Practical Approaches to Remote Asymmetric Induction in Steroidal Side-Chains Utilizing Oxazaborolidine Reagents

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Introduction

There has been considerable effort in preparing 24*R*- and 24*S*-hydroxylated steroids and vitamin-D_3 metabolites, because of the biological importance of molecules such as cerebrosterol (**1**),[1] MC 903 (**2**),[2] 1α,24(*R*)-dihydroxyvitamin D_3 (**3**),[3] and squalamine (**4**) (Chart 1).[4] Our interest was derived from the biological utility of squalamine (**4**), which contains a sulfated 24*R*-alcohol.[5] Squalamine is the first member of a class of natural aminosterols from the shark[4] that has clinical potential in controlling tumors as an antiangiogenic agent.[6] It contains a cholestane ring system with 5α-hydrido, 7α,-24*R*-dihydroxy, 3β-spermidinyl, and 24-sulfate groups. A practical strategy for production of synthetic squalamine was required, because of the low abundance of squalamine in the shark liver. The most important issues in developing a practical synthesis were the steroid side chain stereoselectivity and the availability of a low cost starting material. Two syntheses of squalamine have been published from the expensive and rare steroid 3β-hydroxy-5-cholenic acid, which lacked control of the C24 stereochemistry.[7] A lengthy formal synthesis of squalamine has been reported from stigmasterol that was stereoselective,[5] utilizing the procedure of Koch described below.[1]

There exist several five- to six-step procedures to incorporate a C-24 alcohol stereoselectively (Scheme 1). One approach has been to alkylate a C-22 sulfone with a chiral epoxide (Scheme 1, entry 1). Koch developed this six-step procedure from the C22 aldehyde, utilizing a chiral epoxide reagent, which is made from valine.[1] There has been a successful reduction (entry 2) of a cholest-25-en-24-one system using Noyori's 2,2′-dihydroxy-1,1′-binaphthyl lithium aluminum hydride reagent at −90 °C to give 95:5 selectivity for the 24*R*-alcohol.[8] However, the cholest-25-en-24-one system was not readily accessible (four steps from cholenic acid). Finally, Tanaka has utilized (entry 3) chiral β-amino alcohol catalyzed addition of diisopropylzinc to steroidal 24-aldehydes successfully to provide 24*R*-hydroxycholesterols in good yields with high diastereoselectivities (97:3).[3] Overall, five steps were required to yield the desired diastereomer from a C-22 aldehyde.

A more efficient three-step approach for converting **A** to **D** is delineated in Scheme 2. We anticipated that **B** could be prepared from a C-22 aldehyde **A** and the appropriate Wittig reagent. The cholest-22-en-24-one system could be stereoselectively reduced to **C** with the chiral Corey-Bakshi-Shibata (CBS) oxazaborolidine-borane reagents;[9,10] CBS reagents have been applied to a wide variety of α,β-unsaturated ketones.[11] Hydrogenation of **C** would deliver the desired alcohol **D**. Similarly, we expected that the related cholest-22-yn-24-one system **E** would be reduced stereoselectively with (*S*)-methyl oxazaborolidine borane complex to afford **F**. Recent stereoselective reduction studies of non-steroidal alkynyl ketones[12] with oxazaborolidines supported our expectation. An advantage of having two new methods available for steroidal side chain construction would be the greater diversity in analogs that one could produce for medicinal chemistry studies.

Results and Discussion

Model systems **10** (Scheme 3) and **20** (Scheme 4) were prepared from the inexpensive and readily available steroid, bisnoralcohol (**5**). These substrates were used to explore various reduction conditions for the synthesis of the 24*S*-allylic and 24*S*-propargylic alcohols respectively. Hydrogenation of the allylic or propargylic alcohols would produce the desired 24*R*-alcohol **13**.[13] The cholest-22-en-24-one side chain of substrate **10** was introduced in a single step from the C-22 aldehyde **8** by reaction with Wittig reagent **9** in good yield (Scheme 3).[14] Construction of **8** began with the reduction of steroid **5** with lithium in ammonia to afford **6**[15] with the trans-AB-ring junction contained in **4**. The carbonyl was protected as the ethylene ketal **7**, and the C-22 alcohol was then oxidized to the aldehyde **8** using pyridinium chlorochromate. Although the C21-methyl group of **8** epimerized in chloroform on standing, we were able to synthesize and react **8** without epimerization.

Initially we had to prepare both alcohols **13** and **14** so that we could compare them by ^{13}C NMR spectroscopy. It is known[16] that the signal due to C-24 in the *R*-alcohol

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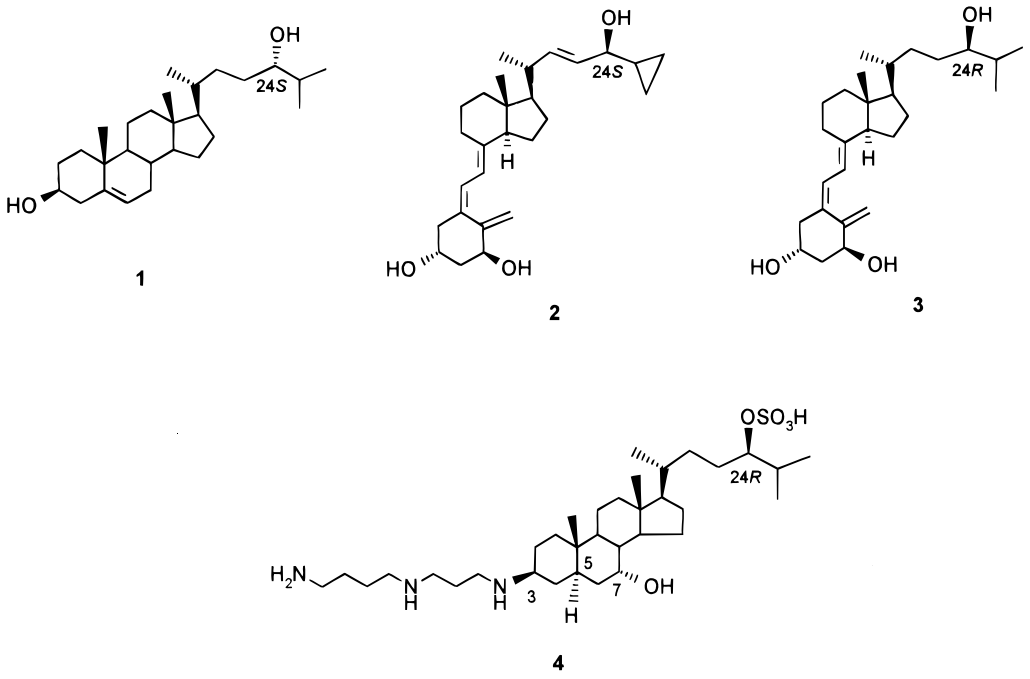
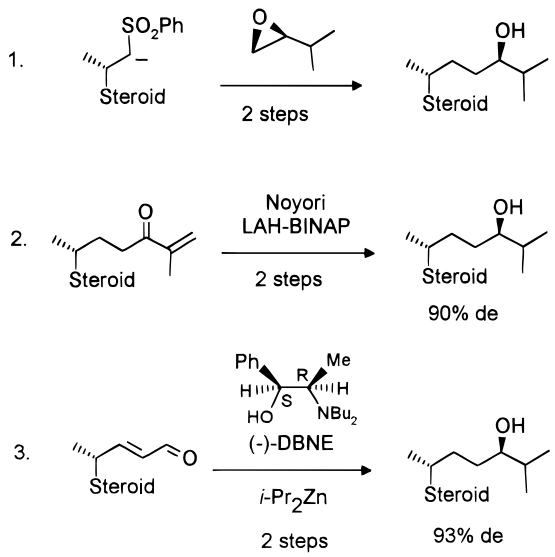
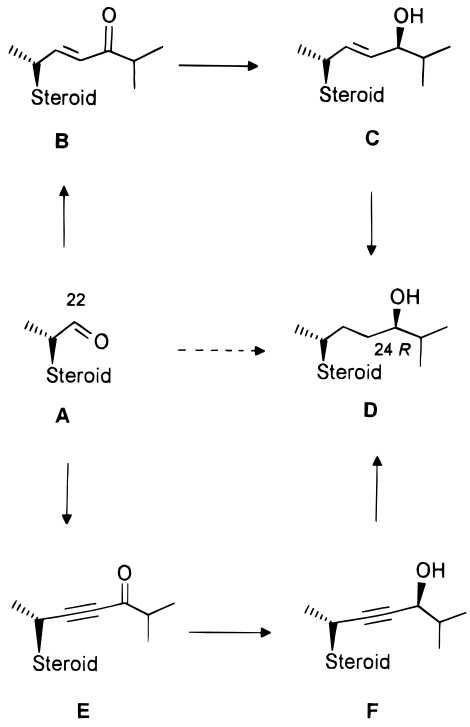
Chart 1



Scheme 1



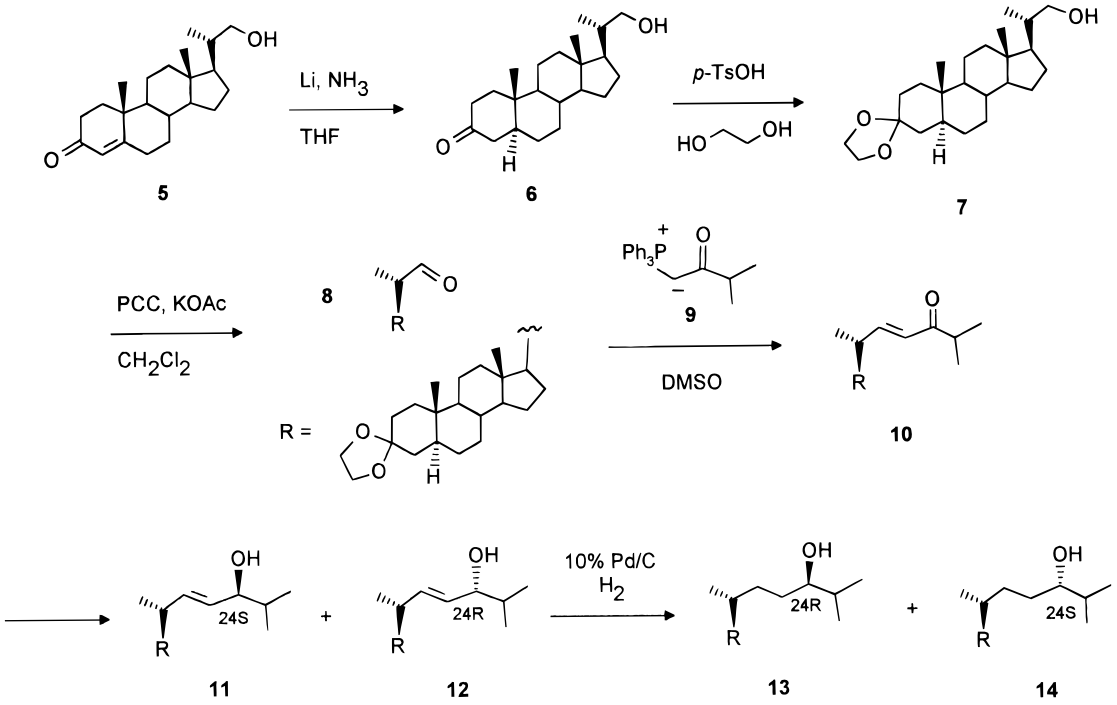
Scheme 2



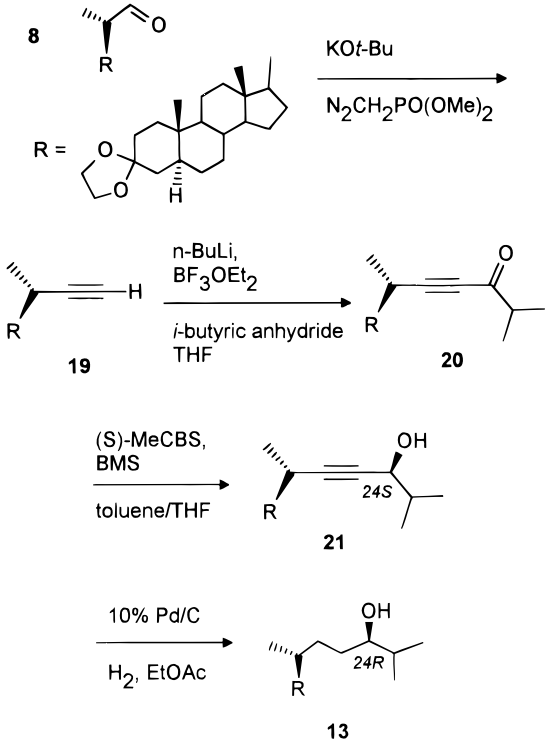
is 0.4 ppm upfield from the corresponding *S*-alcohol with a saturated side chain. Compound **10** was reduced with lithium aluminum hydride to deliver a mixture of allylic alcohols **11** and **12**. The less polar compound **12** was obtained pure and then reduced with hydrogen (Pd/C). A mixture of **11** and **12** was also reduced for comparison, because we were unable to separate pure **11** from **12**. It was found that the less polar allylic alcohol (**12**, faster moving on silica gel TLC plates) yielded the undesired 24*S* alcohol **14**, as evidenced by having a resonance of 77.66 ppm in the ^{13}C NMR (DEPT) spectrum. The mixture of **11** and **12** yielded **13** and **14** with resonances of 77.31 and 77.66 ppm. Therefore, the more polar allylic alcohol **11** must have the 24*S*-stereochemistry and **13** the desired 24*R*-stereochemistry.

Nonsteroidal α,β-unsaturated ketones have been reduced with (*S*)-MeCBS reagent to yield the *R*-allylic alcohols,[9] and with the opposite (*R*)-MeCBS reagent to yield the *S*-allylic alcohols.[10] Therefore, we believed that the (*R*)-MeCBS reagent would reduce **10** to yield the desired *S*-allylic alcohol **11**. A series of reductions were attempted on substrate **10** with selectivities ranging from 30% to greater than 94% de. The optimum conditions involved the use of stoichiometric quantities of (*R*)-MeCBS reagent with 2.5 equiv of borane in good yield (71%) and excellent selectivity (94−98% de by quantitative TLC) to yield **11**. The initial experiment was done with purification by column chromatography. Later experiments demonstrated that this reaction could be accomplished without chromatography in high yield (90%) to afford only **11** within the detection limits of ^{13}C NMR (>95%). Compound **11** was reduced with hydrogen to afford **13**, which had a carbon resonance of 77.29 ppm, confirming the earlier assignment.

Scheme 3



Scheme 4



Alternatively, stereoselective reduction of the cholest-22-yn-24-one system with the (*S*)-MeCBS reagent was also successful in introducing the chiral hydroxyl group at C-24. The substrate for the reduction, acetylenic ketone **20**, was prepared from aldehyde **8** in two steps (Scheme 4). Conventional two step methods to convert aldehydes to acetylenes, using various Wittig reactions followed by reduction of vinyl halides,[17] gave poor yields in our hands. Instead, aldehyde **8** was homologated in one step to the terminal alkyne **19** in 97% yield with Seyferth's diazophosphonate reagent[18] using the methodology developed by Colvin[19] and Gilbert.[20] Next, we explored various acylation reactions[21] of metal acetylide **19** to yield the acetylenic ketone **20**. Methodology developed by Brown in which the lithium alkynyl borate was prepared *in situ* from lithium acetylide and then reacted with isobutyric anhydride gave us the best results.[21c] Attempts to stereoselectively reduce alkynyl ketone **20** with Alpine−borane[22] under various conditions were unproductive. However, the reduction of **20** using 2 equiv of (*S*)-methyl oxazaborolidine and BMS at −30 °C[12a] was stereoselective. The resulting propargylic alcohol **21** was hydrogenated to afford the alcohol **13**. The ^{13}C NMR spectra of this alcohol showed a single signal for the C-24 carbon at 77.29 ppm corresponding to the 24*R* orientation, which is evidence that the CBS reduction was stereospecific within the limits of detection.

Conclusion

It has been shown for the first time that the readily accessible cholest-22-en-24-one system can be selectively reduced with CBS reagents to afford the 24-*S*-allylic alcohol; the C24-*R* alcohol **13** results after removal of the 22,23 multiple bond. This procedure provides the most efficient access to steroids with a C24-*R* alcohol. We have also demonstrated the first example of the stereoselective

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reduction of the related cholest-22-yn-24-one system with the opposite oxazaborolidine−borane complex. The acetylenic ketone was prepared from the aldeyde **8** in two convenient steps, making it a complementary approach to the construction of the steroid side chain containing a C24 alcohol with the *R*-configuration. These two examples represent the first application of the CBS methodology in controlling the steroid side chain stereochemistry, allowing ready access to an interesting class of natural products. The inexpensive starting material, bisnoralcohol, has proven to be a useful starting material for this exploratory chemistry and for the synthesis of squalamine. The application of this approach to the synthesis of squalamine will be reported in due course.

Experimental Section

General. The ^{13}C NMR spectra were generated in deuteriochloroform at 100 MHz, utilizing 77.23 ppm as the reference in ^{13}C NMR experiments. Elemental analysis were performed at Oneida Research Services, Inc., Whitesboro, NY. Fast atom bombardment analysis was carried out at M-Scan Inc., West Chester, PA. The oxazaborolidine reagents (*R*)-Me-CBS and (*S*)-Me-CBS can be purchased from Callery Chemical Company, Evans City, PA 16033. Bisnoralcohol (**5**) was obtained from Pharmacia & Upjohn, Kalamazoo, MI.

Preparation of 6. Ammonia (60 mL) was condensed into a flask under nitrogen, and lithium wire (98 mg, 14 mmol) was added. Steroid **5** (1.0 g, 3.0 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL) and added dropwise. After 40 min the reaction was quenched with solid ammonium chloride until the blue color disappeared and then allowed to evaporate overnight. The resulting solid was partitioned between water (150 mL) and ethyl acetate (200 mL). The aqueous layer was extracted with portions of ether and dichloromethane, and the combined organic layers were washed with brine, dried over sodium sulfate, and evaporated to yield a white solid. This material was dissolved in dichloromethane and purified by flash chromatography (gradient elution with 10 to 40% ethyl acetate in hexane) to afford **6** (710 mg, 71%, mp 168−170 °C, lit. mp 173 °C):[15] ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (d of d, J = 10 and 2 Hz, 1H), 3.36 (d of d, J = 10 and 3 Hz, 1H), 2.33−1.08 (m, 24H), 1.05 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.71 (s, 3H); ^{13}C NMR: δ 212.4, 68.1, 56.2, 53.9, 52.7, 46.8, 44.9, 42.8, 39.9, 38.9, 38.7, 38.4, 35.8, 35.6, 31.9, 29.1, 27.9, 24.5, 21.6, 16.9, 12.3, 11.6. Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.54; H, 10.48.

Preparation of 7. A solution of **6** (710 mg, 2.14 mmol), ethylene glycol (1.13 mL, 20 mmol), and *p*-toluenesulfonic acid monohydrate (41 mg, 0.21 mmol) in benzene (90 mL) was heated at reflux overnight with the removal of water by a Dean−Stark trap. The reaction mixture was cooled, washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated to yield **7** (725 mg, 90%, mp 184−186 °C): ^1H NMR: δ 3.94 (s, 4H), 3.64 (d of d, J = 10.3 and 3.1 Hz, 1H), 3.36 (d of d, J = 10.3 and 6.8 Hz, 1H), 1.98−1.94 (m, 1H), 1.83−1.76 (m, 1H), 1.7−1.0 (m, 22H), 1.04 (d, J = 7.0 Hz, 3H), 0.82 (s, 3H), 0.68 (s, 3H); ^{13}C NMR: δ 109.6, 68.2, 64.3, 56.4, 54.2, 52.7, 43.9, 42.9, 40.1, 39.0, 38.2, 36.2, 35.9, 35.7, 35.6, 32.1, 31.4, 28.8, 27.9, 24.5, 21.4, 16.9, 12.4, 11.6; IR (KBr, cm^{-1}): 3315, 2930, 1447, 1360, 1179, 1101. Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 74.91; H, 10.06.

Preparation of 8. A suspension of potassium acetate (140 mg, 1.43 mmol) and pyridinium chlorochromate (1.09 g, 5.06 mmol) in dichloromethane (20 mL) was treated with **7** (1.0 g, 2.65 mmol) in dichloromethane (10 mL). After 1.25 h, the reaction mixture was diluted with ether and filtered through Celite. The ether layers were combined, washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated to give a white solid. This material was purified by flash chromatography (gradient elution with 5 to 25% ethyl acetate in hexane) to afford **8** (604 mg, 61%, mp 141−144 °C): ^1H NMR: δ 9.56 (d, J = 3.5 Hz, 1H), 3.94 (s, 4H), 2.34 (m, 1H), 1.93−0.86 (m, 23H), 1.11 (d, J = 6.5 Hz, 3H), 0.82 (s, 3H), 0.70 (s, 3H); ^{13}C NMR: δ 205.4, 109.6, 64.3, 55.9, 54.2, 51.3, 49.7, 43.8, 43.4, 39.9, 38.1, 36.2, 35.7, 32.1, 31.4, 28.7, 27.2, 24.8, 21.3, 13.6, 12.7, 11.6; IR (KBr, cm^{-1}): 3478, 2934, 2725, 1721, 1445, 1356, 1101; MS (+FAB): 375.3 (M + 1, 60), 307.1 (100), 289.1 (45).

Preparation of 10. A solution of **8** (820 mg, 2.19 mmol) and **9** (1.52 g, 4.38 mmol)[14] in methyl sulfoxide (4 mL) was heated to 110 °C overnight, cooled, dissolved in ethyl acetate, washed with water, and dried. The crude material was purified by flash chromatography (gradient elution with 5 to 15% ethyl acetate in hexane) to yield **10** (720 mg, 74%, mp 168−169 °C). ^1H NMR: δ 6.71 (d of d, J = 16 and 9 Hz, 1H), 6.06 (d, J = 16 Hz, 1H), 3.94 (s, 4H), 2.83 (hept, J = 7 Hz, 1H), 2.25 (m, 1H), 1.95 (m, 1H), 1.7−1.0 (m, 22H), 1.11−1.08 (m, 9H), 0.82 (s, 3H), 0.69 (s, 3H); ^{13}C NMR: δ 204.9, 152.9, 126.3, 109.6, 64.3, 56.5, 55.2, 54.2, 43.8, 43.2, 40.2, 40.0, 38.4, 38.1, 36.2, 35.6, 32.0, 31.3, 28.7, 28.4, 24.4, 21.3, 19.5, 18.8, 18.7, 12.6, 11.6. Anal. Calcd for $C_{29}H_{46}O_3$-0.1H_2O: C, 78.36; H, 10.48. Found: C, 78.21; H, 10.68.

Preparation of 11 and 12. A solution of **10** (100 mg, 0.226 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL), treated with 1 M lithium aluminum hydride in tetrahydrofuran (380 μL, 0.38 mmol), and refluxed for 1 h under nitrogen. After cooling, the reaction was quenched with methanol, filtered through Celite, and purified by flash chromatography (gradient elution with 7 to 10% ethyl acetate in hexane) to afford pure **12** (18 mg, 18%, mp 147−150 °C, less polar by TLC 5% acetone/chloroform), followed by two mixed fractions of **11** (more polar) and **12** (49 + 15 mg = 64 mg, 64%). **12**: ^1H NMR: δ 5.49 (d of d, J = 15.4 and 8.2 Hz, 1H), 5.37 (d of d, J = 15.4 and 7.0 Hz, 1H), 3.94 (s, 4H), 3.77 (t, J = 6.4 Hz, 1H), 2.3−1.0 (m, 25H), 1.02 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.82 (s, 3H), 0.68 (s, 3H); ^{13}C NMR: δ 139.4, 128.6, 109.6, 78.42 (C24-*R*), 64.3, 56.6, 56.0, 54.2, 43.9, 42.8, 40.1, 40.0, 38.1, 36.2, 35.6, 34.1, 32.1, 31.3, 28.8, 24.4, 21.4, 20.6, 18.4, 12.5, 11.7, 11.6. Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.24; H, 10.87.

11, **12**: ^{13}C NMR: δ 78.80, 78.37 (C24-*S* and -*R*).

Synthesis of 14. A solution of **12** (75 mg, 0.17 mmol) in ethyl acetate (4 mL) was treated with 10% palladium on carbon (76 mg) and hydrogen (40 psi) on a Parr apparatus for 6 h. The reaction was filtered through Celite, evaporated, and recrystallized (ethyl acetate in hexane) to afford **14** (18 mg, 24%, mp 122−132 °C); ^1H NMR: δ 3.30 (m, 1H), 2.0−1.0 (m, 29H), 0.93−0.89 (m, 9H), 0.81 (s, 3H), 0.65 (s, 3H); ^{13}C NMR: δ 109.7, 77.64 (DEPT, C24-*S*), 64.4, 56.7, 56.2, 56.1, 54.2, 43.9, 42.8, 40.2, 38.2, 36.2, 36.1, 35.7, 35.6, 33.4, 32.4, 32.1, 31.4, 30.9, 30.0, 28.8, 28.4, 24.4, 21.4, 19.3, 19.0, 18.7, 18.6, 18.5, 16.9, 12.3, 11.6; MS (+FAB): 447.3 (M + 1, 100), 90.9 (80). Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.34; H, 10.84.

Synthesis of 13 and 14. A mixture of **11** and **12** (8.5 mg, 0.019 mmol) in ethanol (5 mL) was treated with 10% palladium on carbon (22 mg) and hydrogen (40 psi). The reaction mixture was filtered through Celite and evaporated to yield a mixture of **13** and **14** (8 mg); ^{13}C NMR (DEPT): δ 77.66, 77.31 (C24-*S* and *R*).

Stereoselective synthesis of 11. (*R*)-MeCBS was prepared *in situ* by combining (*R*)-diphenylprolinol (0.286 g, 1.13 mmol) and trimethylboroxane (0.14 g, 1.13 mmol) in toluene (30 mL). This mixture was stirred at 50 °C for 1 h and then heated to reflux until 20 mL of an azeotropic mixture was distilled. After cooling, 1 M borane−tetrahydrofuran complex (2.8 mL, 2.8 mmol) was added at room temperature and the solution was stirred for 2 h. Then, a solution of **10** (0.50 g, 1.13 mmol) in toluene (15 mL) was added at −20 °C over 1.75 h. After an additional h, the reaction was quenched with water (20 mL) and 5% hydrochloric acid (20 mL). After stirring for 30 min at rt, toluene (50 mL) was added and the organic phase was washed with brine (3 × 20 mL) to pH 7. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield **11** (0.48 g, de estimated by TLC ($CHCl_3$/*i*-Pr_2O 80:20) calibration = 94−98%). After purification by chromatography, the alcohol was obtained as a white solid (0.36 g, 72%, mp 157 °C); ^1H NMR: δ 5.43 (d of d, J = 15.3 and 8.3 Hz, 1H), 5.34 (d of d, J = 15.3 and 7 Hz, 1H), 3.93 (s, 4H), 3.72 (t, J = 7 Hz, 1H), 2.05 (m, 1H), 1.93 (m, 1H), 1.8−1.0 (m, 23H), 1.02 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.80 (s, 3H), 0.67 (s, 3H); ^{13}C NMR: δ 140.0, 128.6, 109.6, 78.82 (C24-*S*), 64.3, 56.7, 55.8, 54.2, 43.8, 42.8, 40.3, 40.1, 38.1, 36.2, 35.6, 34.1, 32.1, 31.3, 29.0, 28.7, 24.4, 21.4, 20.6, 18.6, 18.4, 12.4, 11.6;

MS (+FAB): 445.3 (M + 1, 48), 427.3 (37), 90.9 (100). Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.22; H, 10.59.

Synthesis of 13. A solution of **11** (19 mg, 0.043 mmol) in ethyl acetate (10 mL) was treated with 10% palladium on carbon (5 mg) and 40 psi of hydrogen for 4 h. The reaction was filtered, concentrated *in vacuo*, recrystallized from ethyl acetate in hexane, and then purified by flash chromatography (1 cm diameter, gradient elution with 7 to 8% ethyl acetate in hexane) to afford **13** (11 mg, 57%,[23] mp 125−127 °C); ^{1}H NMR: δ 3.94 (s, 4H), 3.31 (m, 1H), 2.0−1.0 (m, 29H), 0.92−0.89 (m, 9H), 0.81 (s, 3H), 0.66 (s, 3H); ^{13}C NMR: δ 109.7, 77.29 (DEPT, C24-*R*), 64.3, 56.7, 56.3, 54.2, 43.9, 42.8, 40.2, 38.2, 36.2, 35.9, 35.7, 33.7, 32.2, 32.1, 31.4, 30.8, 28.8, 28.5, 24.4, 21.4, 19.1, 18.8, 17.4, 12.3, 11.6; MS (+FAB): 447.4 (M + 1).

Preparation of 19. To a solution of potassium *tert*-butoxide (1.4 mL, 1 M K^+ $^-$OtBu in THF, 1.4 mmol) in THF (2.4 mL) at −78 °C was added a solution of dimethyl (diazomethyl)phosphonate[18] (205 mg, 1.4 mmol) in THF (1 mL) dropwise. The resulting yellow solution was stirred for 10 min. The aldehyde **8** (394 mg, 1.05 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. The cooled aldehyde solution was quickly transferred to the flask containing the phosphonate using a short cannula. The flask that contained aldehyde was rinsed with THF (3 mL), cooled, and then added in the same manner. The reaction was stirred at −78 °C for about 12 h and was allowed to warm to room temperature over night. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ether (4 × 25 mL). The ether layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude solid. Silica gel chromatography using 15% ethyl acetate in hexanes gave the pure alkyne **19** as a white solid (380 mg, 97%, mp 173−175 °C); ^{1}H NMR: δ 3.94 (s, 4H), 2.45 (m, 1H-20), 2.02 (d, J = 2 Hz, 1H-23), 1.21 (d, J = 7 Hz, 3H-21), 0.81 (s, 3H-19), 0.68 (s, 3H-18); ^{13}C NMR: δ 109.63, 89.68, 68.58, 64.35, 56.36, 55.59, 54.30, 43.90, 42.81, 39.46, 38.16, 36.23, 35.69, 35.61, 32.07, 31.36, 31.18, 28.74, 27.74, 27.45, 24.35, 21.51, 21.24, 12.61; IR (KBr, cm^{-1}): 3257, 2104, 1255, 686; MS (CI, isobutane): 371 ([M + H]$^+$, 100), 307 (20), 154 (82), 136 (72). Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 80.85, H, 9.87.

Preparation of 20. To a solution of alkyne **19** (100 mg, 0.27 mmol) in THF (5 mL) at −78 °C was added a solution of *n*-BuLi in hexanes (0.5 mL, 1.6 M, 0.81 mmol) dropwise. The reaction was stirred for 1 h, and boron trifluoride diethyl etherate (0.1 mL, 0.81 mmol) was added dropwise. After stirring for 15 min at −78 °C, isobutyric anhydride (0.2 mL, 1.2 mmol) was added in one portion. The reaction was stirred at −78 °C for about 30 min and was quenched by adding 0.2 N NaOH solution. The reaction mixture was extracted with ether (3 × 10 mL), and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. Silica gel chromatography using 5% ethyl acetate in hexanes gave the pure acetylenic ketone **20** as a thick oil (86 mg, 72%); ^{1}H NMR: δ 3.94 (s, 4H), 2.63 (m, 2H, H-20 & H-25), 1.95 (m, 1H), 1.83 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H-21), 1.18 (d, J = 6.8 Hz, 6H, H-25 & H-26), 0.82 (s, 3H-19), 0.70 (s, 3H-18); ^{13}C NMR: δ 192.85, 109.59, 99.86, 80.62, 64.36, 56.16, 55.26, 54.28, 43.88, 43.33, 42.99, 39.33, 38.14, 36.23, 35.69, 35.62, 32.05, 31.35, 28.69, 28.18, 27.34, 24.39, 21.21, 20.64, 18.29, 12.78, 11.62; IR (KBr, cm^{-1}): 2206, 1675; MS (CI, isobutane): 441 ([M + H]$^+$, 85), 125 (23), 99 (100), 77 (35). Anal. Calcd for $C_{29}H_{44}O_3$: C, 79.04; H, 10.06. Found: C, 78.45, H, 9.57.

Preparation of 21. A solution of acetylenic ketone **20** (50 mg, 0.11 mmol) in THF (0.5 mL) was dried over 4 Å molecular sieves for 2 h. The ketone solution was then added via syringe to a solution of (*S*)-MeCBS (0.18 mL, 1.3 M in toluene, 0.23 mmol) in THF (0.5 mL) at room temperature. The resulting solution was cooled to −30 °C, and a solution of borane−methyl sulfide in THF (0.28 mL, 2 M in THF, 0.57 mmol) was added dropwise over 5−10 min. The reaction was stirred at −30 °C for about 1 h at which time the TLC indicated that the reaction was complete. The reaction was quenched by slowly adding methanol (1 mL). The solution was diluted with ether and washed with saturated ammonium chloride solution, followed by 5% sodium bicarbonate and then brine. The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography using 20% ethyl acetate in hexanes gave the pure propargyl alcohol **21** as a white solid (36 mg, mp 130−134 °C, 72%); ^{1}H NMR: δ 4.15 (m, 1H-24), 3.94 (s, 4H), 2.48 (m, 1H-20), 1.19 (d, J = 6.9 Hz, 3H-21), 0.98 (d, J = 6.7 Hz, 3H) 0.96 (d, J = 6.7 Hz, 3H), 0.81 (s, 3H-19), 0.67 (s, 3H-18); ^{13}C NMR: δ 109.61, 91.07, 80.39, 68.36, 64.32, 56.35, 55.91, 54.34, 43.90, 42.80, 39.45, 38.16, 36.23, 35.70, 35.62, 34.91, 32.08, 31.36, 28.75, 27.85, 27.55, 24.38, 21.64, 21.23, 18.39, 17.55, 12.73, 11.61; IR (KBr, cm^{-1}): 3464, 2230.

Preparation of 13. A solution of propargyl alcohol **21** (35 mg, 0.08 mmol) in ethyl acetate (3 mL) was treated with 10% palladium on carbon (20 mg, 0.02 mmol), sodum nitrite (~2−3 mg), and hydrogen (40 psig) on a Parr apparatus for 17 h. The reaction was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The crude solid was purified by silica gel column chromatography using 20% ethyl acetate in hexanes to afford the alcohol **13** (27 mg, 77%); ^{1}H NMR: δ 3.92 (s, 4H), 3.32 (m, 1H-24), 1.95 (m, 1H), 1.83 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H, H-25 and H-26), 0.80 (s, 3H-19), 0.65 (s, 3H-18); ^{13}C NMR (DEPT): δ 77.29 (C24-*R*).

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(23) Significant formation of byproducts due to isomerization of the double bond and deoxygenation of the C24-OH can occur under these conditions. Optimization of the hydrogenation conditions for a related allylic alcohol will be reported in a subsequent publication.