367, 1121. HR-MS (FAB+) calcd for $C_{26}H_{39}O_4Si$ (M+1): 443.2613, found 443.2602.

Synthesis of 3-bromo-3,4-dihydro-36b (38b)

To a cooled (−78 °C) solution of trienone 3,4-dihydro-**36b** (35.8 mg, 80.9 μmol; azeotroped twice with benzene) in THF (1.5 mL) was added LiHMDS (1.0 M in THF, 89 μL, 89 μmol) quickly down the side of the flask. The resulting clear, bright yellow solution was stirred at −78 °C for 20 min. A clear, colorless solution of **37** (1.0 M in THF, 100 μL, 100 μmol; freshly prepared) was then added quickly down the side of the flask. After stirring at −78 °C for 50 min (TLC indicated some starting material remained; some di-bromination is also generally observed), the reaction was quenched with $Na_2S_2O_3$ (10% in H_2O, 10 mL) and allowed to warm to room temperature with vigorous stirring. The mixture was then extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. Purification by flash chromatography (5% EtOAc/hexanes) afforded **38b** as a yellow foam in 73% yield (30.7 mg, 58.9 μmol, 1:1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$, peaks for both diastereomers): δ 6.39 (s, 1H), 6.35 (s, 1H), 6.30 (d, J = 9.3 Hz, 1H), 6.29 (d, J = 9.3 Hz, 1H), 6.04 (d, J = 9.5 Hz, 1H), 6.04 (d, J = 9.4 Hz, 1H), 4.77 (dd, J = 14.1, 5.0 Hz, 1H), 4.66 (dd, J = 4.7, 2.2 Hz, 1H), 3.84 (t, J = 8.2 Hz, 1H), 3.83 (t, J = 8.2 Hz, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 2.96 (dd, J = 15.0, 4.8 Hz, 1H), 2.91 (dd, J = 14.0, 12.3 Hz, 1H), 2.66 (dd, J = 12.2, 5.0 Hz, 1H), 2.48 (dd, J = 15.0, 2.0 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.22 – 2.09 (m, 6H), 2.09 – 1.99 (m, 2H), 1.97 – 1.89 (m, 2H), 1.74 – 1.64 (m, 4H), 1.60 – 1.49 (m, 2H), 0.94 (s, 3H), 0.93 (s, 3H), 0.90 (s, 18H), 0.06 (s, 6H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, peaks for both diastereomers): δ 186.2, 186.1, 153.2, 153.1, 146.2, 145.8, 143.6, 143.5, 141.7, 141.5, 125.4, 125.3, 115.1, 115.0, 82.6, 81.5, 78.3, 77.6, 77.1, 60.7, 60.2, 48.4, 47.6, 47.5, 46.0, 45.9, 45.2, 44.8, 40.9, 38.2, 36.6, 31.4, 31.2, 30.3, 25.8, 19.2, 18.0, 14.6, −4.4, −4.9. $[\alpha]_D^{21}$: −16.6 (c = 0.91, CH_2Cl_2).IR (NaCl, cm^{-1}): 2954, 2930, 2884, 2856, 1671, 1580, 1471, 1462, 1439, 1367, 1312, 1302, 1283, 1258, 1213, 1193, 1169, 1120, 1093, 1046, 1031, 1013, 952, 903, 874, 860, 837, 776, 740. HR-MS (FAB+) calcd for $C_{26}H_{38}O\ ^{79}_4BrSi$ (M+1): 521.1723, found 521.1714.

Synthesis of 40b

To a clear, pale yellow solution of **38b** (18.2 mg, 34.9 μmol; azeotroped twice with benzene) in DMF (0.70 mL) was added sodium azide (3.4 mg, 52.3 μmol). The resulting mixture was stirred at room temperature for 1 hr, then a second portion of sodium azide (3.4 mg, 52.3 μmol) was added. A reddish brown color was observed over time. After a total reaction time of 5hrs, TLC analysis indicated consumption of starting material. To this mixture was added paraformaldehyde (11.0 mg, 0.366 mmol, based on monomer), sodium triacetoxyborohydride (37.1 mg, 0.175 mmol), and glacial acetic acid (2 μL, 34.9μmol). The cloudy, orange-brown suspension was then heated in a 50 °C oil bath. Additional portions of paraformaldehyde were added at 2 hrs (11.0 mg, 0.366 mmol) and 5 hrs (5.6 mg, 0.186 mmol). After a total reaction time of 6 hrs, the reaction was quenched at room temperature by dropwise addition NaOH (1.0 M in H_2O, 7 mL). The aqueous phase was saturated by the addition of solid NaCl and extracted with Et_2O (3 × 14 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a clear, yellow-orange oil. Purification by flash chromatography (8% EtOAc/hexanes with 1% Et_3N) afforded **40b** as a clear, yellow-orange oil in 69% yield (11.7 mg, 24.2 μmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 1H), 6.23 (d, J = 9.3 Hz, 1H), 6.05 (d, J = 9.5 Hz, 1H), 5.79 (s, 1H), 3.84 (dd, J = 8.5, 7.8 Hz, 1H), 3.78 (s, 3H), 2.72 (s, 6H), 2.28 (dd, J = 12.3, 7.4 Hz, 1H), 2.24 – 1.93 (m, 4H), 1.93 – 1.66 (m, 3H), 1.63 – 1.48 (m, 1H), 0.95 (s, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 150.4, 147.0, 143.8, 142.5, 142.0, 125.5, 122.1, 115.2, 84.6, 77.1, 76.4, 60.6, 47.4, 46.3, 42.0, 38.3, 30.4, 29.4, 25.8, 19.2, 18.0, 15.0, −4.4, −4.9. $[\alpha]_D^{20}$: −148.3 (c = 0.515, CH_2Cl_2). IR (NaCl, cm^{-1}): 2953, 2857, 2360, 2342, 1650, 1588, 1471, 1462, 1439, 1375, 1322, 1283, 1258, 1215, 1157, 1120, 1098, 1051, 1014, 968, 904, 887, 868, 837, 799, 776. HR-MS (FAB+) calcd for $C_{28}H_{42}O_4NSi$ (M+1): 484.2883, found 484.2893.

Synthesis of 42b

To a clear, yellow solution of **40b** (2.9 mg, 6.0 μmol) in CH_2Cl_2 (0.30 mL) was added sodium triacetoxyborohydride (9.2 mg, 43μmol) and glacial acetic acid (3μL, 52μmol). After 36 hrs, the reaction was quenched by carefully adding it to another flask containing NaOH (1.0 M in H_2O, 3 mL). The aqueous phase was saturated by the addition of solid NaCl, then the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a clear, golden yellow oil. The amine product has a tendency to undergo spontaneous oxidation back to the enamine (and decompose by other pathways), and thus the crude amine **42b** was generally carried directly into the next step without further purification.

Synthesis of 43b

To a cooled (−78 °C) solution of the crude aminoketone (from the previous step) in THF (0.40 mL) was added DIBAL-H (1.0 M in toluene, 10 μL, 10 μmol). The clear, yellow solution was stirred at −78 °C for 30 min, then a second portion of DIBAL-H (1.0 M in toluene, 10 μL, 10 μmol) was added. After a total reaction time of 50 min, the reaction was quenched at −78 °C by the addition of EtOAc (50 μL). Saturated aqueous Rochelle salt (2 mL) was then added, and the mixture was stirred vigorously for ca. 1.5 hrs while allowing to warm to room temperature, resulting in a biphasic mixture with a clear, yellow layer on top, and a clear, colorless layer below. The aqueous phase was extracted with EtOAc (3 × 3 mL), then the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a clear, orange-yellow oil. Purification by flash chromatography (5–20% MeOH/CH_2Cl_2) afforded **43b** as a minor product in < 20% yield and moderate purity (ca. 0.5 mg).

Selected characterization of **43b**: ^{1}H NMR (500 MHz, $CDCl_3$) key peaks: δ 6.21 (s, 1H), 5.97 (d, J = 9.4 Hz, 1H), 5.93 (d, J = 9.4 Hz, 1H), 4.39 (d, J = 8.5 Hz, 1H), 3.79 (t, J = 8.2 Hz, 1H), 3.74 (s, 3H), 2.82 – 2.74 (m, 1H), 2.37 (s, 6H). HR-MS (FAB+) calcd for $C_{28}H_{46}O_4NSi$ (M+1): 488.3196, found 488.3181.

Synthesis of 42a

To a stirred solution of **38a** (111.9 mg, 0.203 mmol) in 5 mL THF was added tetrabutylammonium azide (103.0 mg, 0.363 mmol) in one portion, and 50 min later, the solvent was evaporated and the crude mixture of **40a** was covered by argon and directly used in the next step.

The crude mixture of **40a** was re-dissolved in dichloromethane and $NaBH_3(CN)$ (36 mg) was added, followed by adding HOAc (0.40 mL) dropwise. 5 min later, 138 mg $NaBH_3(CN)$ was added in 3 portions, and the reaction mixture was stirred for 10 min before being quenched by adding $NaHCO_3$ (sat.) slowly. The two phases were separated and the aqueous phase was re-extracted by dichloromethane, and the combined dichloromethane solution was evaporated and immediately used in the next step. The product **41a** is not very stable to air, and rapid operation is recommended.

To a stirred solution of **41a** in 10 mL methanol was added a methanol solution (10 mL) of $CeCl_3 \cdot 7H_2O$ (0.18 g), and stirring continued for 2 min at 0 °C. $NaBH_4$ (0.20 g + 0.24 g + 0.21 g) was added in three portions with an interval of 15 min, and the total reaction lasted for 1 hr. Methanol was evaporated and Et_2O, brine and $NH_3 \cdot H_2O$ (28%) were added, and the organic phase was separated and the aqueous phase was re-extracted with Et_2O twice. The combined organic phase was dried over Na_2SO_4, and prep-TLC (dichloromethane:methanol = 5:1, with a few drops of $NH_3 \cdot H_2O$) gave the desired product **42a** (41.4 mg, 0.085 mmol, 42% yield from **38a**).

42a

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 6.00 (d, J = 9.2 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H), 4.98 (d, J = 6.4 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.06 (d, J = 8.0 Hz, 1H), 3.79 (t, J = 8.0 Hz, 1H), 3.52 (s, 3H), 3.01 (m, 1H), 2.21 – 1.45 (m, 11H), 0.90 (s, 12H, C18 methyl and *tert*-butyl), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 144.5, 138.0, 126.1, 125.6, 114.9, 96.6, 82.1, 78.6, 77.5, 73.7, 56.8, 52.6, 47.0, 46.4, 41.4, 39.4, 33.3, 30.6, 25.7, 19.2, 18.0, 14.3, −4.5, −5.0. $[\alpha]_D^{19}$: +2.18 (c = 1.51, CH_2Cl_2). IR (NaCl, cm^{-1}): 3351, 3287, 2954, 2931, 2886, 2858, 1639, 1470, 1386, 1360, 1303, 1254, 1155, 1119, 1009. HR-MS (FAB+) calcd for $C_{27}H_{44}O_5NSi$ (M + 1): 490.2989, found 490.3006.

Synthesis of 45

To a stirred solution of **36a** (27.3 mg, 0.057 mmol) in 1 mL THF was added 0.063 mL L-Selectride (1.0 M in THF) at −78 °C. 5 min later, 0.10 mL H_2O was added and the whole reaction mixture was warmed to 0 °C. Next, 2 mL MeOH was added, followed by $CeCl_3 \cdot 7H_2O$ (36.3 mg) and then $NaBH_4$ (15.3 mg). 5 min later, aqueous NH_4Cl solution (sat.) was added, followed by Et_2O and brine. After separation, the aqueous layer was re-extracted by Et_2O twice. The combined organic layer was dried over Na_2SO_4, and after evaporation of the solvents, prep-TLC (hexanes : EtOAc = 2 : 1) gave the desired product **45** (18.0 mg, 65% yield from **36a**).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.99 (d, J = 9.6 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H), 4.95 (d, J = 6.4 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.44 (t, J = 8.0 Hz, 1H), 3.79 (t, J = 8.0 Hz, 1H), 3.52 (s, 3H), 3.18 (s, 1H), 2.34 – 2.26 (m, 1H), 2.22 – 2.08 (m, 2H), 2.08 – 1.84 (m, 5H), 1.84 – 1.76 (m, 1H), 1.74 – 1.58 (m, 3H), 1.57 – 1.46 (m, 1H), 0.89 (s, 12H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 145.5, 138.1, 125.6, 115.0, 97.1, 82.1, 79.5, 77.6, 66.2, 56.8, 47.1, 46.6, 39.0, 33.3, 32.4, 30.6, 28.8, 25.8, 19.3, 18.0, 14.4, −4.4, −4.9. $[\alpha]_D^{20}$: −5.14 (c = 2.92, CH_2Cl_2). IR (NaCl, cm^{-1}): 3424, 2954, 2886, 2859, 1637, 1462, 1388, 1361, 1256, 1156, 1120, 1100, 1006, 956, 869, 837, 776. HR-MS (FAB+) calcd for $C_{27}H_{42}O_5Si$ (M^+): 474.2802, found 474.2812.

Acetylation of 45

Compound **45** (15.7 mg, 0.033 mmol) was dissolved in 1 mL CH_2Cl_2. 0.05 mL pyridine and 5.3 mg DMAP were added, followed by 0.03 mL Ac_2O. The reaction was quenched 20 min later by adding MeOH, and aqueous $NaHCO_3$ (sat.) was added 2 min later. The aqueous mixture was extracted with Et_2O three times, and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvents, prep-TLC (hexanes : EtOAc = 3 : 1) gave the desired product (13.6 mg, 0.026 mmol) in 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (s, 1H), 6.01 (d, J = 9.6 Hz, 1H), 5.93 (d, J = 9.6 Hz, 1H), 5.66 (dd, J = 8.8, 7.2 Hz, 1H), 4.87 (d, J = 6.4 Hz, 1H), 4.76 (d, J = 6.0 Hz, 1H), 3.80 (t, J = 8.0 Hz, 1H), 3.43 (s, 3H), 2.43 – 2.34 (m, 1H), 2.09 (s, 3H), 2.26 – 1.46 (m, 12H), 0.90 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 145.8, 142.3, 138.4, 130.1, 125.6, 115.0, 97.2, 82.2, 79.1, 77.6, 68.8, 56.9, 47.1, 46.5, 38.6,

33.1, 32.3, 30.6, 26.5, 25.8, 21.2, 19.3, 18.0, 14.4, −4.4, −4.9. $[\alpha]_D^{17}$: +35.1 (c = 1.36, CH_2Cl_2). IR (NaCl, cm^{-1}): 2954, 2926, 2856, 1739, 1636, 1472, 1369, 1246, 1157, 1120, 1102, 1050, 1013, 951, 895, 867, 837, 775. HR-MS (FAB+) calcd for $C_{29}H_{44}O_6Si$ (M^+): 516.2907, found 516.2934.

Synthesis of 58

To a stirred solution of **43a** (41.4 mg, 0.085 mmol) in 3 mL dioxane was added 0.50 mL 10% aq. Na_2CO_3, and then a solution of 125.0 mg Fmoc-OSu in 2 mL dioxane was added. 2 hrs later, the reaction mixture was evaporated and the residue was taken up by Et_2O, brine and NH_4Cl (sat.), and separated. The aqueous phase was re-extracted by Et_2O twice, and the combined organic phase was dried over Na_2SO_4, and then evaporated. The crude mixture of **44a** was directly used in the next step.

The mixture of **44a** was dissolved in 20 mL dichloromethane, and 4-dimethylaminopyridine (48.0 mg) was added, followed by pyridine (0.40 mL). Acetic anhydride (0.25 mL) was then added dropwise. 10 min later, all volatiles were evaporated and the residue was purified by flash column chromatography (hexanes:EtOAc = 4:1) to give the desired product **58** (44.5 mg, 0.059 mmol) in 70% yield for 2 steps.

58

^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.0 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 6.16 (s, 1H), 6.05 (d, J = 9.0 Hz, 1H), 5.94 (d, J = 9.5 Hz, 1H), 5.68 (d, J = 8.5 Hz, 1H), 5.17 (d, J = 7.5 Hz, 1H), 4.86 (d, J = 6.0 Hz, 1H), 4.77 (d, J = 6.0 Hz, 1H), 4.40 – 4.28 (m, 2H), 4.22 (t, J = 7.5 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.80 (t, J = 8.0 Hz, 1H), 3.43 (s, 3H), 2.28 – 1.48 (m, 14H), 0.91 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 155.8, 146.3, 143,8, 141.2, 140.0, 139.0, 130.0, 127.7, 127.0, 125.4, 125.1, 119.9, 114.5, 97.5, 82.4, 77.9, 77.5, 71.7, 66.9, 57.0, 51.2, 47.2, 47.1, 46.4, 39.4, 38.5, 33.0, 30.5, 25.8, 21.1, 19.2, 18.0, 14.3, −4.4, −4.9. $[\alpha]_D^{18}$: +65.27 (c = 2.95, CH_2Cl_2). IR (NaCl, cm^{-1}): 3314, 2955, 2930, 2886, 2857, 1736, 1694, 1641, 1549, 1450, 1375, 1297, 1260, 1233, 1159, 1119, 1016. HR-MS (FAB+) calcd for $C_{44}H_{55}O_8NSi$ (M^+): 753.3697, found 753.3690.

Synthesis of 61

To a solution of **58** (43.8 mg, 0.058 mmol) in 2 mL THF was added 0.5 mL water, and the reaction mixture was cooled to 0 °C. Then 0.10 mL solution of Br_2 in THF (made by adding 0.033 mL Br_2 into 1.0 mL THF) was added dropwise, and the whole reaction mixture was stirred for 2 min before quenching by 10% aqueous solution of $Na_2S_2O_3$. Et_2O and brine were added, and the two layers were separated. The organic layer was re-extracted by Et_2O twice. The combined organic phase was dried over $MgSO_4$, and after filtration, the solvent was evaporated. The crude mixture **59** (about 49.1 mg) was directly used in the next step. This procedure was used for other bromine-induced MOM deprotection reactions.

The crude mixture of **59** was evenly divided into three batches. In each batch, 16.4 mg crude **59** was dissolved in 0.8 mL C_6D_6 in a J-Young NMR tube, and then a C_6D_6 solution of AIBN (2 mg in 0.20 mL C_6D_6) was added. The whole mixture was degassed twice (freeze-pump-thaw) and refilled with Ar. Then 0.030 mL *n*-Bu_3SnH was added, and the reaction mixture was further degassed four times before being immersed in a 70 °C oil bath. The reaction was carefully monitored by ^1H NMR, and 4 hrs later, the reaction mixture was cooled and combined. After evaporating all the volatiles, prep-TLC (hexanes:EtOAc = 3 :2) gave 11.5 mg crude product **60** which was used directly in the next step.

Intermediate **60** was dissolved in 1 mL dichloromethane/MeOH (1:1) solution, and the reaction mixture was cooled to 0 °C. $CeCl_3 \cdot 7H_2O$ (7.6 mg) was added, and $NaBH_4$ (5.2 mg) was added to this stirred mixture 2 min later. The reaction was quenched by NH_4Cl (sat.) after 5 min, and brine and dichloromethane were added. The separated aqueous layer was re-extracted with dichloromethane twice, and the combined organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated and prep-TLC gave 4.4 mg crude reduction product, which was directly used in the next step.

The Luche reduction product was dissolved in 1 mL dichloromethane, and 5.5 mg DMAP and 0.040 mL pyridine were added, followed by dropwise addition of 0.030 mL Ac_2O. MeOH was added 10 min later and after 2 min, all volatiles were evaporated and prep-TLC (hexanes:EtOAc = 3:2) gave the desired product **61** (2.9 mg, 7% from **58**).

61

^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 6.8 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 5.81 (s, 1H), 5.61 (d, J = 9.2 Hz, 1H), 5.44 (m, 1H), 5.17 (d, J = 8.4 Hz, 1H), 4.92 (t, J = 8.8 Hz, 1H), 4.34 (m, 2H), 4.20 (t, J = 7.2 Hz, 1H), 3.93 (m, 1H), 3.77 (t, J = 8.4 Hz, 1H), 2.15 (s, 3H), 2.02 (s, 3H), 2.36 – ca. 1.20 (m, 13H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 (s, 6H). IR (NaCl, cm^{-1}): 2954, 2928, 2857, 1741, 1540, 1450, 1376, 1278, 1246, 1143, 1106, 1021. HR-MS (FAB+) calcd for $C_{44}H_{56}O_8NSi$ (M + 1): 754.3775, found 754.3773.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is generously supported by National Institute of Health (HL 25848). Z. W. thanks Eli Lilly for a helpful graduate fellowship (2008 - 2009), M. D. thanks Bristol-Myers Squibb, Guthikonda family, and Roche for financial support. P. K. P. thanks Amgen for a postdoctoral fellowship (2009 - 2010). We thank John Hartung Jr., Feng Peng and Dr. Ping Wang for helpful discussions, and Ms. Rebecca Wilson for preparation of this manuscript.

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xli. Compound **45** was made from **36a** by L-Selectride reduction followed by Luche reduction (one pot, 65% yield).

xlii. Compound **50** was made by acetylation of **45** (Ac_2O/py/DMAP in dichloromethane, 80% yield) followed by bromine-induced MOM deprotection (Br_2/H_2O-THF, 0 °C).

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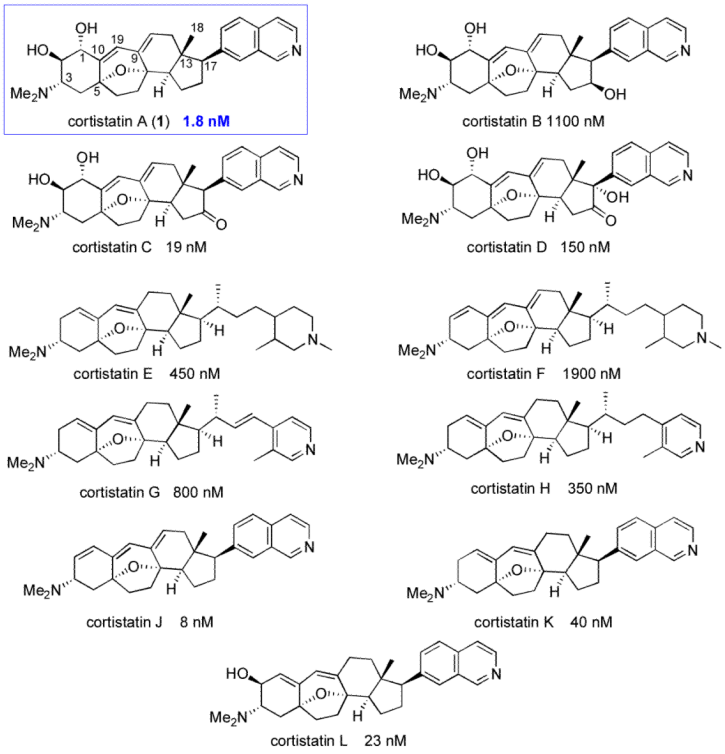
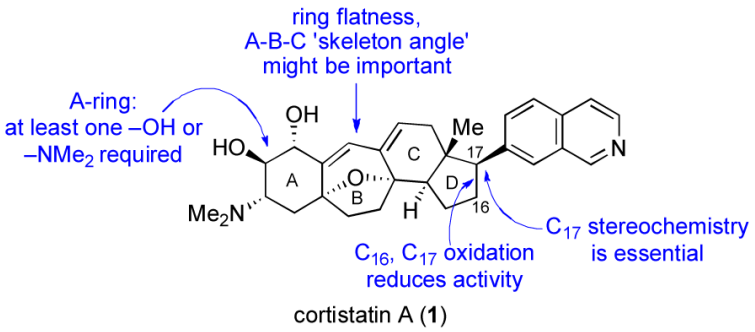
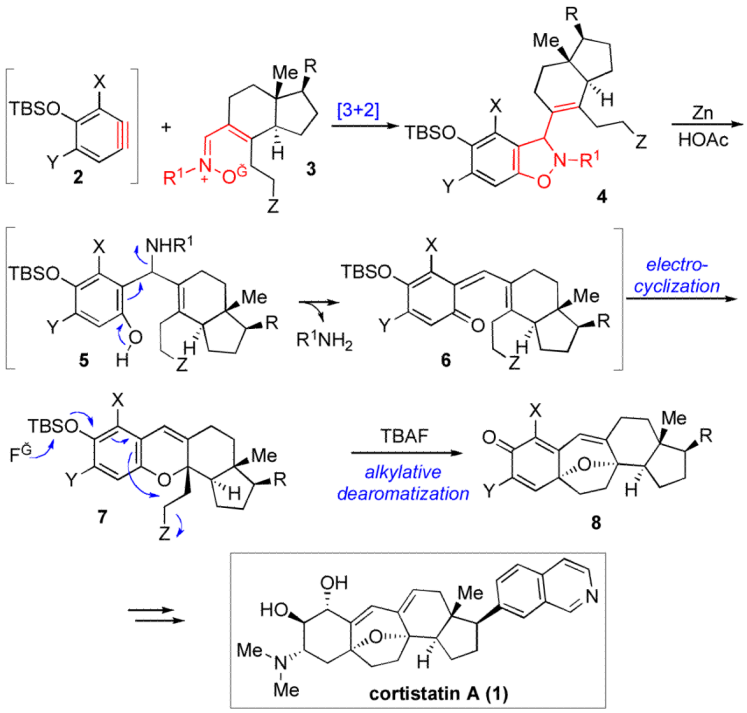


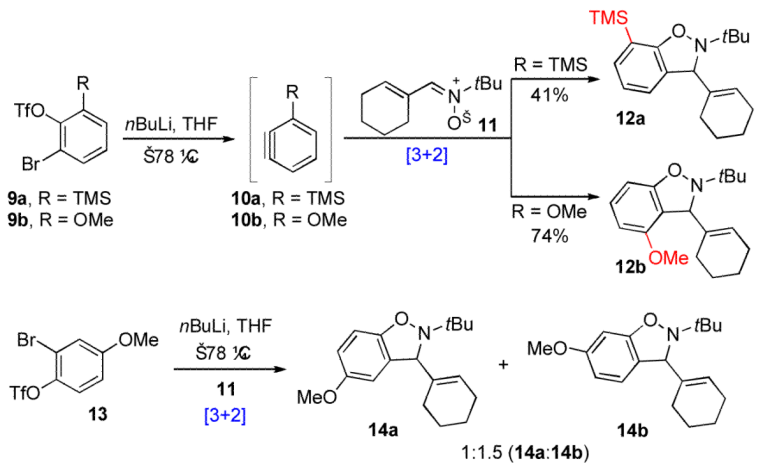
Scheme 1.
Cortistatin family of natural products and their IC_{50} values against HUVECs.



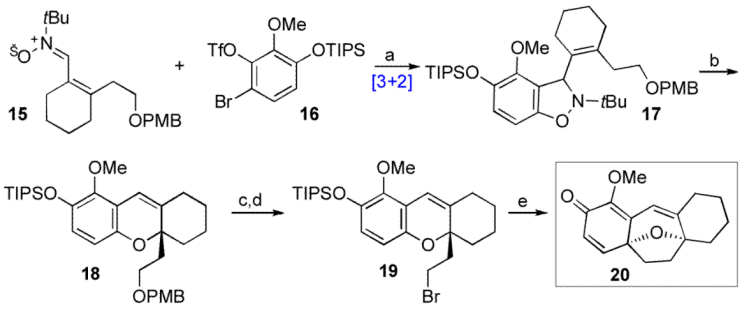
Scheme 2.
Cortistatin: Preliminary SAR Data.



Scheme 3.
[3+2] Cycloaddition–based synthetic strategy toward cortistatin A.



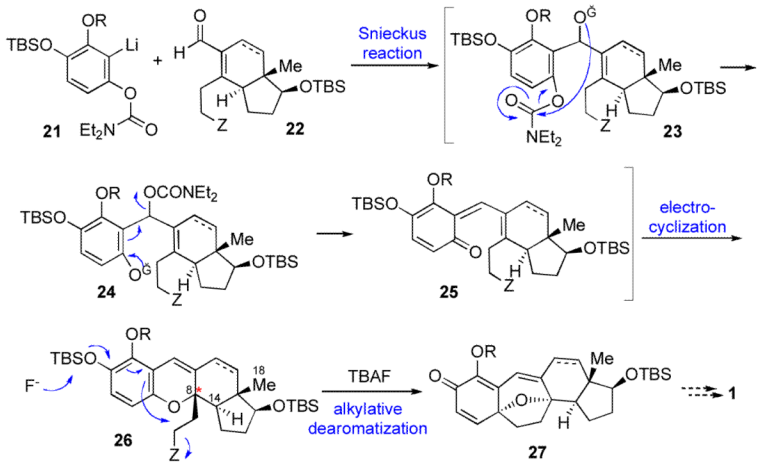
Scheme 4.
Regioselectivity of nitrone-aryne [3+2] cycloaddition



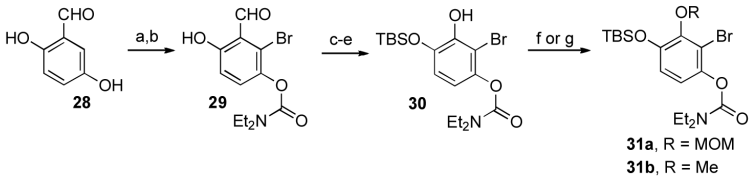
Scheme 5.

[3+2] cycloaddition: Model studies toward the cortistatin core structure.

Key: a) *n*-BuLi, THF, −78 °C; b) Zn, HOAc, RT; then 170 °C, toluene, 55% from **15**; c) Me_2BBr, *i*-Pr_2NEt, anisole, CH_2Cl_2, −78 °C, 84%; d) CBr_4, PPh_3, CH_2Cl_2, 87%; e) TBAF, THF, RT; then 50 °C, 20 min, 52%.



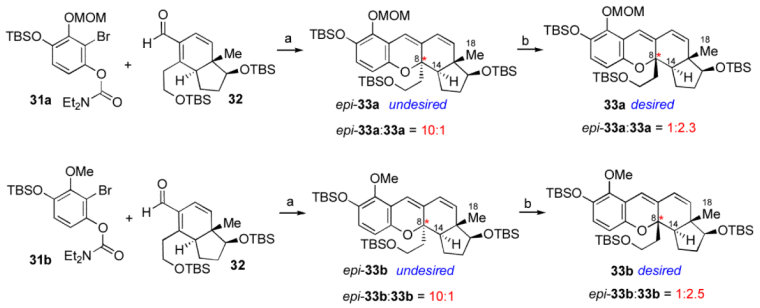
Scheme 6.
Snieckus cascade-based route toward cortistatin A.



Scheme 7.

Synthesis of aromatic A ring fragments (**31a** and **31b**).

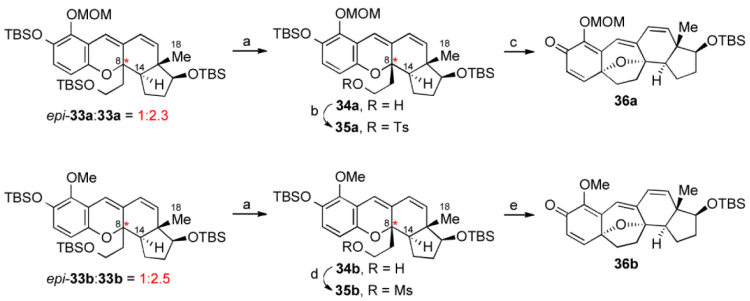
Key: a) Br_2, $CHCl_3$; b) $ClCONEt_2$, pyridine, DMAP, reflux, 48% over 2 steps; c) TBSOTf, lutidine, CH_2Cl_2, 0 °C→RT, 97%; d) mCPBA, CH_2Cl_2; e) K_2CO_3, MeOH; f) MOMCl, *i*-Pr_2NEt, **31a**: 58% over 3 steps; g) $TMSCHN_2$, PhH, MeOH, **31b**: 65% over 3 steps.



Scheme 8.

Snieckus-type domino route to cortistatin core.

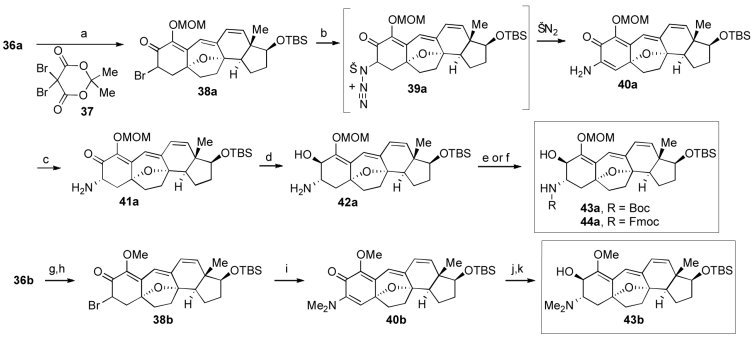
Key: a) *t*-BuLi, then **32**, −78→130 °C, 50% (*epi*-**33a**), 60% (*epi*-**33b**); b) 192–198 °C.



Scheme 9.

Alkylative dearomatization.

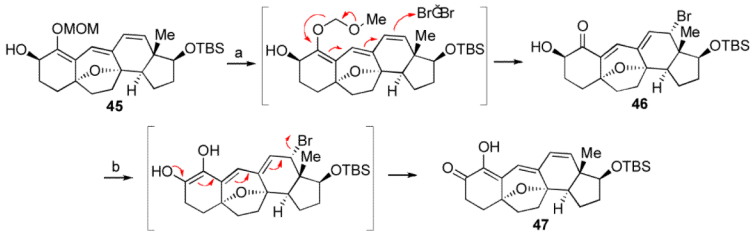
Key: a) I_2, MeOH; chromatographic separation (**34a**), 54% (**34b**), 62%; b) TsCl, pyridine, DMAP, CH_2Cl_2, 95%; c) TBAF, 70 °C, 94%; d) MsCl, pyridine, CH_2Cl_2, 90%; e) TBAF, 130 °C, 95%.



Scheme 10.

A-Ring functionalization: Installation of C_2 and C_3 stereocenters.

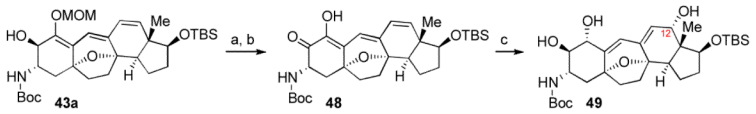
Key: a) L-Selectride; then **37**, 62%, 1.25:1 dr; b) *n*-Bu_4NN_3, THF; c) HOAc, $NaBH_3(CN)$, CH_2Cl_2; d) $NaBH_4$, $CeCl_3$•$7H_2O$, 42% from **38a**; e) Boc_2O, NaOH, THF/H_2O (**43a**); f) Fmoc-OSu, Na_2CO_3, THF/H_2O (**44a**); g) L-Selectride, −78 °C, 80%; h) LiHMDS, then **37**, −78 °C, 73%, 1:1 dr; i) NaN_3, DMF; then $NaBH(OAc)_3$, HOAc, $(HCHO)_X$, 50 °C, 69%; j) $NaBH(OAc)_3$, HOAc, CH_2Cl_2; k) DIBAL-H, −78 °C, < 20% from **40b**.



Scheme 11.

Bromine-induced MOM deprotection

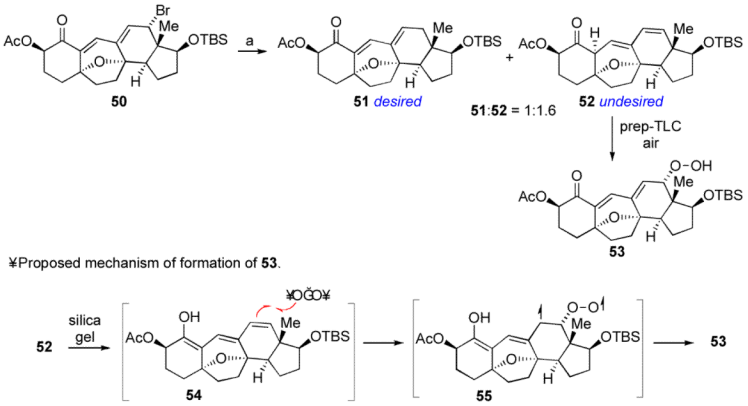
Key: a) Br_2, H_2O, THF, 0 °C; b) silica gel or evaporate EtOAc solution.



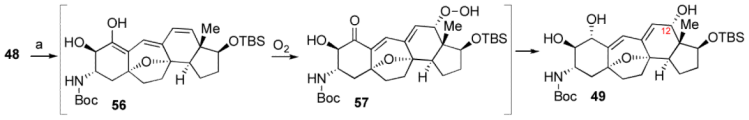
Scheme 12.

MOM deprotection and attempted Luche reduction of ring A.

Key: a) Br_2, H_2O, THF, 0 °C; b) evaporate in EtOAc; c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C.



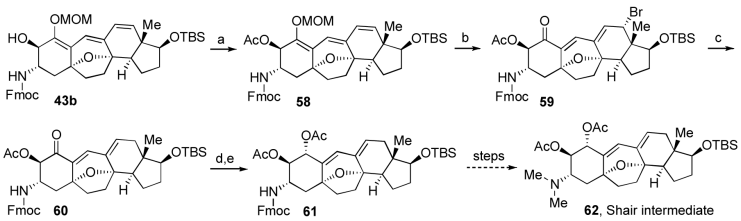
Scheme 13.
Radical debromination: Model studies.
Key: a) AIBN, *n*-Bu_3SnH, PhH, 80–90 °C.



Scheme 14.

Mechanistic rationale for formation of compound **49**.

Key: a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, air, 0 °C.



Scheme 15.

Radical debromination and synthesis of compound **61** *en route* to cortistatin A.

Key: a) Ac_2O, pyridine, DMAP, CH_2Cl_2 (70% from **42**); b) Br_2, H_2O, THF, 0 °C; c) AIBN, *n*-Bu_3SnH, C_6D_6, 70 °C, ~10% from **58**; d) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; e) Ac_2O, pyridine, DMAP, CH_2Cl_2.