Highly Stereocontrolled Formal Synthesis of Brassinolide via Chiral Sulfoxide-Directed S_N2' Reactions

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An efficient stereocontrolled methodology for the preparation of the four contiguous chiral centers of the brassinosteroid side chain is described. Allylic mesyloxy sulfinyl steroids have been found to undergo highly stereoselective S_N2' displacements when treated with cyanocuprates that provide the required acyclic stereocontrol in the key C-24 position of the steroidal side chain. Preparation of a direct precursor of brassinolide **1**, as well as a precursor of naturally occurring (24*R*)-epibrassinolide, **(+)-18**, is carried out in two additional steps utilizing asymmetric dihydroxylations of (22*E*)-olefins **(+)-2** and **(+)-17**. In this manner, a formal synthesis of this plant growth promoter has been completed, and the extension of the scope of this methodology has been explored providing a straightforward route to this family of steroids. Alternative routes to the key olefin **(+)-2** are also outlined. Improved selectivity in the addition to aldehyde **7** for the preparation of the Cram (22*R*)-allylic hydroxy sulfoxides is achieved by controlling the chirality at sulfur or by a condensation−symmetric oxidation sequence employing the analogous vinyl sulfide reagent **22**.

Introduction

The discovery and structural determination of the plant growth regulator brassinolide (**1**), isolated from bee-collected pollen of *Brassica Napus* L., was reported by USDA scientists in 1979[2] and was a breakthrough in the fields of phytochemistry, plant physiology, and agronomy.[3] A large number of analogs of this benign steroidal, highly oxygenated lactone have also been obtained from a wide variety of plants,[3a] many of them holding promising applications in agriculture.[3b] The extremely low abundance in natural sources[3d] and challenging structure of brassinolide have produced an increasing interest and intense activity in the synthesis of these brassinosteroids during the last 15 years.[3e,4] The unique biological activity of this family of plant hormones relies on the specific stereochemistry of its side chain consisting of four contiguous chiral centers. Several routes for the synthesis of brassinolide (**1**) (Scheme 1) and other brassinosteroids have been reported, such as: (a) epoxidation-ring opening of $\Delta^{23(24)}$ olefins,[5] (b) stereocontrolled addition of α-oxygen-substituted organometallic species to steroidal aldehydes,[6] and (c) ring-opening reactions of oxygen-containing cyclic derivatives of the side chain,[7] etc. Despite the numerous reports on this topic, the required acyclic stereocontrol for the construction of the side chain remains a challenging synthetic objective. In this context, a direct access to brassinosteroids *via* osmylations of (22*E*)-$\Delta^{22(23)}$-(24*R*)-methyl or (22*E*)-$\Delta^{22(23)}$-(24*S*)-ethyl olefins[8] derived from ergosterol/brassicasterol or stigmasterol, respectively, has been the subject of limited study since no versatile procedure to generate the key C-24 chiral center has been available. The lack of a general and highly stereoselective methodology that would facilitate the preparation of a variety of brassinosteroidal side chains motivated the research described herein.

In a previous communication, we have shown that the cuprate-mediated reactions of simple, acyclic allylic mesylates activated with a chiral sulfoxide group efficiently proceed with complete S_N2' regioselectivity, high *Z*/*E*

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(2) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature* **1979**, *281*, 216−217.

(3) *Brassinosteroids, Chemistry, Bioactivity and Applications*; Cutler, H. G., Yokota, T., Adam, G., Eds.; ACS Symposium Series 474; American Chemical Society: Washington DC, 1991: (a) Natural occurrences: Kim, S.-K., Chapter 3. (b) Improvements in elongation, yields and resistance of various crops, *inter alia*: Schilling, G.; Schiller, C.; Otto, S., Chapter 18; He, R.; Wang, G.; Wang, X., Chapter 19; Sasse, J. M., Chapter 22. (c) Antitumoral activity: Bach, T. J.; Roth, P. S.; Thompson, M. J., Chapter 15. (d) Isolation: Steffens, G. L., Chapter 1. (e) Synthesis: McMorris, T. C.; Donaubauer, J. R.; Silveira, M. H.; Molinski, T. F., Chapter 4. (f) Biological activity of naturally occurring 24-epibrassinolide: Ikekawa, N.; Zhao, Y.-J., Chapter 24.

(4) For accounts on this topic, see: (a) Zhou, W.-S. *Pure Appl. Chem.* **1989**, *61*, 431−434. (b) Khripach, V. A. *Pure Appl. Chem.* **1990**, *62*, 1319−1324.

(5) For some leading examples, see: (a) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962−964. (b) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580−6581. (c) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491−4492. (d) Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 663−664. (e) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767−1781. (f) Takahashi, T.; Ootake, A.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 69−72. (g) Aburatani, M.; Takeuchi, T.; Mori, K. *Agric. Biol. Chem.* **1986**, *50*, 3043−3047. (h) Shen, Z.-W.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1765−1767. (i) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1991**, *56*, 454−457. (j) Zhou, W.-S.; Jiang, B.; Pan, X.-F. *Tetrahedron* **1992**, *48*, 1837−1852. (k) Back, T. G.; Blazecka, P. G.; Krishna, M. V. *Can. J. Chem.* **1993**, *71*, 156−163. (l) Hazra, B. G.; Joshi, P. L.; Bahule, B. B.; Argade, N. P.; Pore, V. S.; Chordia, M. D. *Tetrahedron* **1994**, *50*, 2523−2532. See also ref 31.

(6) (a) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2833−2834. (b) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055−7060. (c) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143−146. (d) Kametani, T.; Kigawa, M.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1503−1507. (e) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1988**, *53*, 1982−1991. (f) Khripach, V. A.; Zhabinskii, V. N.; Zhernosek, E. V. *Tetrahedron Lett.* **1995**, *36*, 607−608. See also: (g) Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 477−480.

(7) (a) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1984**, *49*, 4297−4300. (b) Zhou, W.-S.; Tian, W.-S. *Tetrahedron* **1987**, *43*, 3705−3712. (c) Zhou, W.-S.; Jiang, B.; Pan, X. *J. Chem. Soc., Chem. Commun.* **1989**, 612−614. (d) Honda, T.; Keino, K.; Tsubuki, M. *J. Chem. Soc., Chem. Commun.* **1990**, 650−652. (e) Zhou, W.-S.; Jiang, B.; Pan, X. *Tetrahedron* **1990**, *46*, 3173−3188.

(8) (a) Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada, K.; Umemura, T.; Yabuta, G.; Kuwahara, S.; Kondo, M. *Tetrahedron* **1982**, *38*, 2099−2109. (b) Anastasia, M.; Ciuffreda, P.; Fiecci, A. *J. Chem. Soc., Perkin Trans 1* **1983**, 379−382. (c) Takatsuto, S.; Ikekawa, N. *Chem. Pharm. Bull.* **1985**, *32*, 2001−2004.

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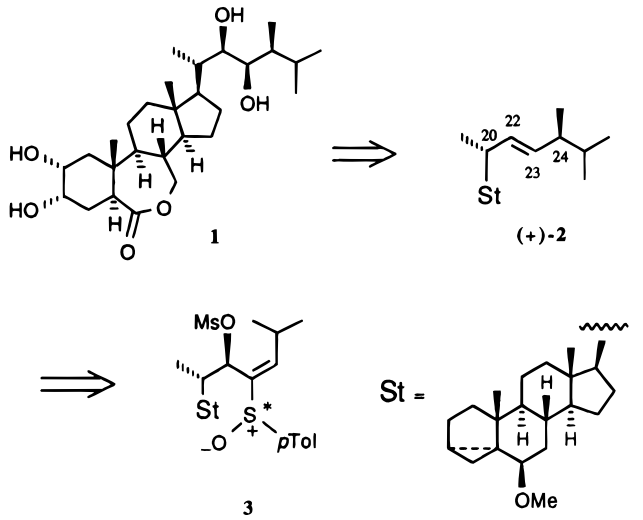
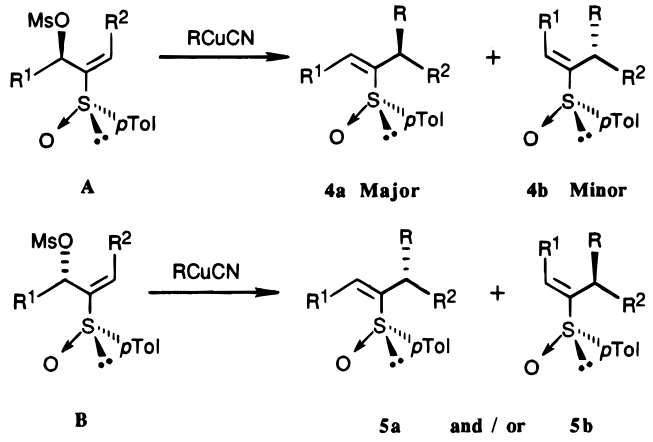
Scheme 1



Scheme 2[a]



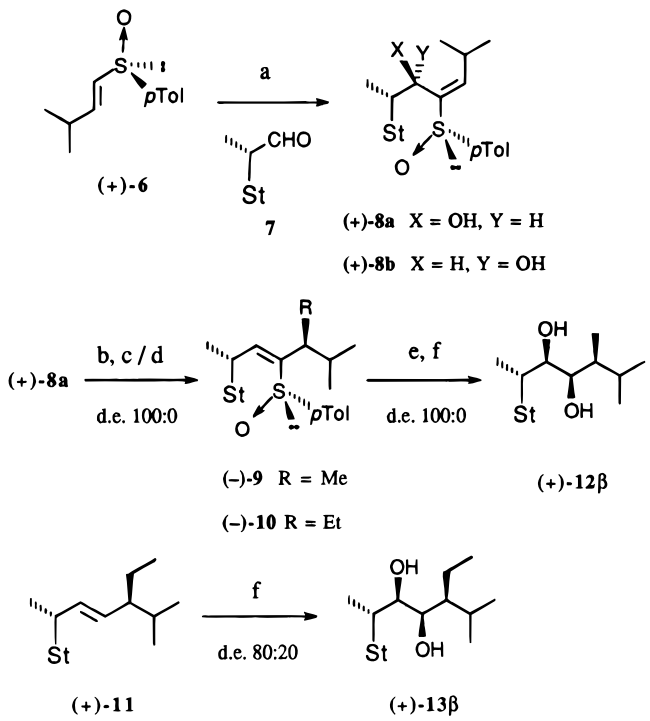
[a] R = Me, *t*-Bu, Ph; R^1 = Et, $Ph(CH_2)_2$−; R^2 = Ph, *n*-Bu, Me.

stereoselectivity (15:1), and high asymmetric induction to produce homochiral trisubstituted vinyl sulfoxides (Scheme 2).[9] When type **A** substrates were employed and regardless of the size of the R ligand introduced, highly selective formation of the (*Z*)-vinyl sulfoxide **4a** was observed. For type **B** diastereomers, either of the two possible substitution products, **5a,b** was obtained. Overall, the results could be rationalized in terms of S_N2' oxidative addition of the cuprate *anti* to the mesylate and *anti* to the *p*-tolyl group.[10] For the latter diastereomer, the observed ratio **5a**/**5b** seems to depend on the reaction conditions and the steric requirements of the substrate. As a result, the new carbon stereocenter is allylic to the synthetically useful vinyl sulfoxide group. Therefore, we envisioned that the absolute configuration at the chiral C-24 position of the brassinosteroidal side chains could be selectively controlled by means of this methodology if C-23 sulfinyl derivatives **3** were employed and led to the steroidal $\Delta^{22(23)}$ olefin **(+)-2** (Scheme 1). Since several disclosures in asymmetric dihydroxylation (ADH) of steroidal olefins[11] and continuous developments of new alkaloidal ligands for ADH have recently appeared,[12] direct precursors of brassinolide should be accessible in

(9) Marino, J. P.; Viso, A.; Fernández de la Pradilla, R.; Fernández, P. *J. Org. Chem.* **1991**, *56*, 1349−1351.

(10) For the proposed predominate conformations in solution of **A** and **B** diastereomeric mesylates showing the most favored approach of the cuprate, see ref 9.

Scheme 3[a]



[a] Key: (a) LDA, THF, −78 °C, **7**, 86% overall. (b) Ms_2O, pyr, 0 °C, 84%. (c) MeCuCNLi or MeCuCNMgBr, THF, −23 to 0 °C, 76%. (d) EtCuCNMgBr, THF, −23 °C to rt, 70%. (e) 1. *t*-BuLi, THF, −78 °C. 2. MeOH, 98%. (f) 10 mol % $K_2OsO_2(OH)_4$, 40 mol % $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH/H_2O, 1:1, rt, 30 h, 70% for (+)-**2**; 5 days, 75% overall for (+)-**11**.

a straightforward and stereoselective manner from **(+)-2** employing ADH reactions.

Results and Discussion

At the initial stage of our investigation, we explored the lithiation of the (R_S)-vinyl sulfoxide **(+)-6** and its condensation with the C-22 steroidal aldehyde **7**[13] (Scheme 3) to produce a disappointing 60:40 mixture of readily separable (22*R*)- and (22*S*)-allylic alcohols **(+)-8a** and **(+)-8b**, respectively, in excellent overall yield. The stereochemistry was unambiguously established from the ^{1}H NMR data (J_{20-22} = 0 Hz for the (22*R*)- and 6.4 Hz for the (22*S*)-alcohol),[14] the major product being the one arising from the Cram attack through the less hindered carbonyl face. Thorough studies of the reaction of lithiated vinyl sulfoxides and nonchiral aldehydes by Posner[15a]

(11) (a) Huang, L.-F.; Zhou, W.-S.; Sun, L.-Q.; Pan, X.-F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1683−1686. (b) McMorris, T. C.; Patil, P. A. *J. Org. Chem.* **1993**, *58*, 2338−2339. (c) Brosa, C.; Peracaula, R.; Puig, R.; Ventura, M. *Tetrahedron Lett.* **1992**, *33*, 7057−7060. (d) Zhou, W.-S.; Huang, L.-F.; Sun, L.-Q.; Pan, X.-F. *Tetrahedron Lett.* **1991**, *32*, 6745−6748.

(12) (a) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317−1349. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(13) Easily available from stigmasterol; see: (a) Anderson, G. D.; Thomas, J. P.; Djerassi, C.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 388−394. (b) Salmond, W. G.; Sobala, M. C. *Tetrahedron Lett.* **1977**, *20*, 1695−1698.

(14) For analogous structural assignments in similar products, see refs 5b, c, e, and k and ref 31.

(15) (a) Posner, G. H.; Mallamo, J. P.; Miura, K.; Hulce, M. *Pure Appl. Chem.* **1981**, *53*, 2307−2314 and references cited therein. (b) Cheng, H.-C.; Yan, T.-H. *Tetrahedron Lett.* **1990**, *31*, 673−676. (c) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097−6098. (d) Fawcett, J.; House, S.; Jenkins, P. R.; Lawrence, N. J.; Russell, D. R. *J. Chem. Soc., Perkin Trans 1* **1993**, 67−72.

and others[15b] failed to result in high levels of diastereoselectivity, although complete selectivity was encountered in one isolated example.[15c] Recent insight in this process[15d] showed that an increase in the steric size of the aldehyde with respect to unbiased substrates should favor (up to 70% diastereomeric excess the formation of type **B** diastereomers (Scheme 2, (*S*)-allylic alcohols when (R_s)-vinyl sulfoxides are employed). We anticipated that useful selectivities in the addition of chiral vinyl sulfoxides to α-substituted chiral aldehydes, an outcome that had not been previously reported, could be eventually obtained.

On the basis of the rationale we previously proposed,[9] the highly diastereoselective *anti* S_N2' displacements[16] on steroidal allylic mesylates appeared feasible. However, steric factors inherent in the steroid nucleus should affect the stereochemical outcome of the cuprate additions. The functionalization of these allylic steroidal alcohols with the appropriate leaving group proved not to be straightforward. After considerable experimentation, only reactions with methanesulfonic anhydride (Ms_2O) in pyridine provided good to excellent yields of the desired mesylate derivatives.[17] When the reaction of the mesylate derived from **(+)-8a** (a type **A** diastereomer) with lower order methyl cyanocuprate was carried out, no reaction was observed between −78 and −30 °C;[18] however, the addition of 3 equiv of MeCuCNLi or MeCuCNMgBr in THF from −23 to 0 °C cleanly afforded a good yield of the desired (22*Z*,24*S*)-vinyl sulfoxide **(−)-9** as a sole product (Scheme 3). No traces of the diastereomeric (22*E*,24*R*)-vinyl sulfoxide **19** (*vide infra*) could be detected within the detection limit of 360 MHz ^{1}H NMR.[19] Reductive desulfurization of **(−)-9** using Okamura's procedure[20] smoothly proceeded in almost quantitative yield. As expected, upon addition of a slight excess[21] of *t*-BuLi, a rapidly formed intermediate[20b] was stereospecifically protonated to yield the (*E*)-alkene **(+)-2**, which upon osmylation led to **(+)-12**β.

In order to secure more evidence on the absolute configuration of the acyclic stereocenter, a reaction of the aforementioned mesylate with ethyl cyanocuprate was performed to give **(−)-10**, followed by *t*-BuLi-mediated removal of the sulfinyl group. In this manner, stigmasterol isomethyl ether, **(+)-11**, was obtained, again with complete stereoselectivity. The spectral and analytical data for **(+)-11** matched those previously described for this product,[22] confirming the stereochemical assignments for the S_N2' products.

It is also known that the observed ratio of diols in the osmium-catalyzed *cis*-dihydroxylations of $\Delta^{22(23)}$ steroidal side chains strongly depends on the specific substitution at the C-24 position. In particular, osmylation of (24*S*)-ethyl substituents leads almost exclusively to the undesired (22*S*,23*S*)-diol (attack from the α face). On the other hand, *ca*. equimolecular mixtures of β/α diols have been obtained in different examples using (24*R*)-methyl derivatives.[8,23] When ADH procedures are utilized with the bis(chinchona) alkaloidal ligands, β diols are obtained selectively.[11b] Thus, we explored the AD-mix-β osmylation[12b,24] of **(+)-11** as a model to afford **(+)-13**β,[11c] which exhibited the side chain of 24-homobrassinolide, along with **(+)-13**α in an 80:20 ratio. On the other hand, we were pleased to discover that under the same conditions, ADH reaction of olefin **(+)-2** gave rise to the (22*R*,23*R*,24*S*)-diol **(+)-12**β ($[\alpha]_D$ = +37.6°, *c* = 1.65, $CHCl_3$, mp 76−78 °C), a known precursor of brassinolide,[5b,c,g] with total stereoselectivity.[25]

Encouraged by these selectivities and in order to extend the scope of our methodology, we addressed the introduction of the opposite C-24 stereochemistry. In the condensation of the 1-(*E*)-propenyl sulfoxide **(+)-14** with **7** (Scheme 4), a 60:40 separable mixture of diastereomers **(+)-15a** and **(+)-15b** was observed. The naturally occurring side chain of (24*R*)-epibrassinolide[3f] could be synthesized following a similar protocol from the (*R*)-alcohol **(+)-15a** to the vinyl sulfoxide **(−)-16** and then to the **(+)-18**β diol. Once again, complete stereoselectivity was encountered for S_N2' displacement using *i*-PrCuCNMgCl and ADH osmylation of desulfurized olefin **(+)-17**.[7a] We also envisioned from our models[9] that brassinolide side chain stereochemistry could be alternatively obtained from **(+)-15b** (type **B** diastereomer) and isopropyl cyanocuprate addition if a (*Z*)-vinyl sulfoxide of type **5a** (Scheme 2) becomes the main product of the reaction. In this case, an inseparable mixture of **(−)-9** (5.64 ppm, d, H-22) and **19** (6.20 ppm, d, H-22) was produced, probably due to the fact that the sterically unbiased methyl group is not bulky enough to favor one of the two possible reaction pathways.

In an effort to improve the initial diastereoselectivity of the vinyl sulfoxide **(+)-6** addition (Scheme 3),[26] we examined the condensation of the (S_s)-vinyl sulfoxide **(−)-6** with **7** (Scheme 5). If double diastereoselection[27] were achieved, an improved ratio of alcohols **(+)-20a** and

(16) For conjugate addition of organometallic reagents to α-sulfinyl enones, see: Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72−78 and references cited therein. For a key reference in asymmetric carbon−carbon bond formation by S_N2' displacements on allylic mesylates, see: Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801−803.

(17) In all cases, any other conditions employing MsCl and/or different solvents and bases led to much slower transformations resulting in extensive decomposition of the reaction mixtures.

(18) It should be pointed out that the use of Gilman cuprates resulted in formation of allenic products derived from 1,2-elimination of sulfoxide and mesyloxy groups. Recently we reported the preparation of allenes, of high enantiomeric purity, from unusually stabilized Cu(III) intermediates in this reaction; see: Fernández de la Pradilla, R.; Rubio, M. B.; Marino, J. P.; Viso, A. *Tetrahedron Lett.* **1992**, *33*, 4985−4988.

(19) The stereochemistry of the double bond in all the adducts can be deduced from the chemical shift of the vinylic proton and by comparison with the model substrates, whose absolute configuration was unambiguously established by X-ray analyses (see ref 9).

(20) (a) Park, G.; Okamura, W. H. *Synth. Commun.* **1991**, *21*, 1047−1054. (b) Theobald, P. G.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 741−750.

(21) In the original procedure (ref 20), 4.0 equiv of organolithium reagent was used. For our substrates, we found much better yields and smooth, instantaneous transformations when only 1.25 equiv of *t*-BuLi is added in THF at −78 °C.

(22) Steele, J. A.; Mosettig, E. *J. Am. Chem. Soc.* **1963**, *85*, 571−572.

(23) Takatsuto, S.; Ikekawa, N. *Chem. Pharm. Bull.* **1982**, *30*, 4181−4185.

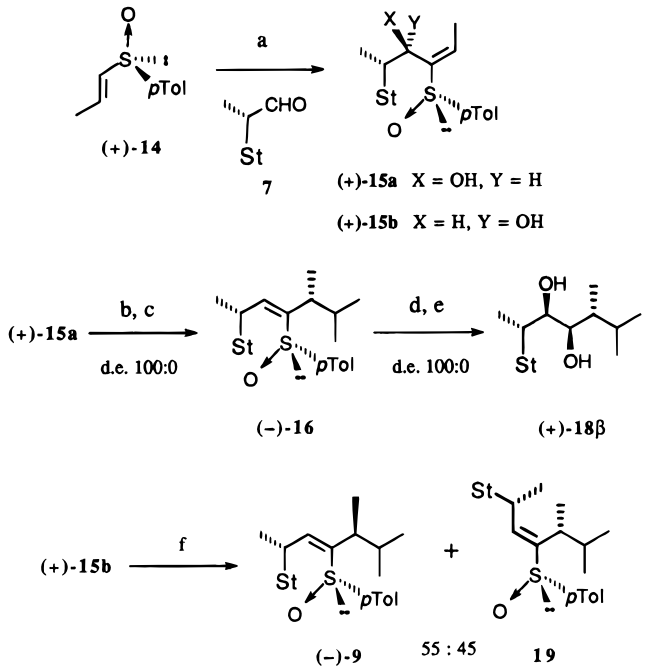
(24) In our hands, larger amounts of osmium catalyst and $(DHQD)_2$-PHAL were required for this transformation (see Experimental Section). The use of the commercially available AD-mix-β reagent resulted in extremely slow olefin conversion.

(25) In contrast with these results, Zhou (ref 10a) has reported identical selectivities (8:1) for ADH of stigmasterol and (24*S*)-ergosterol derivatives using monochinchona ligands, DHQD-PHN and DHQD-*p*-chlorobenzoate, respectively. The spectral and physical data of **(+)-12**β, identical to those reported in the literature, confirms the stereochemistry of all the intermediates (see Experimental Section).

(26) All attempts to interconvert the allylic alcohols **8a** and **b** failed. A large number of conditions for the Mitsunobu protocol or the inversion of the mesylate derivative of **(+)-8b** were unsuccessful. For similar puzzling observations where inversion of propargylic C-22 steroidal alcohols afforded very low yields, see ref 5e.

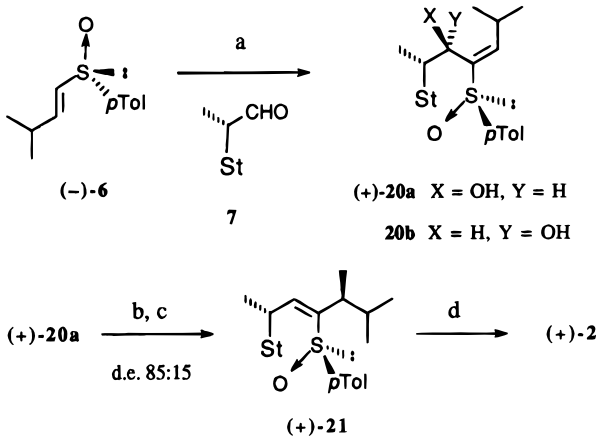
(27) For an elegant approach to brassinosteroids taking advantage of this concept, see: Furuta, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 2981−2982.

Scheme 4[a]



[a] Key: (a) LDA, THF, −78 °C, **7**, 73% overall. (b) Ms_2O, pyr, 0 °C, 82%. (c) *i*-PrCuCNMgCl, THF, −23 °C to rt, 73%. (d) 1. *t*-BuLi, THF, −78 °C. 2. MeOH, 95%. (e) AD-mix-β osmylation (see Scheme 3f), 48 h, 67%. (f) 1. (b) Ms_2O, pyr, 0 °C. 2. *i*-PrCuCNMgCl, THF, −78 °C to rt, 65% overall.

Scheme 5[a]



[a] Key: (a) LDA, THF, −78 °C, **5**, 75% overall. (b) Ms_2O, pyr, 93%. (c) MeCuCNMgBr, THF, 0 °C to rt, 71%. (d) 1. *t*-BuLi, THF, −78 °C. 2. MeOH, 95%.

20b would result. An 80:20 mixture of diastereomers was obtained favoring the Cram product. We propose a chairlike chelation-controlled transition state[15c,d] where the aldehyde adopts a Felkin−Anh rotational conformation.[28] Then, the aldehyde substituent can be either axial or equatorial (Figure 1). For the (R_s)-sulfoxides, Cram transition state **I** would display *p*-tolyl and aldehyde groups in the most favorable equatorial positions, but strong steric interaction between isopropyl and methyl substituents could explain the low ratio of products encountered. In order to relieve this steric hindrance, both *p*-tolyl and the steroid nucleus could adopt axial dispositions with strong 1,3-diaxial interactions. On the other hand, for (S_s)-sulfoxides, one of the two possible Cram transition states, **II**, would present an axial orientation for the aldehyde substituent but no overwhelming steric interactions should occur. As a result, the reaction of **(−)-6** and **7** could be the matched combination in this process consistent with the 4:1 selectivity observed.[29]

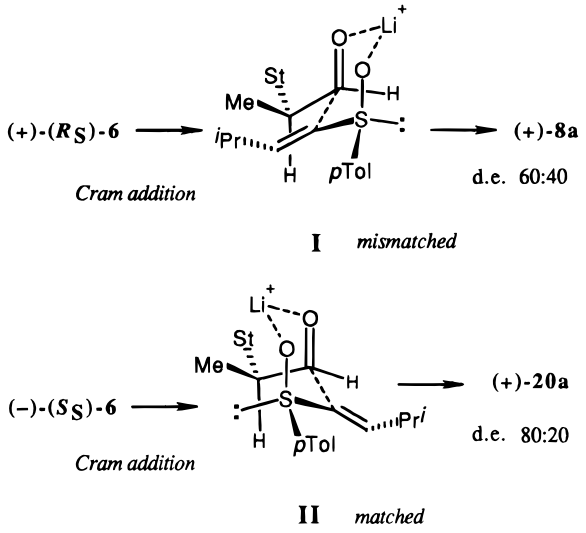


Figure 1.

Since **(+)-20a** is also a type **B** diastereomer with regard to the relative stereochemistry between hydroxyl and *p*-tolyl groups, the stereoselectivity in the nucleophilic displacement on this substrate was not predictable. Then, we were pleased to discover that formation of the mesylate derivative of **(+)-20a** and reaction with MeCuCNMgBr afforded the (*Z*)-vinyl sulfoxide **(+)-21** (5.76 ppm, d, H-22) as the major product (85:15 d.e.). As expected, **(+)-21** also exhibits the required absolute configuration at the key C-24 postition. In this case, the predominate conformation in solution requires that the bulkier isopropyl substituent is displayed away from the steroid nucleus, and then the *anti* attack of the cuprate affords the (*Z*)-olefin with good stereoselectivity. Subsequent addition of *t*-BuLi produced the olefin **(+)-2** in nearly quantitative yield (Scheme 5).

An additional improvement in the stereoselectivity was achieved in the condensation of **7** with the lithio derivative of the α-iodovinyl sulfide **22**[30] (Scheme 6) that smoothly provided the Cram/*anti*-Cram products in a ratio of 92:8 and excellent overall yield.[31] Thus, it seems that the nonchelated transition state clearly favors a higher Cram/*anti*-Cram ratio of adducts than the chelated model. At this point and in an effort to secure an alternative highly stereoselective sequence to obtain **(+)-8a**, the most convenient substrate for the cuprate displacement, we explored different conditions for the oxidation of the vinyl sulfide **(+)-23a**. The results are

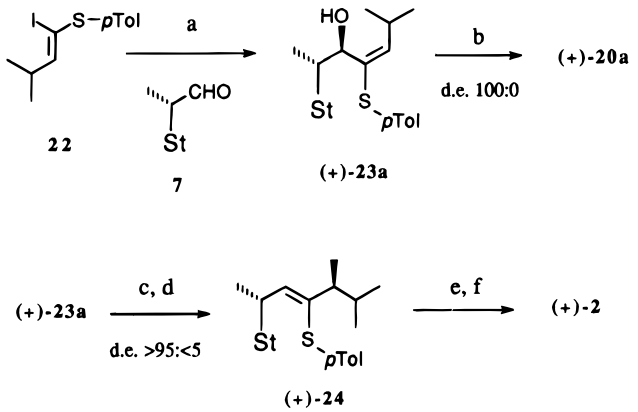
(28) See: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361 and references cited therein.

(29) At this point, a more important influence of the steroid framework cannot be ruled out. More detailed studies to determine if the chirality at sulfur can control the Cram selectivity in additions to different α-branched chiral aldehydes are underway.

(30) Prepared from *p*-tolyl thioacetylene (Magriotis, P. A.; Brown, J. T. *Org. Synth.* **1993**, *72*, 252−264) in one step via addition of 0.5 equiv of *i*-$Pr_2CuMgBr$ in Et_2O at −35 °C followed by addition of iodine (2.0 equiv) 84%; see: (a) Alexakis, A.; Cahiez, G.; Normant, J. F.; Villieras, J. *Bull. Soc. Chim. Fr.* **1977**, 693−698. (b) Vermeer, P.; de Graaf, C.; Meijer, J. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 24−25.

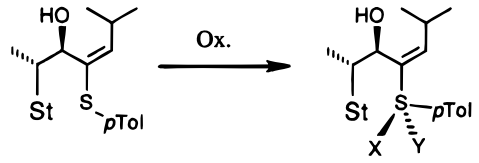
(31) For similar results using an analogous 1-iodovinyl silane, see: Khripach, V. A.; Zhabinskiy, V. N.; Olkhovick, V. K. *Tetrahedron Lett.* **1990**, *31*, 4937−4940.

Scheme 6[a]



[a] Key: (a) *t*-BuLi, THF, −78 °C, **5**, 84% overall. (b) Modified Sharpless oxidation; see Table 1. (c) Ms_2O, Et_3N, cat. DMAP, THF, 0 °C. (d) MeCuCNLi, −78 °C to rt, 55% (2 steps). (e) *m*-CPBA, CH_2Cl_2, 0 °C. (f) *t*-BuLi, THF, −78 °C, 80% (2 steps).

Scheme 7



(+)-23a

(R_S)-(+)-8a X = :, Y = O

(S_S)-(+)-20a X = O, Y = :

Table 1. Oxidation Reactions of Steroidal Vinyl Sulfide (+)-23a

entry	conditions[a]	ratio R_S/S_S	yield[b]
1	*m*-CPBA, 0 °C	13:87	80
2	CHP, Ti(O*i*-Pr)$_4$, (+)-DET, −20 °C	0:100	90
3	CHP, Ti(O*i*-Pr)$_4$, (−)-DET, −20 °C	0:100	82
4	*t*BuOOH, Ti(O*i*-Pr)$_4$, −78 °C	0:100	45[c]
5	Davis reagent,[d] rt	15:85	64

[a] All reactions were carried out in CH_2Cl_2 except for entry 5 where CCl_4 was employed. [b] Unoptimized yields of pure product after chromatography. [c] Significant amounts (ca. 20%) of starting material and corresponding sulfone were removed. [d] (3′*S*,2*R*)-(−)-***N***-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine; see ref 34.

summarized in Scheme 7 and Table 1. Remarkably, the asymmetric oxidation employing the modified Sharpless reagent[32] with cumene hydroperoxide (CHP) and *L*-(+)-diethyl tartrate at low temperature (entry 2) led to the (S_s)-sulfoxide **(+)-20a** as the only product. It is likely that the proximal hydroxyl group, to which the oxidant can bind, enhanced the diastereoselectivity because the simple oxidation employing *m*-CPBA afforded an 87:13 mixture of (S_s)-sulfoxide/(R_s)-sulfoxide, respectively (entry 1).[33] Surprisingly, when the same conditions were utilized in the presence of the *D*-(−)-diethyl tartrate (entry 3) the same stereochemistry at sulfur was obtained. Once again, any traces of the known R_s diastereomer could not be detected. The assumption that the chiral auxiliary might not be really enhancing the diastereoselection in the oxidation process was confirmed with the control experiment (entry 4) which also afforded **(+)-20a**, although with low chemical yield. Finally, the asymmetric oxidation using the most effective Davis reagent, (−)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine,[34] in CCl_4 (entry 5) also favored the same product with high diastereomeric excess. Thus, we can conclude that the stereochemistry at the C-22 hydroxyl group is the determinant for the stereochemical outcome of the oxidation and that only the *S* configuration at sulfur can be selectively obtained from vinyl sulfide **(+)-23a**.

Concurrent model studies from our group employing different oxidation states at sulfur for the S_N2' reaction[35] have indicated that similar stereoselectivities for the cuprate additions could be eventually achieved using the analogous sulfides. Consequently, we also explored the reactivity of the unstable mesylate derived from **(+)-23a** (Scheme 6) with a methyl cyanocuprate and found that the (22*Z*,24*S*)-vinyl sulfide **(+)-24** was produced in a highly stereoselective manner. Subsequent oxidation of **(+)-24** with 1.0 equiv of *m*-CPBA and *t*-BuLi-mediated desulfurization of the crude mixture of sulfoxides led again to the desired olefin **(+)-2**. In this manner, the aforementioned routes of Schemes 5 and 6 also provide a stereoselective alternative for the formal synthesis of **1** outlined in Scheme 1.

In summary, the results described herein conclusively establish a new stereoselective and practical route to brassinolide (**1**), taking advantage of the nucleophilic displacement of allylic mesyloxy vinyl sulfoxides and sulfides. The extension of the scope of this methodology to another episteroidal side chain synthesis has also been successfully developed. The diastereoselective nature of these procedures indicates that our proposed model for acyclic stereocontrol using chiral sulfoxides will provide promising applications in natural product synthesis involving asymmetric carbon−carbon bond formation.

Experimental Section

General Methods. All reactions except bis hydroxylations were carried out under a positive pressure of dry nitrogen using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by using standard syringe techniques. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone, dichloromethane, *N*,*N*-diisopropylamine, and triethylamine from calcium hydride, and pyridine from sodium hydroxide. Commercial methyllithium (low halide solution in ether), *n*-butyllithium (solution in hexanes), and *tert*-butyllithium (solution in pentanes) were purchased from Aldrich and titrated prior to use.[36] Methylmagnesium bromide, ethylmagnesium bromide, and isopropylmagnesium chloride (solutions in diethyl ether) were purchased from Aldrich. Copper cyanide was dried at 50−60 °C/0.2 mmHg for 16 h prior to use. All other reagents were used without further purification. 1,4-Bis(dihydroquinidine)-phthalazine, $(DHQD)_2$-PHAL, was prepared using the procedure reported by Sharpless et al.[12b] Flash chromatography was performed using Baker 40 μm silica gel. Analytical TLC was carried out on 250 micro Analtech silica gel plates with detection by UV light, iodine, or acidic vanillin solution. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 or 360 MHz using $CDCl_3$ as the solvent. The following abbreviations were used to describe peak patterns

(32) (a) Pitchen, P.; Duñach, E.; Deshmunkh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188−8193. (b) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325−326.

(33) The directing effect of a hydroxyl group in *m*-CPBA diastereoselective oxidation of 10-sulfinyl isoborneols is known; see: Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320−323.

(34) Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428−1437. For an account, see: Davis, F. A.; Thimma Reddy, R.; Han, W.; Reddy, R. E. *Pure Appl. Chem.* **1993**, *65*, 633−640.

(35) Marino, J. P.; Fernández de la Pradilla, R.; et al. Manuscript in preparation.

(36) Watson, S. C.; Eastham, J. *J. Organomet. Chem.* **1967**, *9*, 165−168.

when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Optical rotations were measured at 20 °C using a sodium lamp and in $CHCl_3$ solution.

General Procedure for the Condensation of Vinyl Sulfoxides and Steroid Aldehyde 7. To a cold (−78 °C) 0.1 M solution of 1.5 equiv of LDA, previously formed at 0 °C over 30 min, was slowly added 1 equiv of (*E*)-3-methyl-1-*p*-tolylsulfinyl-1-butene, **6**,[37] or (*E*)-1-(*p*-tolylsulfinyl)-1-propene, **14**[38] (0.05 M solution in THF), via syringe. After the mixture was stirred for 10 min, 1.2 equiv of (20*S*)-6*β*-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde, **7**[13] (1.0 M solution), was added dropwise. The reaction mixture was quenched after 1.5 h of stirring at −78 °C with a saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc (40 mL/mmol of starting material), and the combined organic layers were washed with water and a saturated NaCl solution, dried over $MgSO_4$, and filtered. Concentration under reduced pressure gave a crude product, which was purified by column chromatography on silica gel, using the appropriate mixture of hexanes and EtOAc.

(+)-(22*R*,23*E*,*R*$_s$)-22-Hydroxy-6*β*-methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-cholest-23-ene, (+)-8a, and (+)-(22*S*,23*E*,*R*$_s$)-22-hydroxy-6*β*-methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-cholest-23-ene, (+)-8b. From **(+)-6** ($[\alpha]_D$ = +66.0° (*c* = 1.00), 900 mg, 4.32 mmol) and **7** (1.78 g, 5.18 mmol), **(+)-8a** and **(+)-8b** were obtained as a 60:40 mixture (360 MHz ^{1}H NMR) and were separated by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford **(+)-8a** (1.23 g) and **(+)-8b** (825 mg), overall yield 86%. Data of **(+)-8a**: white solid; R_f = 0.39 (hexanes/EtOAc, 2:1); mp: 193−194 °C (Et_2O/hexanes); $[\alpha]_D$= +100.1° (1.03); ^{1}H NMR *δ* 0.44 (d, 1 H, *J* = 7.9, 5.1 Hz), 0.65 (m, 1 H), 0.67 (s, 3 H), 0.84−0.89 (m, 2 H), 1.00−1.15 (m, 3 H), 1.02 (s, 3 H), 1.03 (d, 3 H, *J* = 6.8 Hz), 1.08 (d, 3 H, *J* = 6.5 Hz), 1.10 (d, 3 H, *J* = 6.4 Hz), 1.21−1.32 (m, 4 H), 1.35−1.65 (m, 6 H), 1.71−1.78 (m, 3 H), 1.83−1.97 (m, 2 H), 2.07 (br s, 1 H), 2.34 (s, 3 H), 2.73 (m, 2 H), 3.28 (s, 3 H), 4.58 (br s, 1 H), 6.26 (d, 1 H, *J* = 10.8 Hz), 7.20 (d, 2 H, *J* = 8.1 Hz), 7.49 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR *δ* 12.0, 12.2, 13.0, 14.1, 19.2, 21.3, 21.3, 22.3, 22.5, 22.7, 24.0, 24.9, 27.4, 28.2, 30.5, 33.3, 35.0, 40.1, 42.6, 42.6, 43.3, 47.9, 52.1, 56.3, 56.5, 72.1, 82.3, 125.8, 129.7, 139.6, 141.3, 142.4, 143.5; IR (KBr) 3613, 3673, 2960, 2869, 1596, 1457, 1382, 1247, 1080, 1039, 1015, 928 cm^{-1}; MS (CI/NH_3) *m*/*e* 553 $[M + H]^+$ (100), 521, 505, 381, 237, 109, 91; HRMS calcd for $C_{35}H_{52}SO_3H$ $[M + H]^+$: 553.3715, found 553.3693. Anal. Calcd for $C_{35}H_{52}SO_3$: C, 76.03; H, 9.48. Found: C, 76.25; H, 9.38. Data of **(+)-8b**: white solid; R_f = 0.29 (hexanes/EtOAc, 2:1); mp 143−144 °C (Et_2O/hexanes); $[\alpha]_D$= +76.9° (1.00); ^{1}H NMR *δ* 0.43 (dd, 1 H, *J* = 7.9, 5.1 Hz), 0.65 (apparent t, 1 H, *J* = 4.8 Hz), 0.72 (s, 3 H), 0.78−0.90 (m, 3 H), 0.88 (d, 3 H, *J* = 6.8 Hz), 0.98−1.84 (m, 5 H), 1.01 (s, 3 H), 1.05 (d, 3 H, *J* = 6.5), 1.07 (d, 3 H, *J* = 6.2 Hz), 1.27 (m, 2 H), 1.33−1.56 (m, 4 H), 1.61−1.77 (m, 3 H), 1.80−1.95 (m, 3 H), 2.14 (br d, 1 H, *J* = 5.1 Hz), 2.40 (s, 3 H), 2.77 (br s, 1 H), 3.00 (m, 1 H), 3.32 (s, 3 H), 4.10 (dd, 1 H, *J* = 6.4, 5.3 Hz), 6.14 (d, 1 H, *J* = 10.8 Hz), 7.28 (d, 2 H, *J* = 8.3 Hz), 7.55 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR *δ* 12.3, 13.0, 15.8, 19.2, 21.4, 22.1, 22.6, 22.7, 24.6, 24.9, 28.5, 28.9, 30.4, 33.3, 35.0, 35.2, 40.1, 42.7, 43.3, 43.6, 47.9, 54.1, 56.0, 56.5, 74.7, 82.3, 126.0, 129.9, 140.6, 141.8, 142.0, 142.2; IR (CCl_4) 3358, 2937, 2867, 1459, 1264, 1177, 1097, 1013 cm^{-1}; MS (CI/NH_3) *m*/*e* 553 $[M + H]^+$, 363, 253, 237 (100), 140, 109; HRMS calcd for $C_{35}H_{52}SO_3H$ $[M + H]^+$: 553.3715, found 553.3716. Anal. Calcd for $C_{35}H_{52}SO_3$: C, 76.03; H, 9.48. Found: C, 75.78; H, 9.55.

General Procedure for the Mesylation of Steroidal Allylic Alcohols. To a vigorously stirred cold (0 °C) solution of 22-hydroxyl derivative (*ca.* 0.5 mmol) in pyridine (6 mL) was added methanesulfonic anhydride (amounts shown in each case). The reaction mixture was stirred and warmed to rt over 3 h, after which time it was poured into an ice-cold saturated solution of $NaHCO_3$ and diluted with CH_2Cl_2 (100 mL/mmol of starting alcohol). The aqueous phase was extracted with CH_2Cl_2 (two times, 20 mL/mmol), and the combined organic layers were washed sequentially with 10% aqueous HCl (four times, 20 mL/mmol), water (two times, 15 mL/mmol), and brine (20 mL/mmol). Drying over anhydrous $MgSO_4$, filtration, and evaporation of the solvent *in vacuo* afforded a crude product which was purified by column chromatography on deactivated silica gel (washed with a MeOH/5% aqueous solution of $NaHCO_3$, 95:5) to give the corresponding mesylate derivatives which were used shortly thereafter for the cuprate displacement without further purification. Formation of the mesylates was checked by ^{1}H NMR.

General Procedure for the S$_N$2′ Addition of Methyl Cyanocuprate Reagents to Steroid Mesylates. To a cold (−23 or −78 °C) solution of the organocuprate reagent (formed from CuCN and organolithium or Grignard reagents, amounts shown in each case) in THF (20 mL/mmol of mesylate) was added dropwise the mesylate in THF (2 mL/mmol) with vigorous stirring, and the resulting mixture was stirred and slowly warmed (conditions shown in each case). After completion (TLC) the solution was quenched with a saturated NH_4Cl solution and diluted with ethyl ether. The layers were separated, the aqueous layer was extracted with Et_2O (two times, 20 mL/mmol), the combined organic extracts were washed with a saturated solution of $Na_2S_2O_3$ (two times, 10 mL/mmol) and brine and dried over $MgSO_4$. Removal of the drying agent by filtration and evaporation of the solvent *in vacuo* afforded a crude product which was purified by column chromatography on silica gel with the appropriate eluent.

(−)-(22*Z*,24*S*,*R*$_s$)-6*β*-Methoxy-24-methyl-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-ergost-22-ene, (−)-9. From **(+)-8a** (300 mg, 0.54 mmol) and Ms_2O (280 mg, 1.63 mmol, 3.0 equiv), the mesylate derivative (287 mg, 84%) was obtained. ^{1}H NMR data: *δ* 0.68 (s, 3 H), 1.01 (s, 3 H), 1.05 (d, 3 H, *J* = 6.7 Hz), 1.08 (d, 3 H, *J* = 6.5 Hz), 1.14 (d, 3 H, *J* = 6.4 Hz), 2.41 (s, 3 H), 2.47 (s, 3 H), 2.76 (br s, 1 H), 3.02 (m, 1 H), 3.33 (s, 3 H), 5.29 (br s, 1 H), 6.41 (d, 1 H, *J* = 11.2 Hz), 7.33 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 2 H, *J* = 8.1 Hz). From this compound (400 mg, 0.63 mmol) and 3.0 equiv of MeCuCNLi or MeCuCNMgBr, in THF from −23 to 0 °C over 2 h, **(−)-9** was isolated (265 mg, 76%) as a single isomer (360 MHz ^{1}H NMR), after silica gel chromatography (hexanes/EtOAc, 5:1). Data of **(−)-9**: white solid; R_f = 0.18 (hexanes/EtOAc, 4:1); mp 206−207 °C (EtOH); $[\alpha]_D$ = −81.8° (0.82); ^{1}H NMR *δ* 0.15 (d, 3 H, *J* = 6.6 Hz), 0.44 (dd, 1 H, *J* = 7.9, 5.1 Hz), 0.66 (apparent t, 1 H, *J* = 4.6 Hz), 0.72 (d, 3 H, *J* = 6.5 Hz), 0.85 (s, 3 H), 0.88−0.99 (m, 3 H), 1.04 (s, 3 H), 1.10 (d, 3 H, *J* = 6.8 Hz), 1.14 (d, 3 H, *J* = 6.5 Hz), 1.07−1.30 (m, 7 H), 1.42−1.57 (m, 5 H), 1.59−1.67 (m, 1 H), 1.71−1.83 (m, 3 H), 1.91 (dt, 1 H, *J* = 13.3, 2.8 Hz), 2.02 (dt, 1 H, *J* = 12.8, 2.1 Hz), 2.21 (apparent q, 1 H, *J* = 7.1 Hz), 2.39 (s, 3 H), 2.78 (t, 1 H, *J* = 1.2 Hz), 3.33 (s, 3 H), 5.64 (d, 1 H, *J* = 10.8 Hz), 7.26 (d, 2 H, *J* = 8.1 Hz), 7.41 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR *δ* 13.0, 13.2, 19.1, 19.4, 20.1, 20.7, 21.1, 21.3, 21.7, 22.9, 24.3, 25.1, 28.2, 30.6, 32.0, 33.5, 35.1, 35.2, 35.5, 35.9, 40.5, 43.2, 43.5, 48.3, 56.5, 56.6, 56.7, 82.4, 124.4, 129.4, 139.9, 140.3, 141.8, 146.3; IR (CCl_4) 2957, 2868, 1456, 1372, 1261, 1099, 1082, 1045, 1015 cm^{-1}; MS (CI/NH_3) *m*/*e* 551 $[M + H]^+$ (100), 519, 503, 247; HRMS calcd for $C_{36}H_{54}SO_2H$ $[M + H]^+$: 551.3923, found 551.3936. Anal. Calcd for $C_{36}H_{54}SO_2$: C, 78.49; H, 9.88. Found: C, 78.37; H, 9.84.

(−)-(*R*$_s$)-23-(*p*-Tolylsulfinyl)stigmasteryl Isomethyl Ether, (−)-10. From the mesylate derivative of **(+)-8a** (260 mg, 0.42 mmol) and 3.0 equiv of EtCuCNMgBr, in THF from −23 °C to rt over 4 h, **(−)-10** was isolated (170 mg, 73%) as a single isomer after silica gel chromatography (hexanes/EtOAc, 5:1). Data of **(−)-10**: white solid; R_f = 0.27 (hexanes/EtOAc, 4:1); mp 203−204 °C (EtOH); $[\alpha]_D$= −63.7° (1.10); ^{1}H NMR *δ* 0.27 (d, 3 H, *J* = 4.7 Hz), 0.45 (dd, 1 H, *J* = 7.9, 5.2 Hz), 0.64 (d, 3 H, *J* = 6.6 Hz), 0.65 (apparent t, 1 H, *J* = 4.8 Hz), 0.83−0.92 (m, 2 H), 0.85 (t, 3 H, *J* = 6.6 Hz), 0.86 (s, 3 H), 1.04 (s, 3 H), 1.15 (d, 3 H, *J* = 6.5 Hz), 1.02−1.29 (m, 5 H), 1.42−1.63 (m, 10 H), 1.73−1.78 (m, 4 H), 1.91 (dt, 1 H, *J* = 13.0, 2.7 Hz), 2.02 (br d, 1 H, *J* = 12.8 Hz), 2.21 (m, 1 H), 2.39 (s, 3 H), 2.78 (br s, 1 H), 3.34 (s, 3 H), 5.63 (d, 1 H, *J* = 10.7 Hz), 7.26 (d, 2 H, *J* = 8.2 Hz), 7.43 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR *δ* 10.6, 12.7, 13.0, 18.3, 19.3, 20.1, 20.7, 21.3, 21.4, 22.7, 23.8, 24.3,

(37) Prepared by the Horner−Wittig procedure; see: Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473−478.

(38) Prepared from commercially available 1-bromo-1-propene.

24.9, 28.5, 30.2, 30.4, 33.3, 35.0, 35.2, 35.5, 40.3, 41.0, 43.0, 43.3, 48.0, 56.2, 56.5, 56.5, 82.3, 124.3, 129.4, 140.0, 140.4, 142.7, 143.6; IR (CCl_4) 2958, 2869, 1549, 1455, 1253, 1082, 1048, 1016 cm^{-1}; MS (EI/70 eV) *m/e* 564 $[M]^+$, 547, 393, 261 (100), 253, 109, 83, 69; HRMS calcd for $C_{37}H_{56}SO_2$: 564.4001, found 564.4006. Anal. Calcd for $C_{37}H_{56}SO_2$: C, 78.67; H, 9.99. Found: C, 79.09; H, 9.61.

General Procedure for the Reductive Desulfurization of Vinyl Sulfoxides. To a *ca.* 0.02 M solution of starting vinyl sulfoxide in THF at −78 °C was added MeLi (1.4 M, 0.25 equiv). After the mixture was stirred for 3 min, *t*-BuLi (1.7 M, 1.25 equiv) was added dropwise, and the reaction was stirred for an additional 3 min period. The solution was quenched with methanol (>20 equiv) at −78 °C and diluted with water (15 mL/mmol) and diethyl ether (35 mL/mmol). The aqueous phase was extracted with Et_2O (two times, 10 mL/mmol), and the combined organic layers were washed with brine (15 mL/mmol) and dried over $MgSO_4$. Removal of the drying agent and evaporation gave a crude product which was purified by silica gel chromatography with the appropriate eluent.

(+)-(22*E*,24*S*)-6*β*-Methoxy-3α,5-cyclo-5α-ergostan-22-ene, (+)-2. From **(−)-9** (252 mg, 0.60 mmol), MeLi (1.4 M, 0.10 mL), and *t*-BuLi (1.7 M, 0.44 mL), **(+)-2** (236 mg, 98%) was obtained. No traces of the (22*Z*)-olefin could be detected by 360 MHz ^1H NMR. Data of **(+)-2**: white solid; R_f = 0.37 (hexanes/EtOAc, 19:1); mp 73−74 °C (acetone/H_2O, 50:1, v/v); $[\alpha]_D$ = +50.9° (1.18); ^1H NMR δ 0.43 (dd, 1 H, *J* = 7.9, 5.0 Hz), 0.65 (dd, 1 H, *J* = 4.9, 4.1 Hz), 0.73 (s, 3 H), 0.82 (d, 3 H, *J* = 6.6 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz), 0.89 (m, 2 H), 0.93 (d, 3 H, *J* = 7.2 Hz), 1.00 (d, 3 H, *J* = 6.6 Hz), 1.02 (s, 3 H), 1.04−1.25 (m, 6 H), 1.37−2.02 (m, 14 H), 2.77 (t, 1 H, *J* = 2.7 Hz), 3.32 (m, 3 H), 5.16 (m, 2 H); ^{13}C NMR δ 12.4, 13.1, 18.0, 19.3, 19.6, 20.1, 21.0, 21.5, 22.7, 24.2, 25.0, 28.9, 30.5, 33.2, 33.3, 35.1, 35.3, 40.2, 40.3, 42.7, 43.1, 43.4, 48.1, 56.1, 56.5, 56.6, 82.4, 131.8, 136.1; IR (CCl_4) 2957, 2868, 1551, 1456, 1372, 1260, 1098, 1016 cm^{-1}; MS (EI/70 eV) *m/e* 412 $[M]^+$, 397, 380, 357 (100), 255, 69; HRMS calcd for $C_{29}H_{48}O$: 412.3705, found 412.3696. Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.60; H, 11.75.

General Procedure for the AD-Mix-*β Cis*-Dihydroxylation of Steroidal Olefins. To a vigorously stirred cold solution of $(DHQD)_2$-PHAL (40 mol %), $K_2OsO_2(OH)_4$ (10 mol %), $K_3Fe(CN)_6$ (6.0 equiv), and K_2CO_3 (6.0 equiv) in a mixture of *t*-BuOH/H_2O, 1:1 (20 mL/mmol) at 0 °C, methanesulfonamide (2.0 equiv) was added, and the resulting sluggish solution was stirred for 10 min, after which time the olefin (1.0 equiv) was added. Stirring was continued, and the reaction was monitored by TLC until total disappearance of the starting material. Then, Na_2SO_3 (500 mg/mmol) was added, and the mixture was stirred overnight. After dilution with EtOAc (80 mL/mmol) and water (25 mL/mmol), the aqueous phase was extracted with EtOAc (three times, 25 mL/mmol), and the combined organic layers were washed with 2 N KOH (10 mL/mmol) and brine (20 mL/mmol), dried over $MgSO_4$, and filtered off to give, after evaporation of the solvents, a crude oil that was purified by silica gel chromatography (hexanes/EtOAc, 4:1).

(+)-(22*R*,23*R*,24*S*)-22,23-Dihydroxy-6*β*-methoxy-3α,5-cyclo-5α-ergostane (+)-12*β*. From **(+)-2** (120 mg, 0.29 mmol), $(DHQD)_2$-PHAL (90 mg, 0.12 mmol), $K_2OsO_2(OH)_4$ (10.8 mg, 0.029 mmol), $K_3Fe(CN)_6$ (575 mg, 1.75 mmol), K_2CO_3 (240 mg, 1.75 mmol), and methanesulfonamide (56 mg, 0.58 mmol) in a mixture of *t*-BuOH/H_2O, 1:1 (4 mL) stirred over 30 h, **(+)-12***β* (91 mg, 70%) was isolated as a colorless syrup which was recrystallized from a mixture of $CHCl_3$/hexanes. No other products could be detected by 360 MHz ^1H NMR of the crude materials. The physical and analytical data for **(+)-12***β* matched those previously described in the literature. Data of **(+)-12***β*: white solid; R_f = 0.38 (hexanes/EtOAc, 2:1); mp 76−78 °C ($CHCl_3$/hexanes) (lit. mp 70−73 °C,[5b] 84−90 °C,[5g] 76−79 °C);[5k] $[\alpha]_D$ = +37.6° (1.65); ^1H NMR δ 0.43 (dd, 1 H, *J* = 8.0, 5.1 Hz), 0.64 (apparent t, 1 H, *J* = 4.7 Hz), 0.72 (s, 3 H), 0.80−0.91 (m, 4 H), 0.84 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.2 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 1.01 (s, 3 H), 1.02−1.27 (m, 6 H), 1.36−1.43 (m, 2 H), 1.47−1.54 (m, 4 H), 1.60−1.67 (m, 2 H), 1.71−1.76 (m, 2 H), 1.88 (dt, 1 H, *J* = 13.4, 2.9 Hz), 1.95 (dt, 1 H, *J* = 12.5, 3.2 Hz), 2.01 (br s, 1 H), 2.05 (br s, 1 H), 2.77 (t, 1 H, *J* = 2.7 Hz), 3.32 (s, 3 H), 3.55 (br d, 1 H, *J* = 8.5 Hz), 3.70 (br d, 1 H, *J* = 8.5 Hz); ^{13}C NMR δ 10.1, 11.9, 12.1, 13.1, 19.3, 20.7, 20.9, 21.4, 22.8, 24.0, 24.9, 27.9, 30.6, 30.8, 33.3, 35.1, 35.2, 36.8, 40.0, 40.3, 42.6, 43.3, 47.9, 52.5, 56.4, 56.6, 73.5, 74.9, 82.4; IR (CCl_4) 3406, 2943, 2868, 1549, 1458, 1381, 1098, 978 cm^{-1}; MS (EI/70 eV) *m/e* 446 $[M]^+$, 391, 346, 313 (100), 295, 121, 43; HRMS calcd for $C_{29}H_{50}O_3$: 446.3760, found 446.3751. Anal. Calcd for $C_{29}H_{50}O_3$: C, 78.02; H, 11.29. Found: C, 77.78; H, 11.55.

(+)-(22*R*,23*R*,24*S*)-22,23-Dihydroxy-24-ethyl-6*β*-methoxy-3α,5-cyclo-5α-cholestane, (+)-13*β*, and (+)-(22*S*,23*S*,24*S*)-22,23-Dihydroxy-24-ethyl-6*β*-methoxy-3α,5-cyclo-5α-cholestane, (+)-13α. From **(+)-11** (990 mg, 2.33 mmol), $(DHQD)_2$-PHAL (725 mg, 0.93 mmol), $K_2OsO_2(OH)_4$ (86 mg, 0.23 mmol), $K_3Fe(CN)_6$ (4.60 g, 14 mmol), K_2CO_3 (1.93 mg, 14 mmol), and methanesulfonamide (442 mg, 4.66 mmol) in a mixture of *t*-BuOH/H_2O, 1:1 (50 mL) stirred over 5 days, **(+)-13***β* (600 mg) and **(+)-13**α (150 mg) were obtained after separation by silica gel chromatography, overall yield 70%. The NMR data for these compounds matched those previously described.[11c] Data of **(+)-13***β*: R_f = 0.40 (hexanes/EtOAc, 2:1); $[\alpha]_D$ = +69.1° (1.38); MS (EI/70 eV) *m/e* 460 $[M]^+$, 445, 428, 405, 346, 313 (100), 295, 255, 213, 145, 121, 85, 43; HRMS calcd for $C_{30}H_{52}O_3$: 460.3916, found 460.3918. Data of **(+)-13**α: R_f = 0.49 (hexanes/EtOAc, 2:1); $[\alpha]_D$ = +32.7° (0.75); MS (EI/70 eV) *m/e* 460 $[M]^+$, 445, 428, 405, 346, 313 (100), 295, 255, 213, 145, 121, 81, 43; HRMS calcd for $C_{30}H_{52}O_3$: 460.3916, found 460.3902.

(+)-(22*R*,23*E*,*R*$_s$)-22-Hydroxy-6*β*-methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-26,27-dinorcholest-23-ene, (+)-15a, and (+)-(22*S*,23*E*,*R*$_s$)-22-hydroxy-6*β*-methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-26,27-dinorcholest-23-ene, (+)-15b. From **(+)-14** (900 mg, 5.0 mmol) and **7** (2.07 g, 6.0 mmol), **(+)-15a** and **(+)-15b** were obtained as a 60:40 mixture (360 MHz ^1H NMR) and were separated by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford **(+)-15a** (1.06 g) and **(+)-15b** (850 mg), overall yield, 73%. Data of **(+)-15a**: white solid; R_f = 0.22 (hexanes/EtOAc, 2:1); mp 191−192 °C (Et_2O/hexanes); $[\alpha]_D$ = +59.7° (1.24); ^1H NMR δ 0.42 (dd, 1 H, *J* = 7.9, 5.1 Hz), 0.63 (m, 1 H), 0.64 (s, 3 H), 0.72−0.91 (m, 4 H), 0.95−1.19 (m, 4 H), 1.00 (s, 3 H), 1.01 (d, 3 H, *J* = 6.5 Hz), 1.24−1.61 (m, 7 H), 1.69−1.75 (m, 3 H), 1.85 (dt, 1 H, *J* = 13.4, 2.9 Hz), 1.92 (m, 1 H), 1.92 (d, 3 H, *J* = 7.3 Hz), 2.36 (s, 3 H), 2.40 (d, 1 H, *J* = 3.8 Hz), 2.75 (t, 1 H, *J* = 2.6 Hz), 3.30 (s, 3 H), 4.63 (brs, 1 H), 6.56 (qd, 1 H, *J* = 7.3 Hz, 1.0 Hz), 7.23 (d, 2 H, *J* = 8.1 Hz), 7.53 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR δ 12.1, 12.5, 13.1, 14.7, 19.2, 21.3, 21.5, 22.8, 24.1, 25.0, 27.5, 30.6, 33.4, 35.2, 35.3, 40.3, 41.8, 42.8, 43.4, 48.1, 52.3, 56.5, 56.5, 72.4, 82.4, 125.8, 129.0, 129.7, 141.2, 142.4, 147.2. IR (CCl_4) 3356, 2937, 2868, 1492, 1455, 1378, 1098, 1082, 1013 cm^{-1}; MS (CI/NH_3) *m/e* 525 $[M+H]^+$, 507, 330, 313, 295, 181 (100); HRMS calcd for $C_{33}H_{48}SO_3H$ $[M+H]^+$: 525.3402, found 525.3405. Anal. Calcd for $C_{33}H_{48}SO_3$: C, 75.54; H, 9.22. Found: C, 75.28; H, 9.34. Data of **(+)-15b**: white solid; R_f = 0.15 (hexanes/EtOAc, 2:1); mp 156−157 °C (Et_2O/hexanes); $[\alpha]_D$ = +68.0° (0.95); ^1H NMR δ 0.42 (dd, 1 H, *J* = 7.9, 5.1 Hz), 0.64 (apparent t, 1 H, *J* = 4.5 Hz), 0.71 (s, 3 H), 0.74−0.90 (m, 3 H), 0.86 (d, 3 H, *J* = 6.9 Hz), 0.94−1.18 (m, 4 H), 1.01 (s, 3 H), 1.21−1.77 (m, 8 H), 1.85−2.04 (m, 5 H), 1.98 (d, 3 H, *J* = 7.3 Hz), 2.31 (br d, 1 H, *J* = 4.6 Hz), 2.39 (s, 3 H), 2.77 (t, 1 H, *J* = 2.6 Hz), 3.32 (s, 3 H), 4.18 (br dd, 1 H, *J* = 5.9, 3.8 Hz), 6.42 (q, 1 H, *J* = 7.2 Hz), 7.28 (d, 2 H, *J* = 8.1 Hz), 7.54 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR δ 12.4, 13.1, 15.1, 15.8, 19.2, 21.4, 21.6, 22.8, 24.7, 25.0, 28.8, 30.6, 33.5, 35.1, 35.4, 40.3, 42.9, 43.4, 43.8, 48.2, 54.3, 56.2, 56.5, 74.6, 82.5, 126.0, 129.9, 130.5, 140.8, 141.9, 146.3; IR (CCl_4) 3380, 2934, 2868, 1455, 1374, 1324, 1214, 1098, 1015 cm^{-1}; MS (CI/NH_3) *m/e* 525 $[M + H]^+$, 507, 313, 295, 181 (100); HRMS calcd for $C_{33}H_{48}SO_3H$ $[M + H]^+$: 525.3402, found 525.3400. Anal. Calcd for $C_{33}H_{48}SO_3$: C, 75.54; H, 9.22. Found: C, 75.20; H, 9.41.

(−)-(22*Z*,24*R*,*R*$_s$)-6*β*-Methoxy-24-methyl-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-ergost-22-ene, (−)-16. From **(+)-15a** (350 mg, 0.67 mmol) and Ms_2O (345 mg, 2.0 mmol, 3.0

equiv), the mesylate derivative (330 mg, 82%) was obtained. ^{1}H NMR data: δ 0.60 (s, 3 H), 0.98 (d, 3 H, J = 6.6 Hz), 0.99 (s, 3 H), 2.06 (d, 3 H, J = 7.4 Hz), 2.39 (s, 3 H), 2.49 (s, 3 H), 2.75 (br s, 1 H), 3.31 (s, 3 H), 5.21 (br s, 1 H), 6.75 (q, 1 H, J = 7.4 Hz), 7.31 (d, 2 H, J = 8.2 Hz), 7.52 (d, 2 H, J = 8.2 Hz). From this compound (240 mg, 1.26 mmol) and 3.0 equiv of *i*-PrCuCNMgCl, in THF from −23 °C to rt over 4 h, **(−)-16** was isolated (160 mg, 73%) as a single isomer (360 MHz ^{1}H NMR), after silica gel chromatography (hexanes/EtOAc, 5:1). Data of **(−)-16**: white solid; R_f = 0.18 (hexanes/EtOAc, 4:1); mp 210−211 °C (EtOH); $[\alpha]_D$ = −87.6° (0.91); ^{1}H NMR δ 0.15 (d, 3 H, J = 6.6 Hz), 0.45 (dd, 1 H, J = 7.9, 5.4 Hz), 0.66 (apparent t, 1 H, J = 4.4 Hz), 0.72 (d, 3 H, J = 6.6 Hz), 0.85 (s, 3 H), 0.87−1.01 (m, 3 H), 1.04 (s, 3 H), 1.07−1.39 (m, 7 H), 1.11 (d, 3 H, J = 6.9 Hz), 1.14 (d, 3 H, J = 6.5 Hz), 1.42−1.60 (m, 6 H), 1.72−1.78 (m, 3 H), 1.88 (dt, 1 H, J = 13.0, 2.1 Hz), 2.03 (dt, 1 H, J = 12.9, 2.0 Hz), 2.22 (m, 1 H), 2.39 (s, 3 H), 2.78 (t, 1 H, J = 1.0 Hz), 3.33 (s, 3 H), 5.64 (d, 1 H, J = 10.8 Hz), 7.27 (d, 2 H, J = 7.9 Hz), 7.41 (d, 2 H, J = 8.2 Hz); ^{13}C NMR δ 12.8, 13.1, 19.2, 19.3, 20.6, 21.3, 21.3, 21.5, 21.7, 22.8, 24.2, 25.0, 28.2, 30.5, 31.9, 33.4, 35.0, 35.2, 35.8, 40.3, 43.0, 43.4, 48.1, 56.3, 56.6, 82.3, 124.3, 129.5, 139.7, 140.4, 141.8, 146.1; IR (CCl_4) 2957, 2869, 1082, 1046 cm^{-1}; MS (CI/NH_3) m/e 551 $[M + H]^+$ (100), 519, 503, 247; HRMS calcd for $C_{36}H_{54}SO_2H$ $[M + H]^+$: 551.3923, found 551.3915. Anal. Calcd for $C_{36}H_{54}SO_2$: C, 78.49; H, 9.88. Found: C, 78.78; H, 9.77.

(+)-(22*E*,24*R*)-6β-Methoxy-3α,5-cyclo-5α-ergostan-22-ene, (+)-17. From **(−)-16** (200 mg, 0.36 mmol), MeLi (1.4 M, 0.09 mL), and *t*-BuLi (1.7 M, 0.25 mL), **(+)-17** (140 mg, 95%) was obtained. No traces of the (22*Z*)-olefin could be detected by 360 MHz ^{1}H NMR. The analytical data for this compound matched those described in the literature.[7a] Data of **(+)-17**: white solid; R_f = 0.37 (hexanes/EtOAc, 19:1); mp 74−75 °C (acetone/H_2O, 50:1, v/v) (lit.[7a] mp 72−74 °C); $[\alpha]_D$ = +17.6° (0.72); ^{1}H NMR δ 0.43 (dd, 1 H, J = 8.0, 5.1 Hz), 0.65 (dd, 1 H, J = 4.6, 4.2 Hz), 0.72 (s, 3 H), 0.82 (d, 3 H, J = 6.6 Hz), 0.84 (d, 3 H, J = 5.8 Hz), 0.88 (m, 2 H), 0.91 (d, 3 H, J = 6.8 Hz), 1.01 (d, 3 H, J = 6.7 Hz), 1.02 (s, 3 H), 1.05−1.27 (m, 6 H), 1.40−2.07 (m, 14 H), 2.77 (t, 1 H, J = 2.6 Hz), 3.32 (s, 3 H), 5.18 (m, 2 H); ^{13}C NMR δ 12.4, 13.1, 17.6, 19.3, 19.6, 20.0, 20.9, 21.5, 22.8, 24.2, 25.0, 28.6, 30.5, 31.4, 33.1, 33.4, 35.1, 40.2, 40.2, 42.7, 42.8, 43.4, 48.1, 56.2, 56.5, 56.6, 82.4, 131.7, 136.0; IR (CCl_4) 2957, 2869, 1550, 1456, 1372, 1324, 1295, 1200, 1098, 1016, 970 cm^{-1}; MS (EI/70 eV) m/e 412 $[M]^+$, 397, 380, 357 (100), 255, 69; HRMS calcd for $C_{29}H_{48}O$: 412.3705, found 412.3695. Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.81; H, 11.72.

(+)-(22*R*,23*R*,24*R*)-22,23-Dihydroxy-6β-methoxy-3α,5-cyclo-5α-ergostane, (+)-18β. From **(+)-17** (120 mg, 0.29 mmol), $(DHQD)_2$-PHAL (90 mg, 0.12 mmol), $K_2OsO_2(OH)_4$ (10.8 mg, 0.029 mmol), $K_3Fe(CN)_6$ (575 mg, 1.75 mmol), K_2CO_3 (240 mg, 1.75 mmol), and methanesulfonamide (56 mg, 0.58 mmol) in a mixture of *t*-BuOH/H_2O, 1:1 (4 mL) stirred over 48 h, **(+)-18β** (87 mg, 67%) was isolated as a colorless syrup. No other products could be detected by 360 MHz ^{1}H NMR. Data of **(+)-18β**: R_f = 0.37 (hexanes/EtOAc, 2:1); $[\alpha]_D$ = +18.3° (0.47); ^{1}H NMR δ 0.43 (dd, 1 H, J = 8.0, 4.8 Hz), 0.65 (apparent t, 1 H, J = 4.6 Hz), 0.74 (s, 3 H), 0.79−0.93 (m, 4 H), 0.86 (d, 3 H, J = 6.6 Hz), 0.88 (d, 3 H, J = 6.3 Hz), 0.94 (d, 3 H, J = 6.8 Hz), 0.96 (d, 3 H, J = 6.8 Hz), 1.02 (s, 3 H), 1.06−1.43 (m, 8 H), 1.49−1.67 (m, 6 H), 1.71−1.78 (m, 2 H), 1.86−2.12 (m, 4 H), 2.77 (t, 1 H, J = 2.5 Hz), 3.33 (s, 3 H), 3.41 (br dd, 1 H, J = 5.1, 3.9 Hz), 3.70 (br d, 1 H, J = 3.9 Hz); ^{13}C NMR δ 11.0, 12.2, 12.6, 13.2, 17.5, 19.3, 21.6, 22.2, 22.9, 24.2, 25.1, 27.2, 28.1, 30.7, 33.5, 35.2, 35.4, 40.4, 40.4, 41.7, 42.8, 43.5, 48.1, 53.1, 56.5, 56.9, 72.9, 76.5, 82.5; IR (CCl_4) 3420, 2958, 2865, 1549, 1466, 1383, 1098, 1015 cm^{-1}; MS (EI/70 eV) m/e 446 $[M]^+$, 391, 346, 313 (100), 295, 282, 227, 159, 121; HRMS calcd for $C_{29}H_{50}O_3$: 446.3760, found 446.3764.

(+)-(22*R*,23*E*,*S*$_s$)-22-Hydroxy-6β-methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-cholest-23-ene, (+)-20a. From **(−)-6** ($[\alpha]_D$ = −66.5° (c = 1.00), 500 mg, 2.40 mmol) and **7** (1.07 g, 3.12 mmol), **(+)-20a** and **20b** were obtained as an 80:20 mixture (360 MHz ^{1}H NMR) and were partially separated by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford pure **(+)-20a** (690 mg) and an enriched sample of **20b** (305 mg), overall yield, 75%. Data of **(+)-20a**: white solid; R_f = 0.31 (hexanes/EtOAc, 2:1); mp 196−197 °C (Et_2O/hexanes); $[\alpha]_D$= +24.7° (1.50); ^{1}H NMR δ 0.42 (m, 1 H), 0.42 (s, 3 H), 0.64 (apparent t, 1 H, J = 4.3 Hz), 0.76−0.90 (m, 4 H), 0.84 (d, 3 H, J = 6.2 Hz), 1.00−1.18 (m, 3 H), 1.00 (s, 3 H), 1.06 (d, 3 H, J = 6.5 Hz), 1.09 (d, 3 H, J = 6.5 Hz), 1.23−1.58 (m, 7 H), 1.66−1.79 (m, 2 H), 1.83−1.87 (m, 4 H), 2.38 (s, 3 H), 2.76 (br s, 1 H), 3.03 (m, 1 H), 3.24 (br s, 1 H), 3.32 (s, 3 H), 4.69 (br s, 1 H), 6.17 (d, 1 H, J = 10.8 Hz), 7.27 (d, 2 H, J = 8.2 Hz), 7.44 (d, 2 H, J = 8.1 Hz); ^{13}C NMR δ 11.9, 12.4, 13.1, 19.2, 21.3, 21.5, 22.4, 22.4, 22.8, 24.1, 25.0, 27.6, 28.6, 30.6, 33.4, 35.1, 35.3, 40.1, 41.6, 42.6, 43.4, 48.0, 52.0, 56.3, 56.5, 72.0, 82.4, 124.5, 129.6, 140.4, 140.7, 143.7, 145.1; IR (CCl_4) 3392, 2962, 2869, 1422, 1264, 1080, 1042, 908, 896 cm^{-1}; MS (CI/NH_3) m/e 553 $[M + H]^+$, 519, 487, 323, 305, 251, 237, 209 (100), 165, 117; HRMS calcd for $C_{35}H_{52}SO_3H$ $[M + H]^+$: 553.3715, found 553.3694. Anal. Calcd for $C_{35}H_{52}SO_3H$: C, 76.03; H, 9.48. Found: C, 75.80; H, 9.57.

(−)-(22*Z*,24*S*,*S*$_s$)-6β-Methoxy-23-(*p*-tolylsulfinyl)-3α,5-cyclo-5α-ergost-22-ene, (+)-21. From **(+)-20a** (150 mg, 0.27 mmol) and Ms_2O (115 mg, 0.67 mmol, 2.5 equiv), the mesylate derivative was obtained (158 mg, 93%). ^{1}H NMR data: δ 0.29 (s, 3 H), 0.85 (d, 3 H, J = 6.5 Hz), 0.99 (s, 3 H), 1.00 (d, 3 H, J = 6.8 Hz), 1.13 (d, 3 H, J = 6.2 Hz), 2.39 (s, 3 H), 2.76 (br s, 1H), 2.89 (s, 3 H), 3.07 (m, 1 H), 3.32 (s, 3 H), 5.25 (d, 1 H, J = 1.0 Hz), 6.40 (d, 1 H, J = 11.3 Hz), 7.31 (d, 2 H, J = 8.0 Hz), 7.45 (d, 2 H, J = 8.2 Hz). From this compound (150 mg, 0.24 mmol) and 3.0 equiv of MeCuCNMgBr in THF from −23 °C to rt over 4 h, a 85:15 mixture of S_N2' products was obtained. 360 MHz ^{1}H NMR of the crude materials showed doublets at 5.75 ppm (J = 10.2 Hz) and 6.17 ppm (J = 10.9 Hz) for (22*Z*,24*S*) and (22*E*,24*R*) isomers, respectively. Major isomer **(+)-21** was isolated (94 mg, 71%) after silica gel chromatography (hexanes/EtOAc, 5:1). Data of **(+)-21**: white solid; R_f = 0.26 (hexanes/EtOAc, 5:1); mp 195−196 °C (EtOH); $[\alpha]_D$ = +115.9° (0.95); ^{1}H NMR δ 0.44 (dd, 1 H, J = 8.0, 5.2 Hz), 0.58 (d, 3 H, J = 7.0 Hz), 0.66 (apparent t, 1 H, J = 4.5 Hz), 0.82 (s, 3 H), 0.86 (d, 3 H, J = 6.7 Hz), 0.87 (d, 3 H, J = 6.6 Hz), 1.04 (s, 3 H), 1.06−1.14 (m, 2 H), 1.17−1.37 (m, 3 H), 1.18 (d, 3 H, J = 6.6 Hz), 1.41−1.59 (m, 6 H), 1.64 (m, 6 H), 1.74 (m, 2 H), 1.88 (m, 1 H), 2.02 (m, 1 H), 2.14 (quintet, 1 H, J = 7.4 Hz), 2.39 (s, 3 H), 2.78 (t, 1 H, J = 2.6 Hz), 3.33 (s, 3 H), 5.76 (d, 1 H, J = 10.2 Hz), 7.27 (d, 2 H, J = 8.2 Hz), 7.50 (d, 2 H, J = 8.2 Hz); ^{13}C NMR δ 12.8, 13.1, 19.1, 19.2, 19.2, 19.3, 21.0, 21.3, 21.4, 22.7, 24.2, 24.9, 28.5, 30.5, 33.3, 33.7, 35.1, 35.2, 35.4, 36.4, 40.1, 43.1, 43.4, 48.0, 56.4, 56.4, 56.6, 82.2, 124.6, 129.5, 140.0, 140.5, 143.9, 145.6; IR (CCl_4) 2961, 2869, 1473, 1081, 1030, 928 cm^{-1}; MS (CI/CH_4) m/e 551 $[M + H]^+$, 519, 503, 381, 321 (100), 305, 247, 209, 97; HRMS calcd for $C_{36}H_{54}SO_2H$ $[M + H]^+$: 551.3923, found 551.3914. Anal. Calcd for $C_{36}H_{54}SO_2$: C, 78.49; H, 9.88. Found: C, 78.71; H, 9.76.

(+)-(22*R*,23*E*)-22-Hydroxy-6β-methoxy-23-(*p*-tolylsulfenyl)-3α,5-cyclo-5α-cholest-23-ene, (+)-23a. To a cold (−78 °C) stirred solution of 1-iodo-3-methyl-1-*p*-tolylsulfenyl-1-butene, **22**[30] (1.52 g, 4.80 mmol, 1.2 equiv), in THF (50 mL), *t*-BuLi (1.7 M, 5.6 mL, 2.4 equiv) was added dropwise. The resulting mixture was stirred for 10 min, after which time **7** (1 M solution in THF, 1.37 g, 1.0 equiv) was added. The reaction was quenched after 15 min by addition of methanol (1 mL) at −78 °C and diluted with Et_2O (150 mL) and water (50 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (two times, 30 mL), and the combined organic layers were washed with brine (two times, 30 mL). Drying over $MgSO_4$, removal of the drying agent by filtration, and evaporation *in vacuo* gave a crude product (92:8 mixture of (22*R*)- and (22*S*)-alcohols by 360 MHz ^{1}H NMR), which was purified by silica gel chromatography (hexanes/EtOAc, 19:1) to yield pure **(+)-23a** (1.65 g) and **23b** (150 mg) as colorless syrups, overall yield, 84%. Data of **(+)-23a**: R_f = 0.25 (hexanes/EtOAc, 19:1); $[\alpha]_D$ = +65.2° (1.00); ^{1}H NMR δ 0.43 (dd, 1 H, J = 7.9, 4.9 Hz), 0.65 (apparent t, 1 H, J = 4.2 Hz), 0.71 (s, 3 H), 0.80−0.92 (m, 4 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.98 (d, 3 H, J = 6.4 Hz), 1.00 (d, 3 H, J = 6.7 Hz), 1.02 (s, 3 H), 1.04−1.21 (m, 4 H), 1.36−1.42 (m, 2 H), 1.47−1.55 (m, 4 H), 1.60 (m, 2 H), 1.75 (m, 2 H), 1.86−1.97 (m, 2 H), 2.14 (d, 1 H, J = 7.9 Hz), 2.30 (s, 3 H), 2.77 (m, 2 H), 3.33 (s, 3 H),

4.65 (br d, 1 H, $J = 7.9$ Hz), 5.71 (d, 1 H, $J = 10.6$ Hz), 7.08 (d, 2 H, $J = 8.1$ Hz), 7.23 (d, 2 H, J = 8.1 Hz); ^{13}C NMR δ 12.1, 12.5, 13.1, 19.2, 21.0, 21.4, 22.6, 22.8, 24.1, 24.5, 24.9, 27.1, 27.8, 28.5, 30.6, 33.3, 35.0, 35.2, 40.1, 42.6, 42.7, 47.9, 49.5, 52.5, 56.3, 56.5, 72.9, 82.4, 129.2, 129.7, 133.6, 134.8, 146.9; IR (CCl_4) 3480, 2938, 2868, 1491, 1457, 1380, 1324, 1270, 1183, 1098, 1016, 1002, 944 cm^{-1}; MS (EI/70 eV) *m/e* 536 $[M]^+$, 283, 269, 222 (100), 213, 159, 133, 121, 91; HRMS calcd for $C_{35}H_{52}SO_2$: 536.3688, found 551.3679.

Asymmetric Oxidation of (+)-23a. $Ti(OiPr)_4$ (0.05 mL, 0.26 mmol, 1.0 equiv) was added at room temperature to a solution of (*L*)-(+)-diethyl tartrate (0.09 mL, 0.52 mmol, 2.0 equiv) in CH_2Cl_2 (3 mL), and the mixture was stirred for 10 min. To this solution, cooled at −20 °C, were added cumene hydroperoxide (0.3 mL of solution at 80% of peroxide) and sulfide **(+)-23a** (140 mg, 0.26 mmol, 1.0 equiv) dissolved in 1 mL of CH_2Cl_2, sequentially. The reaction mixture was kept at −20 °C, and aliquots of cumene hydroperoxide were added every 12 h until the starting sulfide was completely consumed (TLC, 60 h). The reaction was quenched at −20 °C with 1 mL of H_2O, diluted with CH_2Cl_2, and warmed to room temperature. After 1 h, the layers were separated, and the organic phase was washed with water, stirred with 5% NaOH (5 mL) and brine (5 mL) for 3 h, washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 19:1 to 4:1) to afford pure (S_s)-sulfoxide **(+)-20a** (130 mg, 90%) as a colorless oil. No traces of the (R_s)-sulfoxide **(+)-8a** could be detected by 360 MHz ^{1}H NMR analysis of the crude product.

(+)-(22*Z*,24*S*)-6β-Methoxy-23-(*p*-tolylsulfenyl)-3α,5-cyclo-5α-ergost-22-ene, (+)-24. To a vigorously stirred solution of **(+)-23a** (190 mg, 0.35 mmol, 1.0 equiv) in THF (3 mL) at 0 °C were added Et_3N (0.15 mL, 1.06 mmol, 3.0 equiv), a catalytic amount of DMAP (10 mol %), and Ms_2O (122 mg, 0.70 mmol, 2.0 equiv), sequentially. After 10 min at 0 °C the reaction mixture was added via cannula to a cold (−78 °C) solution of MeCuCNLi (5.0 equiv) in THF. The reaction was stirred and warmed to room temperature over 5 h and quenched with a saturated solution of NH_4Cl. Standard workup and evaporation of the solvents afforded a crude product (diastereomeric excess of **(+)-24** at least 95:5 by 360 MHz ^{1}H NMR), which was purified by silica gel chromatography (hexanes/EtOAc, 49:1 to 19:1) to give pure **(+)-24** (100 mg, 55% overall). Data of **(+)-24**: $R_f = 0.44$ (hexanes/EtOAc, 19:1); $[\alpha]_D = +63.8°$ (0.73); ^{1}H NMR δ 0.42 (dd, 1 H, $J = 8.0$, 5.1 Hz), 0.64 (br t, 1 H, $J = 4.5$ Hz), 0.72 (s, 3 H), 0.74−0.93 (m, 4 H), 0.77 (d, 3 H, $J = 6.6$ Hz), 0.83 (d, 3 H, $J = 6.7$ Hz), 0.97−1.29 (m, 3 H), 0.98 (d, 3 H, $J = 6.8$ Hz), 0.99 (d, 3 H, $J = 6.6$ Hz), 1.01 (s, 3 H), 1.37−1.57 (m, 6 H), 1.67−1.78 (m, 4 H), 1.85−2.01 (m, 4 H), 2.31 (s, 3 H), 2.76 (br t, 1 H, $J = 2.5$ Hz), 2.92 (m, 1 H), 3.31 (s, 3 H), 5.60 (d, 1 H, $J = 9.5$ Hz), 7.06 (d, 2 H, $J = 8.0$ Hz), 7.16 (d, 2 H, $J = 8.2$ Hz); ^{13}C NMR δ 12.6, 13.0, 15.6, 18.0, 19.3, 20.4, 21.0, 21.6, 22.8, 24.3, 25.0, 28.2, 29.7, 30.3, 30.5, 30.9, 33.3, 35.0, 35.3, 37.0, 40.2, 42.9, 43.4, 46.3, 48.1, 56.4, 56.6, 82.4, 125.5, 128.6, 129.2, 134.2, 136.9, 142.9; IR (CCl_4) 2957, 2868, 1549, 1491, 1456, 1381, 1211, 1098, 1016, 972 cm^{-1}; MS (EI/70 eV) *m/e* 534 $[M]^+$, 283, 256, 247 (100), 245, 160, 128, 121, 81; HRMS calcd for $C_{36}H_{54}SO$: 534.3895, found 534.3888.

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