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Synthetic Studies toward Highly Functionalized 5β-Lanosterol Derivatives: A Versatile Approach Utilizing Anionic Cycloaddition

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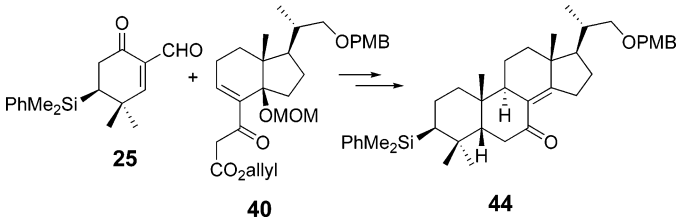

Stereoselective synthesis of the potentially biologically valuable 5β-lanosteroidal-type backbone was achieved via anionic cycloaddition. Synthesis of the two new bicyclic Nazarov intermediates **14** and **40** and their cycloaddition with chiral cyclohexenone **25** and further functional group manipulations resulted in highly functionalized tetracyclic intermediates **28** and **44**. These synthetic intermediates could lead to the total synthesis of new lanosterol-based inhibitors.

Introduction

Functionalized lanosterol derivatives present unique and significant importance due to their interesting biological properties. Recent studies have shown that steroids having the general structure **1** (Figure 1) exhibit 14α-demethylase inhibitory activity[1] and lanosterol derivatives such as **2** possess antitumor properties.[2] Studies from Merck laboratories have identified recently isolated natural product clavaric acid **3**, a similar structural analogue, as a potential human farnesyl-protein transferase (FPTase) inhibitor.[3]

It is worth noting that development of a common intermediate possessing the basic skeleton of these steroids would lead to a library of potential candidates for biological evaluation. In this paper, we describe a general synthetic strategy for the stereoselective construction of 5β-analogues having a lanosterol-type backbone via anionic cycloaddition.

Recently our laboratory was involved in developing a novel methodology for the construction of a steroid backbone via anionic cycloaddition between a functionalized cyclohexenone and a bicyclic Nazarov intermediate resulting in stereoselective formation of a highly functionalized tetracycle.[4] A representative example of this strategy is shown in Scheme 1.

On the basis of this strategy we envisaged the construction of a functionalized lanosterol moiety having an A−B *cis*-junction, which could serve as a key intermediate for the synthesis of a library of potential 14α-demethylase inhibitors. The proposed retrosynthetic analysis (Scheme 2) revealed that the intermediate **4** could be easily developed into potential candidates, which in turn could be obtained from **5**, the tetracylic intermediate of anionic cycloaddtion between cyclohexenone **6** and Nazarov intermediate **7**.

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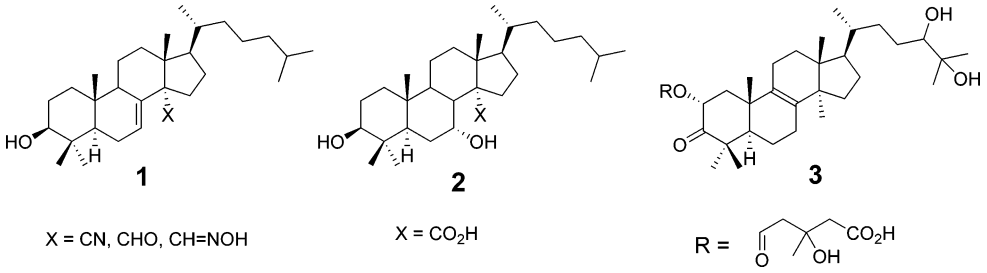
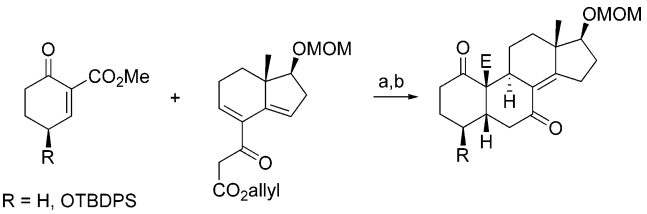


FIGURE 1. Functionalized lanosterol-based inhibitors.

SCHEME 1[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, (b) $Pd(PPh_3)_4$, morpholine, THF, 87% (2 steps).

Results and Discussion

Our investigation toward this goal was commenced by the synthesis of Nazarov intermediate **14** (Scheme 3). The Hajos-Parish ketone **8**[5] was identified as the suitable starting material for this purpose. The ketone **8** was transformed into nitrile **9** as previously reported.[6,4b] The enone thus obtained was subjected to carboxylation using magnesium methyl carbonate[7] followed by esterification with diazomethane[8] to furnish β-keto ester **10** in 65−70% yield in two steps. To obtain the desired ester **12**, we opted for triflation of ester **10** followed by hydrogenolysis.

Under optimized conditions, ester **10** was transformed into triflate **11**[9] using *N*,*N*-diisopropylethylamine and triflic anhydride at −78 °C. Hydrogenolysis of triflate **11** was achieved by a standard protocol.[10] The ester **12** was then saponified with KOH to furnish acid **13**. This acid was converted into the corresponding acid chloride with oxalyl chloride[11] in the presence of catalytic DMF, and the product was then allowed to react with the lithium enolate of allyl acetate prepared in situ to give the desired Nazarov intermediate **14** in 78% yield from acid **13**.

The functionalized cyclohexenone **6** that would serve as the ring A precursor was synthesized according to the previously reported procedure.[12]

With both components in hand, the anionic cycloaddition between cyclohexenone **6** and Nazarov intermediate **14** was studied (Scheme 4). Under optimized conditions, cycloaddition carried out using Cs_2CO_3 in ethyl acetate followed by dealkoxycarbonylation[13] and purification by silica gel chromatography furnished the two diastereomers **15** and **16** in 4:1 ratio.

The structures of both diastereomers **15** and **16** were confirmed by single-crystal X-ray analysis. The major diastereomer **15** was then converted into an advanced intermediate **18** by the following transformations (Scheme 5). The aldehyde at C_{10} (steroid numbering) was selectively reduced using $NaBH_4$ in methanol to alcohol **17**, which was then converted into the corresponding xanthate derivative[14] by standard procedure followed by Barton-McCombie deoxygenation[15] to furnish the tetracycle **18**. It is also interesting to note that the minor diastereomer **16** obtained by anionic cycloaddition could well serve as an advanced precursor for the synthesis of the unnatural enantiomer of biologically active friedolanostanes.[16]

Recently we have shown that the use of enantiomerically pure 5-(trialkylsilyl)-2-cyclohexenones as ring A precursor will efficiently control the stereoselectivity of anionic cycloaddition.[17,18] Hence we decided to synthesize enatiomerically pure 5-(trialkylsilyl)-2-cyclohexenone **25** with a 4,4′-*gem*-dimethyl group (Scheme 6). The synthesis starts with the 1,4-addition of a dimethylphenylsilylzinc species to 4,4′-dimethyl-2-cyclohexenone in the presence of catalytic CuI as previously reported.[19] The ketone **20** was then reduced diastereoselectively using tri-*tert*-butoxylithiumalumium hydride to furnish *syn*-alcohol **21** (*syn*:*anti* 9:1), which was separated from the *anti*-alcohol by chromatography. Kinetic resolution of the racemic *syn*-alcohol **21** using Lipase B Candida antarctica[20] with vinyl acetate as solvent furnished enantiomerically pure (+)-*syn*-alcohol **22** in 48% yield and ≥98% ee[21a] along with acetate enantiomer **22a**. The absolute configuration of compounds **22** and **22a** were determined on the basis of the empirical rule by Kazlauskas,[21b] commonly used for the lipase-catalyzed enzymatic resolution reactions and later confirmed by X-ray analysis

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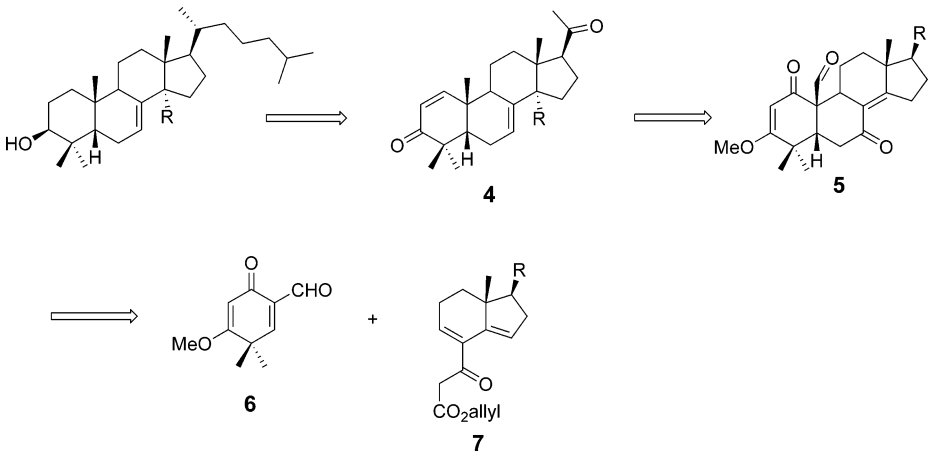
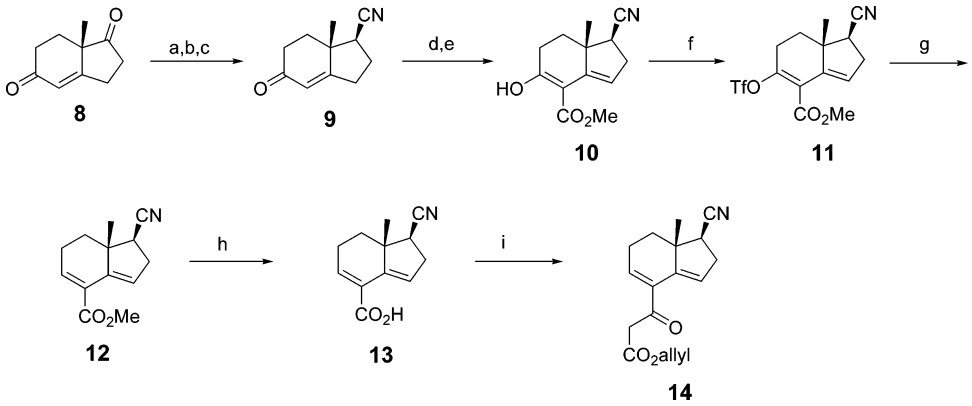
SCHEME 2

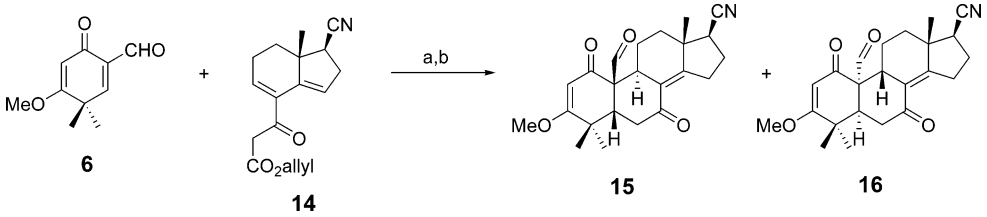


SCHEME 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, −15 °C, 94%, (b) *p*-TsCl, pyridine, DMAP, rt, 4 days, 90%, (c) NaCN, DMSO, rt, 3 h, 86%, (d) $MeOMgOCO_2Me{\cdot}xCO_2$, 125−130 °C, DMF, 3 h, 75%, (e) CH_2N_2, Et_2O/DCM, −78 °C, 30 min, 65% (f) DIPEA, Tf_2O, CH_2Cl_2, − 78 °C, 92%, (g) Bu_3N, $Pd(OAc)_2$, PPh_3, DMF, HCO_2H, 60 °C, 70%, (h) KOH, MeOH/H_2O (1:1), rt, 6h, 85%, (i) (1) $(COCl)_2$, cat. DMF, toluene, rt, 2 h, (2) allyl acetate, LHMDS, THF, −78 °C, 78%.

SCHEME 4[a]



[a] Reagents and conditions: (a) Cs_2CO_3, EtOAc, rt, (b) (1) 5 mol % $Pd(PPh_3)_4$, morpholine, THF, 2 h, (2) toluene, reflux, 1 h, 59% (4:1) over 2 steps.

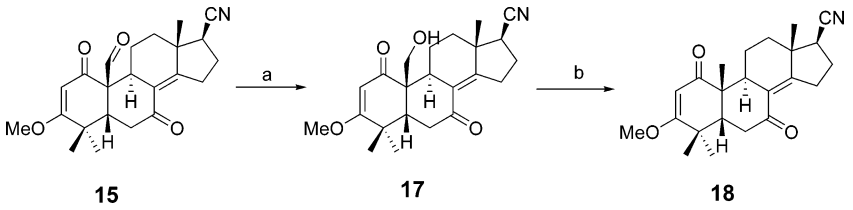
for cycloadduct **26**. The alcohol **22** was then oxidized under standard Swern conditions to give the ketone **23**, which was then subjected to formylation using ethyl formate in the presence of NaH/KH to furnish the β-keto aldehyde **24**. The introduction of the double bond was carried out by the conversion of aldehyde **24** to the selenium intermediate **24a**, followed by oxidation using H_2O_2 to furnish the ring A precursor **25**.

Having achieved the synthesis of enantiomerically pure cyclohexenone **25**, we then tried the anionic cycloaddition with Nazarov intermediate **14** (Scheme 7).

Under optimized conditions, the anionic cycloaddition followed by dealkoxycarbonylation furnished a single diastereomer **26** in good yield. The structure and absolute configuration of the tetracycle **26** was further confirmed by a single-crystal X-ray analysis. Thus it became evident that the dimethylphenylsilyl group in cyclohexenone controls the diastereoselectivity of anionic cycloaddition. We believe that the anionic cyclization takes place either via a highly asynchronous Diels−Alder reaction or by two consecutive Michael additions where the first step would be reversible. The fact that cycloaddition proceeded only on the β face of the Nazarov reagent **14** can be explained

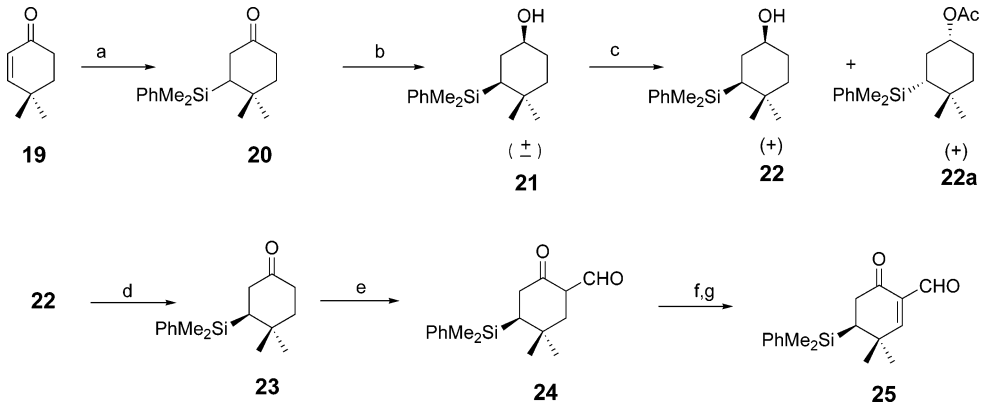
(21) (a) The enantiomeric excesses for compounds **22** and **22a** were determined using chiral HPLC (CHIRACEL OD-H, for **22** hexane/isopropanol 99:1, flow 0.6 mL/min. Retention time (+)-alcohol, 20.1 min; (−)-alcohol, 26.3 min. For **22a** gradient 0−50 min (0.2 mL/min, hexane 100%) 50−60 min (hexane/isopropanol 95:5; flow 0.6 mL/min). Retention time (+)-acetate, 54.2 min; (−)-acetate, 57.3 min). (b) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis; Regio and Stereoselective Biotransformations*; Wiley-VCH: Weinheim, 1999.

SCHEME 5[a]



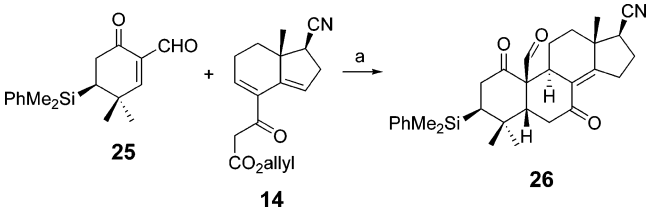
[a] Reagents and conditions: (a) $NaBH_4$, MeOH, −15 °C, 70%, (b) (1) NaH, CS_2, MeI, THF, 60 °C, 84%, (2) **17a**, *n*-Bu_3SnH, AIBN (cat.), toluene, 120 °C, 2 h, 75%.

SCHEME 6[a]



[a] Reagents and conditions: (a) $PhMe_2SiLi$, $ZnCl_2$, CuI (5 mol %), toluene, −20 °C, 6 h, 84%, (b) $LiAl(^tBuO)_3H$, THF, −50 °C, 12 h, 96%, *syn:anti* (9:1), (c) Lipase B *Candida antarctica*, vinyl acetate, rt, 48 h, 48%, (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 87%, (e) NaH, KH, EtOCHO, THF, rt, 4 h, 73%, (f) PhSeCl, pyridine, CH_2Cl_2, (g) H_2O_2, CH_2Cl_2, rt, 78% over 2 steps.

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) Cs_2CO_3, EtOAc, rt, 6 h, 70%, (ii) $Pd(PPh_3)_4$ (5 mol %), morpholine, THF, reflux, 2 h, 90%.

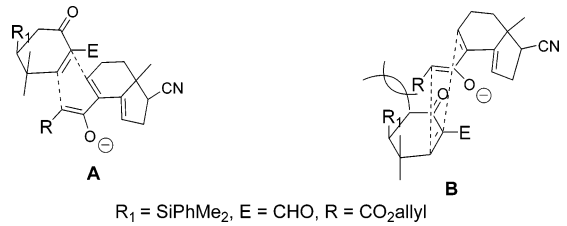


FIGURE 2. Comparison of the cycloaddition approaches for the reaction of **14** with **25**.

by the steric interaction created by the C_3 $SiPhMe_2$ group on the cyclohexenone **25** and hence explains the diastereoselectivity of the reaction (Figure 2; approach **A** is favored over approach **B**).

The tetracyclic intermediate **26** thus obtained was further transformed into the deoxygenated derivative **28** by the following pathway (Scheme 8).

The aldehyde **26** was selectively reduced to alcohol **27** using tetramethylammonium triacetoxyborohydride in CH_3CN. The alcohol thus formed was transformed into xanthate **27a** under standard conditions and subjected to Barton-McCombie deoxygenation using tris-trimethylsilyl silane and AIBN to furnish the tetracycle **28**.

To have a functionalized side chain at C_{17} (steroid numbering) of the tetracycle, we have prepared Nazarov intermediate **40** according to the following synthetic sequence (Scheme 9). Vitamin D2 was selected as the starting material for this purpose, which was converted to diol **29** by ozonolysis followed by reduction according to the reported procedure.[22] The primary alcohol was selectively benzoylated as reported[23] to furnish the alcohol **30**, which was dehydrated under Mitsunobu conditions and further hydrolyzed with 1 M NaOH to afford the alcohol **31**. The alcohol was then protected as PMB ether **32**, which on epoxidation followed by ring opening with KOH afforded a mixture of diastereomeric diols (4:1), which were separated by column chromatography. The major diastereomer **33** was then transformed to the MOM-protected alcohol **34**, which was then oxidized using NMO and TPAP to furnish the ketone **35**. Trapping the enolate of ketone **35** using Comins' reagent[24] afforded the triflate **36**, which was subjected to a one-carbon homologation using a carbonylation reaction[25] to furnish the ester **37**. Reduction of the ester using DIBAL-H followed by Swern oxidation of the alcohol furnished the aldehyde **39**.

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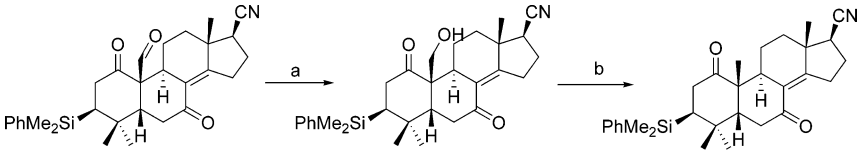
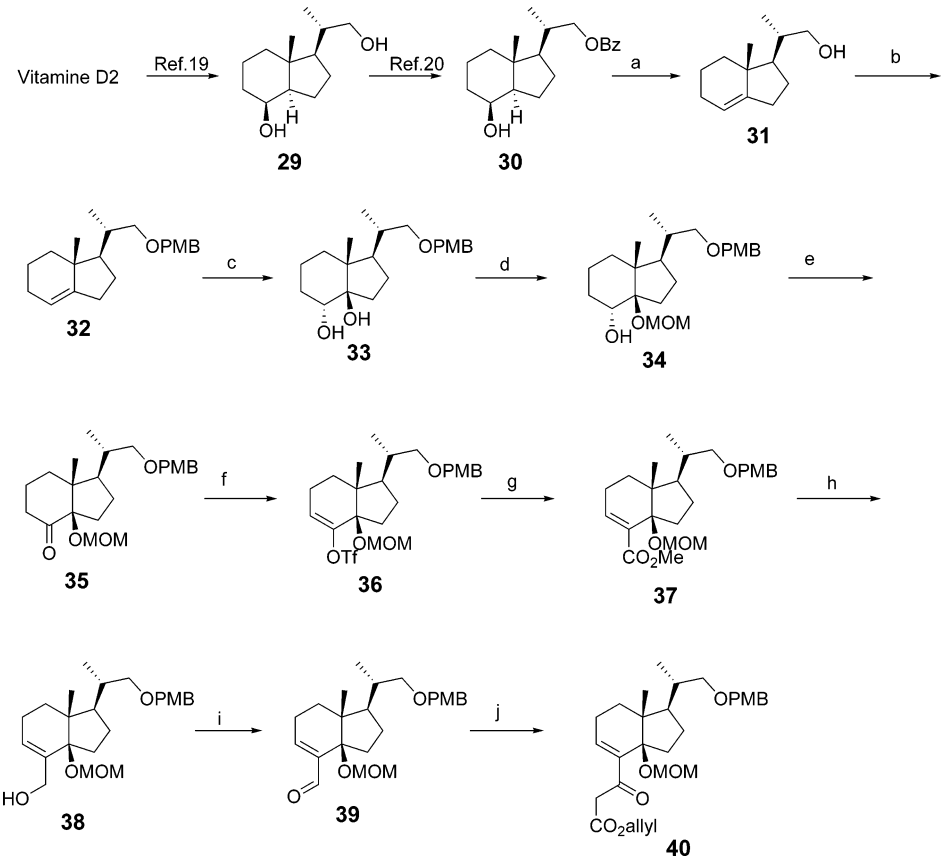
SCHEME 8[a]



26 **27** **28**

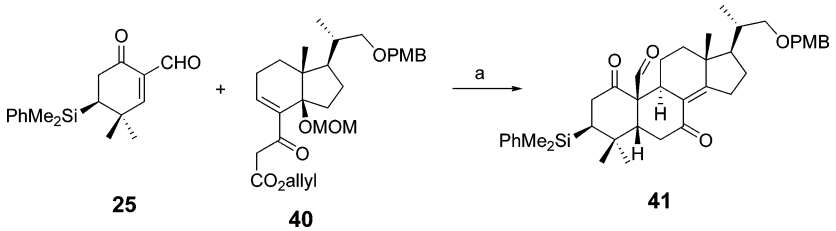
[a] Reagents and conditions: (a) $Me_4NBH(OAc)_3$, CH_3CN, −20 °C, 90%, (b) (1) *n*-BuLi, CS_2, MeI, THF, −40 °C, 80%, (2) **27a**, $(Me_3Si)_3SiH$, AIBN (cat.), toluene, 120 °C, 2 h, 55%.

SCHEME 9[a]



[a] Reagents and conditions: (a) (1) DEAD, PPh_3, THF, reflux, (2) NaOH 1 M, MeOH, rt, 93% (over 2 steps), (b) NaH, PMBCl, TBAI, THF, reflux, 74%, (c) (1) *m*-CPBA, CH_2Cl_2, −15 °C, (2) KOH, DMSO/H_2O, 140 °C, 58% (4:1) (over 2 steps), (d) (1) TMSCl, Et_3N, THF, rt, (2) MOMCl, DIPEA, DMAP, CH_2Cl_2, rt, (3) TBAF, THF, rt, 84% (over 3 steps), (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 98%, (f) LHMDS, Comin's reagent, THF, −10 °C, 81%, (g) $PdCl_2(PPh_3)_2$, CO (24 atm), Et_3N, MeOH, DMF, 55 °C, 87%, (h) DIBAL-H, CH_2Cl_2, −78 °C, 79%, (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 98%, (j) (1) allyl acetate, LHMDS, THF, −78 °C, (2) **39**, THF, −78 °C, 94%, (3) **39a**, Dess−Martin periodinane, CH_2Cl_2, rt, 79%.

SCHEME 10[a]



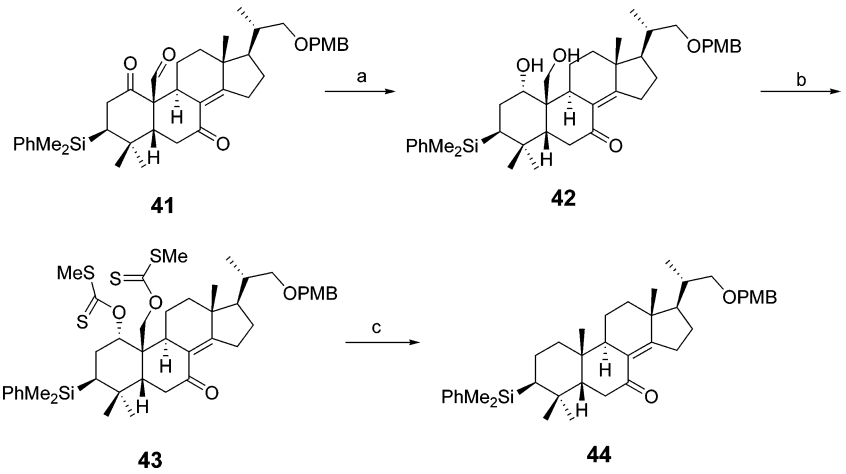
25 **40** **41**

[a] Reagents and conditions: (a) (i) Cs_2CO_3, CH_3CN, rt, 3 h, 55%, (ii) $Pd(PPh_3)_4$, morpholine, THF, reflux, 2 h, 90%.

Finally an aldol condensation of the aldehyde **39** with the lithium enolate of allyl acetate followed by oxidation of the resulting alcohol afforded the desired Nazarov intermediate **40**.

We then investigated the anionic cycloaddition reaction between the newly synthesized Nazarov intermediate **40** and the cyclohexenone **25** (Scheme 10).

SCHEME 11[a]



[a] Reagents and conditions: (a) $Me_4NBH(OAc)_3$, CH_3CN, −20 °C to rt, 6 h, 60%, (b) NaH, CS_2, MeI, THF, 60 °C, 6 h, 61%, (c) $(Me_3Si)_3SiH$, AIBN (cat.), toluene, reflux, 50%.

The best results were obtained when acetonitrile was used as a solvent and Cs_2CO_3 as base, affording the tetracycle **41** after dealkoxycarbonylation as a single diastereomer. The tetracycle **41** was further transformed into the advanced intermediate **44** according to the following reactions (Scheme 11). The β-keto aldehyde **41** was selectively reduced to 1,3-diol **42** as a single diastereomer using tetramethylammonium triacetoxy borohydride in CH_3CN. The diol **42** was then converted to bis-xanthate **43** by standard protocol in good yield. Exposing the product to the silyl radical generated from $(Me_3Si)_3SiH$ and AIBN resulted in a double deoxygenation to afford the tetracycle **44** in moderate yield.

Having achieved the synthesis of an advanced intermediate **44**, we are planning to introduce α-C_{14} functional groups and to evaluate the biological activity of these steroidal derivatives against different cell lines. Work toward this direction will be reported in due course.

Conclusion

In summary, we have explored the scope and utility of anionic cycloaddition as a powerful synthetic tool for the stereoselective construction of tetracyclic intermediates having a lanosteroidal-type framework. It was shown that the use of a chiral ring A precursor with a dimethylphenyl silyl group imparts a complete stereocontrol for the anionic cycloaddition reaction. We were also able to achieve the synthesis of advanced intermediates **18** and **28** along with a C_{17} functionalized tetracyclic intermediate **44**. It would be worth noting that this methodology will allow the synthesis of C_1, C_7, C_{10}, and C_{14} functionalized (steroid numbering) steroid analogues of lanosterol, which are otherwise difficult to synthesize starting from lanosterol itself. It is conceivable that these 5β-analogues should provide interesting insight into the structure−activity relationship of lanosterol-based inhibitors.

Experimental Section

Tetracycles 15 and **16.** Cs_2CO_3 (547 mg, 1.678 mmol) was added to a stirring solution of Nazarov intermediate **14** (478 mg, 1.678 mmol) in EtOAc (110 mL), and stirred for 5 min. Cyclohexenone **6** (303 mg, 1.678 mmol) was added, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was then diluted with EtOAc (100 mL), and the organic phase was washed with water (3 × 20 mL) and saturated NH_4Cl solution (20 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and then the crude product was chromatographed over SiO_2 (eluent 1:4 EtOAc/hexane) to furnish the two diasteromers **15a** (406 mg, 52%) and **16a** (95 mg, 12%).

$Pd(PPh_3)_4$ (52 mg, 45 μmol, 5 mol %) was added followed by morpholine (375 mg, 0.37 mL, 4.3 mmol) in THF (2 mL) to a stirring solution of aldehyde **15a** or **16a** (400 mg, 0.86 mmol) in THF (40 mL). The reaction mixture was stirred for 2 h at room temperature. The solvent was then removed in vacuo, and toluene was added (30 mL). The reaction mixture was refluxed for 1 h and diluted with EtOAc (50 mL). The organic layer was washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo followed by chromatography over SiO_2 (eluent 3:7 EtOAc/hexane) to furnish pure aldehyde **15** (270 mg, 88%) and **16** (280 mg, 90%).

Diastereomer 15. $[\alpha]^{20}_D = -10°$ ($c = 1.6$, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2919, 2853, 2227, 1722, 1683, 1638, 1599, 1459, 1353, 1218, 754. ^1H NMR (300 MHz, $CDCl_3$): δ 9.75 (1H, s); 5.39 (1H, s); 3.76 (3H, s); 3.25−3.18 (1H, m); 2.98−2.95 (1H, m); 2.77−2.55 (3H, m); 2.43−2.32 (2H, m); 2.22−2.02 (4H, m); 1.86−1.78 (1H, m); 1.37−1.30 (1H, m); 1.26 (3H, s); 1.24 (3H, s); 1.20 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5; 198.8; 196.7; 181.9; 159.7; 125.1; 119.8; 99.3; 61.5; 56.5; 46.3; 40.8; 40.4; 39.8; 39.2; 38.9; 33.5; 29.9; 29.7; 26.3; 22.9; 21.6; 21.3 EI-MS *m*/*z* (% rel int): 381 (M^+); 369 (10); 352 ($M - CHO)^+$; 338; 310; 277. HRMS (*m*/*z*): calcd for $C_{23}H_{27}NO_4$ 381.1940, found 381.1947 ± 0.0011.

Diastereomer 16. $[\alpha]^{20}_D$: +61.5 ° ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2919, 2853, 2227, 1722, 1683, 1638, 1599, 1459, 1353, 1218, 754. ^1H NMR (300 MHz, $CDCl_3$): δ 9.90 (1H, s); 5.36 (1H, s); 3.75 (3H, s); 3.11−3.00 (1H, m); 2.94−2.89 (1H, m); 2.82−2.68 (1H, m); 2.64−2.51 (3H, m); 2.48−2.35 (2H, m); 2.28−2.06 (2H, m); 1.92−1.78 (2H, m); 1.37−1.20 (1H, m); 1.16 (3H, s); 1.15 (3H, s); 1.12 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9; 198.9; 196.8; 181.5; 161.4; 125.8; 119.8; 98.9; 61.9; 56.4; 46.2; 40.8; 39.9; 39.1; 38.1; 37.7; 31.4; 30.5; 26.4; 22.8; 19.9; 19.7. EI-MS *m*/*z* (rel int): 381 (M^+); 369 (10); 352 ($M - CHO)^+$; 338; 310; 277. HRMS (*m*/*z*): calcd for $C_{23}H_{27}NO_4$ 381.1940, found 381.1947 ± 0.0011

Alcohol 17. Powdered $NaBH_4$ (12 mg, 0.32 mmol) was added in one portion to the stirring solution of aldehyde **15** (240 mg, 0.63 mmol) in mixed solvent system THF/MeOH (10:5 mL) at −15 °C. The reaction mixture was stirred at the same temperature for 2 h. The excess $NaBH_4$ was quenched by addition of acetone (2 mL) at the same temperature. Then the reaction mixture was allowed to

warm to room temperature, the solvent was removed in vacuo, and the residue was dissolved in EtOAc (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and the crude product was chromatographed over SiO_2 (eluent 3:2 EtOAc/hexane) and furnished pure alcohol **17** (168 mg, 70%). $[\alpha]^{20}_D$: −76.77° (c = 1.3, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 3550−3265 (broad peak); 2968, 2363, 2232, 1677, 1642; 1606, 1463, 1363, 1244, 1214, 1167, 1042, 912, 846. ^1H NMR (300 MHz, $CDCl_3$): δ 5.37 (1H, s); 4.54 (1H, d, J = 11.7 Hz); 3.73 (3H, s); 3.39 (1H, d, J = 11.7 Hz); 3.35−3.22 (1H, m); 3.08−2.99 (1H, m); 2.75−2.64 (4H, m); 2.39 (1H, dd, J = 12.06, 7.32 Hz); 2.26−1.79 (5H, m); 1.49−1.40 (1H, m); 1.34−1.28 (1H, m); 1.25 (3H, s); 1.22 (3H, s); 1.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7; 200.4; 181.1; 159.2; 125.7; 119.7; 99.5; 59.3; 56.1; 51.8; 46.1; 40.2; 39.3; 39.3; 39.2; 38.5; 33.1; 29.6; 29.2; 26.1; 23.2; 21.9; 20.4. EI-MS m/z (rel int): 383 (M^+); 365 ($M - H_2O)^+$; 352 (100). HRMS m/z: calcd for $C_{23}H_{29}NO_4$ 383.2096, found 383.2093 ± 0.0011.

Xanthate 17a. NaH (36 mg, 940 μmol, 60% dispersion in oil) was successively washed with hexanes and then cooled to 0 °C. Alcohol **17** (80 mg, 208.8 μmol) in THF (10 mL) was added dropwise to the NaH, and it was stirred at 0 °C for 15 min and then at room temperature for 1 h. CS_2 (160 mg, 0.13 mL, 940 μmol) in THF (2 mL) was added, and the solution was stirred for 1 h at room temperature followed by addition of MeI (296 mg, 0.13 mL). The reaction mixture was stirred for 1 h and then warmed in a preheated oil bath at 55−60 °C for 2 h. The reaction mixture was then cooled to room temperature and quenched with addition of 2−3 drops of saturated NH_4Cl. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (20 mL). The organic layer washed with water (5 mL) and saturated NH_4Cl solution (5 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo followed by chromatography over SiO_2 (eluent 2:3 EtOAc/hexane) to yield xanthate derivate **17a** (85 mg, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (1H, s); 5.30 (1H, dd, J = 11.19 Hz); 4.67 (1H, d, J = 11.18 Hz); 3.74 (3H, s); 3.28−3.26 (1H, m); 3.08−3.06 (1H, m); 2.70−2.68 (1H, m); 2.64−2.44 (3H, m); 2.51 (3H, s); 2.37−1.99 (3H, m); 1.82−1.77 (1H, m); 1.58−1.56 (1H, m); 1.35−1.31 (1H, m); 1.27 (3H, s); 1.22 (3H, s); 1.19 (3H, s).

Tetracycle 18. n-Bu_3SnH (50 mg, 168 μmol) was added to a stirring solution of xanthate **17a** (53 mg, 112 μmol) and catalytic amount of AIBN (0.1 equiv) in toluene (5 mL) at room temperature. The reaction mixture was degassed twice and then refluxed for 2 h. It was cooled to room temperature, the solvent was removed in vacuo, and the residue was purified by chromatography (eluent 3:7 EtOAc/hexane) to furnish **18** (30 mg, 73%). $[\alpha]^{20}_D$: −106.57° (c = 1.4, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2972, 2363, 2319, 2242, 1678, 1645, 1612, 1595, 1456, 1351, 1224, 1191, 1168, 1130, 986, 914, 726, 671. ^1H NMR (300 MHz, $CDCl_3$): δ 5.35 (1H, s); 3.72 (3H, s); 3.35−3.27 (1H, m); 2.95−2.89 (1H, m); 2.75−2.71 (1H, m); 2.67−2.60 (2H, m); 2.40 (1H, dd, J = 12, 7.48 Hz); 2.30−2.06 (3H, m); 1.98 (1H, dt, J = 7.4, 3.4 Hz); 1.76−1.69 (1H, m); 1.45−1.30 (2H, m); 1.23 (3H, s); 1.20 (3H, s); 1.18 (3H, s); 1.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8; 200.4; 179.9; 159.5; 126.2; 119.8; 98.9; 56.0; 47.7; 47.2; 46.1; 40.8; 40.4; 39.6; 39.1; 32.9; 29.6; 29.3; 26.2; 22.9; 21.9; 21.1; 16.9. EI-MS m/z (rel int): 367 (M^+); 352 (90); 324 (15); 269 (14); 240; 167 (100). HRMS m/z: calcd for $C_{23}H_{29}NO_3$ 367.2147, found 367.2150 ± 0.0011.

Tetracycle 26. To a stirred solution of Nazarov intermediate **14** (0.6 g, 2.1 mmol) and cyclohexenone **25** (0.603 g, 2.1 mmol) in EtOAc (100 mL) was added Cs_2CO_3 (0.685 g, 2.1 mmol), and the reaction mixture was stirred at room temperature for 6 h. Water was added to quench the reaction, which was extracted with EtOAc, dried, and column chromatographed over silica gel to afford the carboxyallyl cycloadduct **26a** (0.85 g, 70%) as a viscous liquid. $[\alpha]^{20}_D$: + 52.2° (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 12.94 (s, 1H, enol proton), 9.01 (s, 1H), 7.52−7.48 (m, 2H), 7.37−7.31 (m, 3H), 5.96−5.88 (m, 1H), 5.38−5.28 (m, 2H), 4.61 (d, J = 8.52 Hz, 2H), 3.46 (d, J = 3.96 Hz, 1H), 3.13−2.91 (m, 2H), 2.72−2.38 (m, 2H), 2.26−2.03 (m, 4H), 1.57−1.32 (m, 3H), 1.29 (s, 3H), 1.26−1.15 (m, 1H), 1.08 (s, 3H), 1.03 (s, 3H), 1.00−0.87 (m, 1H), 0.45 (s, 3H), 0.42 (s, 3H).

$Pd(PPh_3)_4$ (0.077 g, 0.06 mmol, 5 mol %) was added followed by morpholine (0.59 mL, 6.65 mmol) to a stirring solution of carboxyallyl cycloadduct **26a** (0.76 g, 1.3 mmol) obtained above in THF (20 mL), and the resulting solution was refluxed for 1 h. Solvent was evaporated off, and the residue was column chromatographed over silica gel to give the tetracycle **26** (0.58 g, 90%) as a colorless crystalline solid. Mp: 110−112°C. $[\alpha]^{20}_D$: +52.27° (c = 1.1, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2962, 2236, 1718, 1689, 1624, 1261, 811, 736. ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.52−7.24 (m, 5H), 3.07−2.88 (m, 3H), 2.62−1.56 (m, 12H), 1.37−1.23 (m, 1H), 1.16 (s, 3H), 0.93 (s, 3H), 0.82 (s, 3H), 0.42 (s, 3H), 0.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.1, 200.9, 199.7, 158.1, 133.7, 129.4, 128.9, 128.1, 125.6, 119.5, 48.3, 46.0, 40.3, 39.9, 39.2, 37.8, 36.8, 33.9, 30.0, 28.9, 27.0, 26.3, 26.1, 21.4, 20.5, −1.9, −2.2. EI-MS m/z (rel int): 458 (60), 390 (10), 219 (10), 135 (100), 107 (10). HRMS m/z: calcd for $C_{30}H_{37}N_1O_3Si$ 487.2543, found 487.2540 ± 0.0014.

Alcohol 27. To a stirred solution of aldehyde **26** (0.1 g, 0.2 mmol) in CH_3CN (10 mL) at −20 °C was added $Me_4NBH(OAc)_3$ (0.054 g, 0.2 mmol), and the reaction mixture was stirred at that temperature for 1 h. The reaction was quenched by the addition of saturated $NaHCO_3$, extracted with ethyl acetate, dried, and column chromatographed over silica gel to afford the alcohol **27** (0.09 g, 90%) as a colorless oil. $[\alpha]^{20}_D$: +102.8° (c = 1.5, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 3510, 2966, 2240, 1686, 1627, 1258, 1184, 911, 810. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.38−7.34 (m, 3H), 3.82 (dd, J = 9.0, 5.6 Hz, 1H), 3.14−3.12 (m, 1H), 2.98−2.82 (m, 2H), 2.70−1.88 (m, 12H), 1.56−1.23 (m, 3H), 1.17 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H), 0.41 (s, 3H), 0.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.8, 200.4, 158.3, 138.0, 133.7, 129.3, 128.0, 125.7, 119.5, 64.1, 53.7, 49.9, 45.8, 40.2, 40.1, 39.1, 39.0, 38.5, 37.4, 33.9, 29.6, 28.6, 28.4, 27.4, 26.2, 25.8, 20.7, −1.9, −2.2. EI-MS m/z (rel int): 471 (30), 460 (13), 458 (30), 428 (3) HRMS m/z: calcd for $C_{30}H_{39}NO_3Si$ 489.2699, found 489.2693 ± 0.0014.

Xanthate 27a. To a stirred solution of alcohol **27** (0.069 g, 0.14 mmol) in THF (5 mL) at − 40 °C was added n-BuLi (0.087 mL, 0.14 mmol, 1.6M), and the mixture was stirred for 10 min. To this was added CS_2 (0.017 mL, 0.28 mmol) followed by MeI (0.017 mL, 0.28 mmol), and the reaction mixture was stirred for 1 h, slowly warming to room temperature. The reaction was quenched by the addition of saturated NH_4Cl, extracted with EtOAc, dried, and column chromatographed over silica gel to afford the xanthate **27a** (0.065 g, 80%). $[\alpha]^{20}_D$: +60.4° (c = 1.2, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2966, 2239, 1690, 1628, 1208, 1072, 910, 811, 733. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.39−7.34 (m, 3H), 4.67 (d, J = 11.4 Hz, 1H), 4.44 (d, J = 11.4 Hz, 1H), 3.11−2.88 (m, 2H), 2.76−2.67 (m, 1H), 2.49 (s, 3H), 2.34−2.00 (m, 8H), 1.70−1.65 (m, 2H), 1.40−1.23 (m, 3H), 1.11 (s, 3H), 0.89 (s, 3H), 0.42 (s, 3H), 0.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.0, 213.0, 199.7, 158.1, 138.0, 133.7, 129.3, 128.0, 125.6, 119.5, 74.3, 60.3, 52.3, 50.0, 45.7, 40.3, 40.1, 38.7, 37.8, 37.4, 33.6, 29.8, 28.7, 26.4, 26.3, 25.9, 20.8, 20.5, 19.2, −1.9, −2.2. EI-MS m/z (rel int): 562 (10), 471 (25), 147 (40), 135 (100), 91 (40). HRMS m/z: calcd for $C_{32}H_{42}NO_3S_2Si$ 580.2375, found 580.2381 ± 0.0017.

Tetracycle 28. To a stirred solution of above xanthate **27a** (0.015 g, 0.025 mmol) in toluene (1 mL) at room temperature was added $(Me_3Si)_3SiH$ (0.024 mL, 0.078 mmol) and catalytic AIBN. The reaction mixture was then refluxed for 2 h, solvent was evaporated off, and the residue was then column chromatographed over silica gel to afford the tetracycle **28** (0.006 g, 55%). $[\alpha]^{20}_D$: +48.2° (c = 1, $CHCl_3$). IR ($CHCl_3$, ν, cm^{-1}): 2961, 2239, 1691, 1627, 1260, 1112, 916, 811. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.38−7.33 (m, 3H), 3.0−2.88 (m, 2H), 2.73−2.64 (m, 1H), 2.53−1.97 (m, 8H), 1.69−1.54 (m, 2H), 1.42−1.28 (m, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H), 0.41 (s, 3H), 0.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.3, 200.1, 158.0, 138.2,

133.7, 129.2, 128.0, 125.5, 119.3, 56.5, 49.9, 45.6, 40.3, 40.0, 39.7, 39.1, 38.4, 37.3, 33.7, 29.6, 28.6, 26.3, 25.9, 20.9, 20.6, 19.5, 19.2, −1.9, −2.2. EI-MS *m*/*z* (rel int): 458 (40), 395 (35), 326 (25), 259 (25), 135 (100), 91 (30). HRMS *m*/*z*: calcd for $C_{30}H_{39}NO_2Si$ 473.2750, found 473.2760 ± 0.0014.

Tetracycle 41. To a stirred solution of cyclohexenone **25** (0.064 g, 0.22 mmol) and Nazarov reagent **40** (0.112 g, 0.22 mmol) in CH_3CN (15 mL) was added Cs_2CO_3 (0.007 g, 0.022 mmol), and the reaction mixture was stirred for 6 h at room temperature. It was quenched by the addition of water, extracted with EtOAc, dried, and column chromatographed over silica gel to afford the carboxyallyl cycloadduct **41a** (0.090 g, 55%). $[\alpha]^{20}_D$: +41.2° (*c* = 1, $CHCl_3$). IR ($CHCl_3$, *ν*, cm^{-1}): 2957, 1743, 1686, 1613, 1512, 1248, 1034, 821. ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.77 (s, 1H), 7.51−7.48 (m, 2H), 7.38−7.34 (m, 3H), 7.26−7.21 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.99−5.89 (m, 1H), 5.37−5.21 (m, 2H), 4.68−4.65 (m, 2H), 4.39 (d, *J* = 11.6 Hz, 2H), 3.80 (s, 3H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.42−3.38 (m, 1H), 3.27−3.15 (m, 3H), 2.69−2.66 (m, 1H), 2.48−2.28 (m, 2H), 2.08−1.95 (m, 3H), 1.81−1.72 (m, 2H), 1.49−1.28 (m, 3H), 1.25 (s, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H), 0.84 (s, 3H), 0.41 (s, 3H), 0.39 (s, 3H).

To a stirred solution of carboxyallyl cycloadduct **41a** (0.040 g, 0.05 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (0.003 g, 0.002 mmol) followed by morpholine (0.01 mL, 0.11 mmol), and the reaction mixture was refluxed for 2 h. Solvent was evaporated off, and the residue was column chromatographed over silica gel to afford the tetracycle **41** (0.031 g, 90%). $[\alpha]^{20}_D$: +44.0° (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$, *ν*, cm^{-1}): 2923, 1723, 1687, 1613, 1512, 1248, 1111, 1034. ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.93 (s, 1H), 7.52−7.49 (m, 2H), 7.39−7.34 (m, 3H), 7.26−7.21 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.40 (dd, *J* = 23.2, 11.6 Hz, 2H), 3.80 (s, 3H), 3.41 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.27−3.21 (m, 1H), 3.12−3.06 (m, 1H), 2.74−2.37 (m, 6H), 2.05−1.71 (m, 5H), 1.46−1.25 (m, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.79 (s, 3H), 0.41 (s, 3H), 0.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 213.0, 201.9, 199.5, 168.5, 159.0, 155.2, 133.7, 129.3, 129.0, 128.0, 122.5, 113.6, 104.6, 74.7, 72.7, 61.9, 55.2, 52.5, 48.0, 45.6, 40.3, 39.6, 38.1, 36.8, 36.2, 35.0, 30.4, 28.9, 27.0, 26.1, 21.6, 18.2, 17.8, −1.8, −2.4. HRMS *m*/*z*: calcd for $C_{40}H_{52}O_5Si$ 640.3584, found 640.3589 ± 0.0019.

1,3-Diol 42. To a stirred solution of *β*-keto aldehyde **41** (0.061 g, 0.09 mmol) in CH_3CN (5 mL) at − 20 °C was added $Me_4NBH(OAc)_3$ (0.075 g, 0.29 mmol), and the reaction mixture was stirred for 6 h, slowly warming to room temperature. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (2 mL), extracted with EtOAc, washed with water, dried, and column chromatographed over silica gel to afford the 1,3-diol **42** (0.037 g, 60%). $[\alpha]^{20}_D$: −6.8° (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$, *ν*, cm^{-1}): 3422, 2960, 1670, 1512, 1364, 1247. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.54−7.51 (m, 2H), 7.36−7.32 (m, 3H), 7.25−7.21 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.40 (d, *J* = 11.5 Hz, 2H), 4.13 (dd, *J* = 12.0, 3.5 Hz, 2H), 3.80 (s, 3H), 3.54−3.19 (m, 3H), 3.10−2.92 (m, 1H), 2.53−2.17 (m, 2H), 2.04−1.92 (m, 3H), 1.84−1.68 (m, 4H), 1.48−1.28 (m, 6H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.46 (s, 3H), 0.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.2, 168.3, 159.5, 155.0, 133.6, 130.7, 129.1, 127.8, 127.7, 113.6, 104.1, 74.8, 72.7, 62.3, 61.8, 55.2, 52.3, 48.0, 45.1, 40.8, 39.2, 37.5, 35.1, 34.2, 31.9, 29.6, 26.8, 17.8, 17.3, 14.0, −1.8, −2.3. HRMS *m*/*z*: calcd for $C_{40}H_{56}O_5Si$ 644.3897, found: 644.3891 ± 0.0014.

***bis*-Xanthate 43.** To a stirred solution of 1,3-diol **42** (0.039 g, 0.06 mmol) in THF (5 mL) was added NaH (0.014 g, 0.3 mmol, 60% in mineral oil) at room temperature, and the reaction mixture was stirred for 1 h. To this was added CS_2 (0.01 mL, 0.18 mmol) followed by MeI (0.011 mL, 0.18 mmol), and the reaction mixture stirred at room temperature for 1 h and then heated at 60 °C for 6 h. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl, extracted with ether, dried, and column chromatographed over silica gel to afford the bis-xanthate **43** (0.03 g, 61%). $[\alpha]^{20}_D$: −5.1° (*c* = 1, $CHCl_3$). IR ($CHCl_3$, *ν*, cm^{-1}): 2919, 2849, 1681, 1611, 1512, 1463, 1207, 1056, 813. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.50−7.47 (m, 2H), 7.35−7.30 (m, 3H), 7.26−7.22 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.67−4.34 (m, 4H), 3.80 (s, 3H), 3.43 (dd, *J* = 3.4, 9.0 Hz, 1H), 3.25−3.23 (m, 1H), 2.68−2.60 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.22−1.72 (m, 10H), 1.47−1.28 (m, 5H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.52 (s, 3H), 0.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 195.9, 177.3, 159.1, 155.3, 138.5, 133.7, 129.1, 128.0, 127.3, 113.6, 104.5, 74.6, 72.7, 63.1, 61.2, 60.0, 55.2, 52.2, 48.0, 45.3, 40.5, 39.6, 38.0, 35.1, 34.2, 31.8, 29.7, 26.9, 25.1, 18.0, 17.3, 14.0, −1.8, −2.4. HRMS *m*/*z*: calcd for $C_{43}H_{57}O_5S_3Si$ (M − SCH_3) 777.3137, found 777.3122 ± 0.0023.

Tetracycle 44. To a stirred solution of bis-xanthate **43** (0.010 g, 0.012 mmol) in toluene (1 mL) was added catalytic AIBN followed by $(Me_3Si)_3SiH$ (0.019 mL, 0.06 mmol), and the reaction mixture was refluxed for 2 h. The solvent was evaporated off, and the residue was column chromatographed over silica gel to afford the tetracycle **44** (3.7 mg, 50%). $[\alpha]^{20}_D$: +21.2° (*c* = 1, $CHCl_3$). IR ($CHCl_3$, *ν*, cm^{-1}): 2921, 2850, 1671, 1514, 1458, 1249, 1079, 814. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.53−7.50 (m, 2H), 7.35−7.30 (m, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.40 (d, *J* = 10.5 Hz, 2H), 3.80 (s, 3H), 2.48−2.40 (m, 1H), 2.21−1.70 (m, 12H), 1.42−1.28 (m, 6H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.44 (s, 3H), 0.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 197.3, 168.5, 158.9, 155.8, 135.0, 130.1, 129.5, 127.8, 127.1, 113.0, 104.1, 74.6, 52.3, 48.0, 45.1, 40.7, 39.3, 37.1, 35.2, 34.0, 31.5, 30.1, 29.6, 28.5, 26.8, 25.7, 23.2, 20.0, 17.8, 17.1, −1.8, −2.4. HRMS *m*/*z*: calcd for $C_{40}H_{56}O_3Si$ 612.3999, found 612.3985 ± 0.0014.

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Supporting Information Available: Experimental details and characterization data for compounds **10**−**14**, **21**−**25**, and **31**−**40** and X-ray crystal structure data in CIF format for compounds **15**, **16**, and **26**. Copies of ^1H NMR for all new compounds are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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