104228-59-3; (*E*)-**40a**, 104228-60-6; (*Z*)-**40a**, 104324-43-8; **40b**, 104228-62-8; **40c**, 104324-53-0; **40d**, 104228-65-1; **40e**, 104228-64-0; **40f**, 104228-63-9; **41a**, 104324-49-4; **41b**, 104324-60-9; **41c**, 104324-49-4; **41d**, 104324-61-0; **41e**, 104324-62-1; **42a**, 104324-50-7; **42b**, 104324-63-2; **42c**, 104324-50-7; **42d**, 104324-64-3; **42e**, 104324-65-4; **43**, 104324-66-5; **43**-Na, 104324-67-6; **44**, 104324-68-7; **45**, 104324-44-9; **46**, 104324-45-0; **47**, 104324-46-1; **48a**, 104324-47-2; **48b**, 104324-54-1; **48d**, 104324-55-2; **48e**, 104324-56-3; **49a**, 104324-48-3; **49b**, 104324-57-4; **49d**, 104324-58-5; **49e**, 104324-59-6; H_2C=$CHCH_2SSSMe$, 34135-85-8; CH_3CH=$CHSSPr$, 5905-46-4; $EtO_2C(CH_2)_3Br$, 2969-81-5; AcSLi, 84434-88-8; $EtO_2C(CH_2)_3SAc$, 104228-51-5; $EtO_2C(CH_2)_3S(O)Cl$, 104228-52-6; $EtO_2C(CH_2)_3S(O)S(CH_2)_3CO_2Et$, 104228-54-8; (*E*)-$CH_3CH$=$CHCH_2SH$, 58688-79-2; $CH_3(CH_2)_5SH$, 111-31-9; (*E*)-PrCH=$CHCH_2SH$, 89222-69-5; (*Z*)-PrCH=$CHCH_2SH$, 104108-89-6; $PhCH_2SH$, 100-53-8; $PhCH_2SSO_2Me$, 7559-62-8; allyl sulfide, 592-88-1; 2-propenethiol, 870-23-5; ethyl propiolate, 623-47-2; 2-carbethoxy-4-pentenethial *S*-oxide, 104324-39-2; propene, 115-07-1; methanesulfinyl chloride, 676-85-7; 1-propanethiol, 107-03-9; lithium 1-propanethiolate, 16203-40-0; 2-chlorotetrahydrofuran, 13369-70-5; *o*-thiosalicyclic acid, 147-93-3; allyl methanethiosulfonate, 14202-77-8; 18-mercaptomethyl-1,4,7,10,13,16-hexaoxacyclononadecane, 77661-77-9.

Supplementary Material Available: Synthese and IR, ^1H NMR, and ^{13}C NMR data for **29**, **35**, **36**, **40–43**, **50–52**, **54–58**, and **60–66** (23 pages). Ordering information is given on any current masthead page.

One-Step Stereochemical Determination of Contiguous Four Acyclic Chiral Centers on the Steroidal Side Chain: A Novel Synthesis of Brassinolide

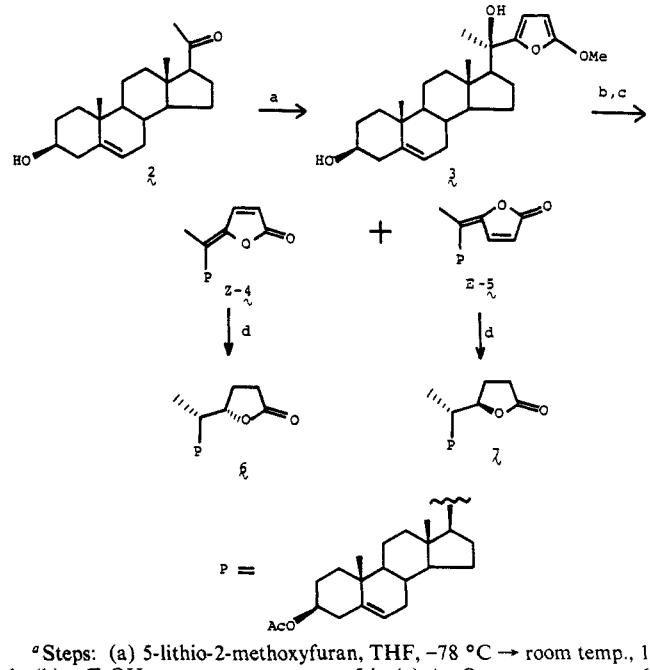
Tetsuji Kametani,* Tadashi Katoh, Masayoshi Tsubuki, and Toshio Honda

Contribution from the Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan. *Received March 12, 1986*

Abstract: The stereoselective synthesis of brassinolide and its enantiomer (22*S*,23*S*,24*R*)-24-epibrassinolide was accomplished. The key feature of this synthesis is based on the stereoselective reduction of the 5-ylidenetetronate derivative to control the stereochemistry of the contiguous four acyclic chiral centers on the steroid side chain in one-step, wherein the stereochemically determinitive step was carried out in a cyclic system. The addition reaction of the dianion of the tetronate derivative to the 20-oxo steroid afforded the adduct, whose syn-dehydration reaction brought about the formation of the desired (*Z*)-5-ylidenetetronate. The stereoselective reduction of the (*Z*)-5-ylidenetetronate afforded the key intermediate for the synthesis of brassinolide. On the other hand, the (*E*)-5-ylidenetetronate could also be prepared from the same adduct by manipulation of the dehydration reaction, and this approach led to the synthesis of (22*S*,23*S*,24*R*)-24-epibrassinolide.

Naturally occurring steroids,[1] with their wide range of structural and stereochemical features, continue to provide challenging synthetic targets.[2] In particular, stereoselective construction of steroidal side chains has been the subject of extensive synthetic efforts,[3] because their physiological activity has been reflected in the stereochemistry of the side chain.[1] In conjunction with the synthesis of physiologically active steroids, we have been interested in the stereocontrolled construction of the polyhydroxylated steroid side chains, and here report a novel synthesis of brassinolide (**1**),[4]

Scheme I[a]



[a] Steps: (a) 5-lithio-2-methoxyfuran, THF, −78 °C → room temp., 1 h; (b) *p*-TsOH, acetone, room temp., 5 h; (c) Ac_2O, py, room temp., 6 h; (d) 10% Pd–C, H_2, EtOAc, 1 atm, room temp., 6 h.

(1) Reviews: (a) Ecdysones: Bergamasco, R.; Horn, D. H. S. *Progress in Ecdysone Research*; Hoffmann, J. A., Ed.; Elsevier/North Holland Biomedical Press: Amsterdam, 1980; p 299. (b) Vitamin D_3 metabolites: Norman, A. W., Schaefer, K., Herrath, D. V., Grigoleit, H.-G., Eds.; *Vitamin D Chemical, Biochemical and Clinical Endocrinology of Calcium Metabolism*; Gruyter: Berlin, 1982. (c) Withanolides: Glotter, E.; Kirson, I.; Lavie, D.; Abraham, A. *Bio-Organic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. II, p 57.

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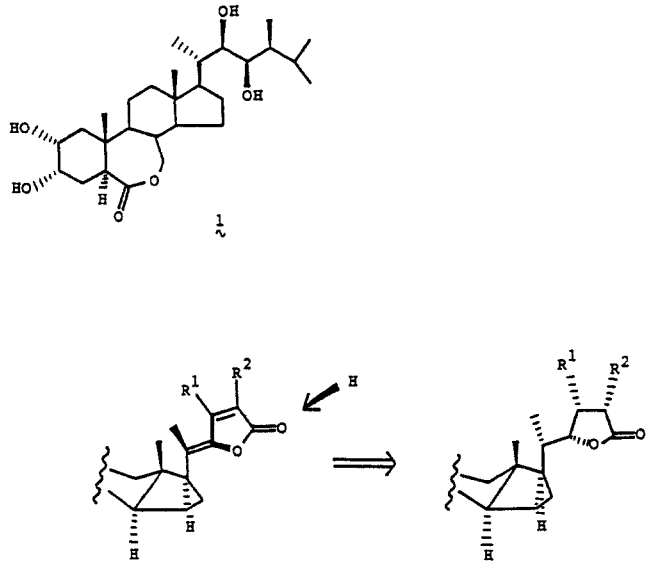
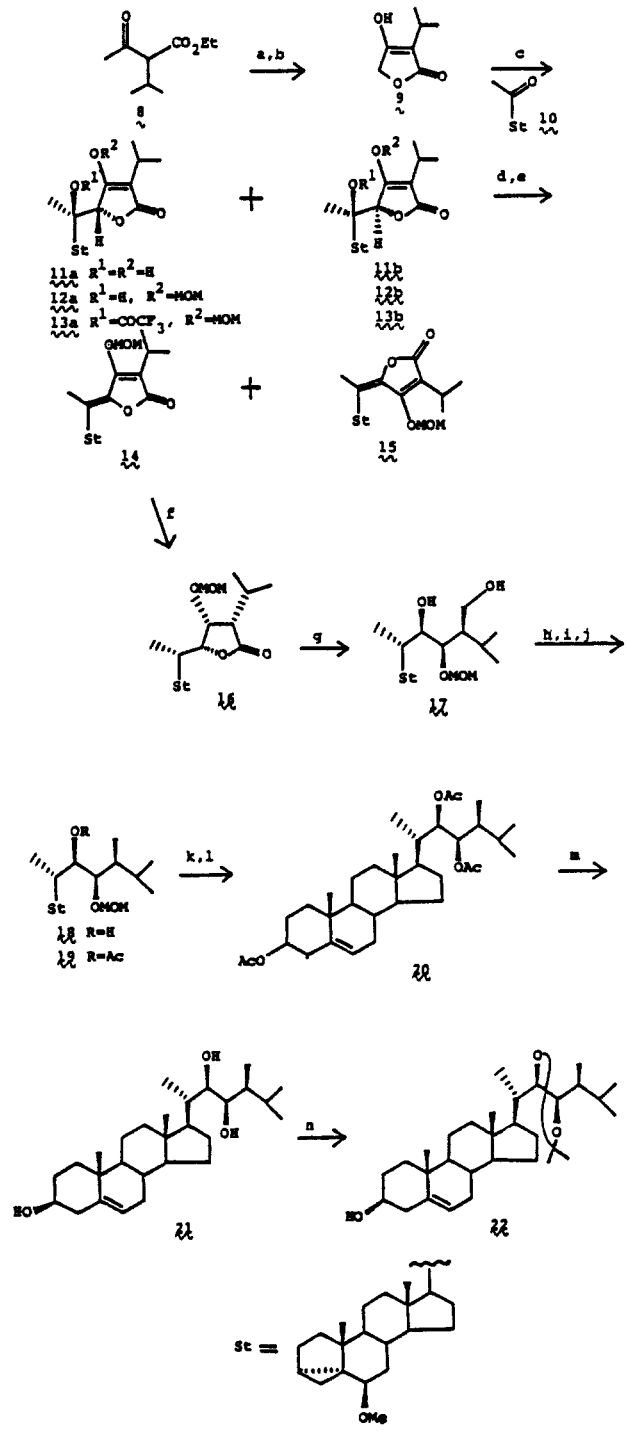


Figure 1.

a plant growth promoting steroid bearing contiguous four chiral centers in its side chain. Although a number of syntheses of **1** have been published to date,[5] the starting material used has mainly been the (20*S*)-20-carboxaldehyde, and many steps have been required to arrange the configurations at the C-22, C-23, and C-24 positions. The key feature of our approach to the synthesis of **1** is based on the stereoselective reduction of the 5-ylidenetetronate derivative to control the stereochemistry of the contiguous four acyclic chiral centers, simultaneously, in one step, wherein the stereochemically determinitive step was carried out in a cyclic system,[6] because such reduction would be expected to occur from the back side of the steroid nucleus owing to steric hindrance (see Figure 1).

With that precedent in mind, we prepared the 4-ylidenebutenolides **4** and **5**[7] in order to investigate the stereoselectivity of the reduction. The addition of 5-lithio-2-methoxyfuran to pregnenolone (**2**) afforded the alcohol **3**, whose dehydration,[8] followed by acetylation, gave the desired 4-ylidenebutenolides **4** and **5** as a mixture of E and Z isomers in the ratio of 71:29, in 88% overall yield from **2**. Catalytic reduction of the less polar E isomer **5** furnished the saturated lactone **7** in 97% yield, as a single product, whose stereochemistry was deduced to be (20S,22R) by direct comparison with an authentic specimen,[9] a key intermediate for the synthesis of ecdysone.[9,10] On the other hand, the catalytic reduction of the Z isomer **4** also yielded the (20S,22S) isomer **6** as a sole product in 98% yield. These results

Scheme II[a]



[a] Steps: (a) Br_2, $CHCl_3$, 0 °C → room temp., 1 h; (b) neat, 130 °C, 2 h; (c) LDA, **12**, THF, −78 °C → room temp.; (d) MOMCl, K_2CO_3, DMF, 100 °C, 2 h; (e) TFAA, Et_3N, PPY, CH_2Cl_2, room temp., 1 h; DBU, benzene, reflux, 20 min; (f) 5% Rh-Al_2O_3, H_2, EtOAc, 7 atm, 13 h; (g) $LiAlH_4$, THF, room temp., 0.5 h; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (i) $LiAlH_4$, Et_2O, room temp., 0.5 h; (j) Ac_2O, py, DMAP, room temp., 12 h; (k) *p*-TsOH, dioxane-H_2O, 90 °C, 1 h; (l) Ac_2O, py, DMAP, room temp., 15 h; (m) 5% KOH-MeOH, reflux, 1 h; (n) Me_2CO, *p*-TsOH, room temp., 2 h.

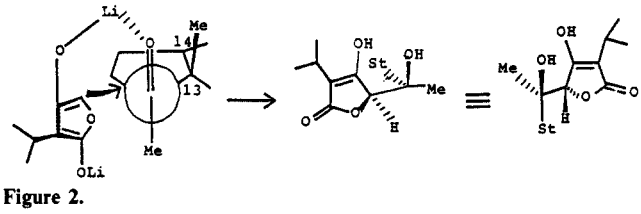


Figure 2.

(5) (a) Fung, S.; Siddal, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (b) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (c) Thompson, M. J.; Mandava, N. B.; Mendt, W. J.; Lusby, W. R.; Spaulding, D. W. *Steroids* **1981**, *38*, 567. (d) Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada, K.; Umemura, T.; Yabuta, G.; Kuwahara, S.; Kondo, M.; Minobe, M.; Sogabe, A. *Tetrahedron* **1982**, *38*, 2099. (e) Anastasia, M.; Ciuffreda, P.; Del Puppo, M.; Fiecchi, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 383. (f) Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 663. (g) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491. (h) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767. (i) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2833. (j) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, *139*. (k) Ferraboschi, P.; Santaniello, E. *Synth. Commun.* **1984**, *14*, 1199. (l) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1984**, *49*, 4297. (m) Takahashi, T.; Ootake, A.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 69.

(6) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647, and references cited therein.

(7) All new compounds have been fully characterized spectrally including elemental composition determined by combustion analysis.

(8) Kraus, G. A.; Sugimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 30.

(9) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *Chem. Lett.* **1985**, 485.

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indicated that the catalytic reduction of the 4-ylidenebutenolides occurred from the less hindered side with high stereoselectivity as expected.

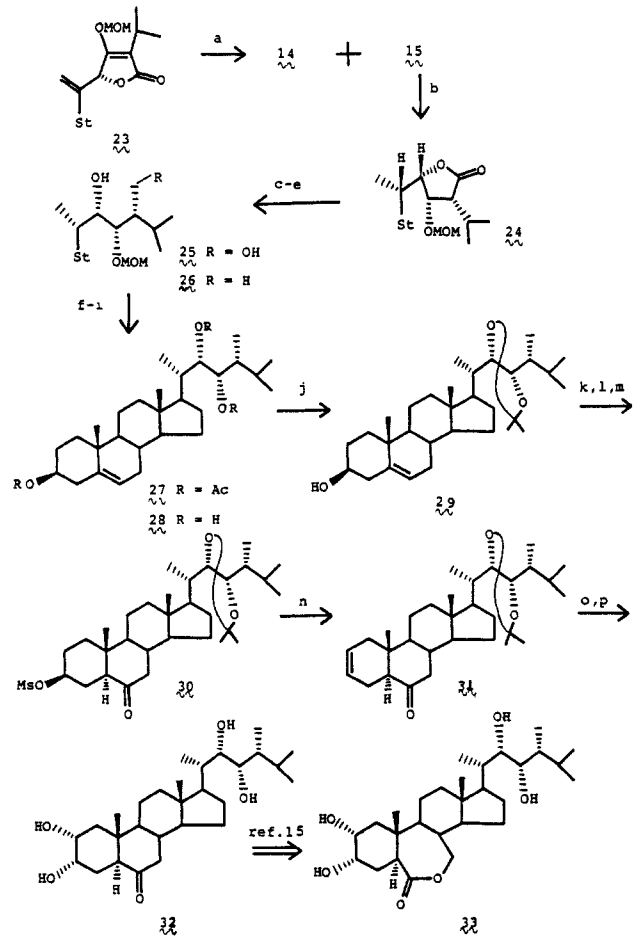
The remaining crucial step in the synthesis of brassinolide would be stereoselective preparation of the Z isomer of the appropriate tetronate with the desired functionality. For this purpose, 3-isopropyltetronic acid (**9**) was prepared from ethyl α-isopropylacetoacetate by two steps according to Reichert's procedure.[11] First, the addition reaction of the methoxymethyl (MOM) ether or benzyl ether of **9** to the 20-oxo steroid **10** was investigated under various reaction conditions. However, none of the addition product was isolated, whereas, treatment of **10** with four equimolar amounts of the dianion of **9** in tetrahydrofuran at −78 °C provided the desired two adducts **11a** and **11b** whose hydroxyl groups were then protected as the MOM ethers to give the tetronates **12a** and **12b** as diastereoisomers at the C-22 position in 84% yield from **10** in the ratio of 91:9. Although the stereochemistry of the C-22 position of **12** could not be determined at this stage, the major isomer (**12a**) was assumed to have the C-22R configuration, because this addition reaction would be expected to proceed via the chelation intermediate affording the C-22R isomer predominantly, as depicted in Figure 2. Thus, the major isomer (**12a**) was subjected to syn-dehydration reaction to produce the desired (*Z*)-5-ylidenetetronate.

The tertiary alcohol of **12a** was converted into the corresponding trifluoroacetate[12] **13a** by treatment with trifluoroacetic anhydride, triethylamine, and 4-pyrrolidinopyridine at ambient temperature; acetate **13a** was heated in benzene at reflux in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish the 5-ylidenetetronates (**14** and **15**) in 73% yield in the ratio 82:18. Catalytic hydrogenation of the major compound (**14**) (2.4 mmol) over rhodium–alumina yielded the saturated lactone as the sole product in 90% yield. Since all the carbon framework for the synthesis of brassinolide had been prepared, we next focused our attention to the conversion of **16** into **22**. Lithium aluminum hydride reduction of **16** afforded the diol **17**, whose primary alcohol was further transformed into the methyl group by successive mesylation and reduction of the resulting mesylate in 82% overall yield. After protection of the secondary alcohol of **18** as its acetate, the MOM group and the cyclopropane ring were cleaved by treatment with *p*-toluenesulfonic acid in aqueous dioxane, and the subsequent acetylation of the product furnished the triacetate **20**, in 85% yield. Hydrolysis of **20** with 5% potassium hydroxide solution gave the triol **21** which was further converted to the acetonide **22** in 95% yield from **20**. Since **22** was already converted into **1**,[5a,j] this synthesis constitutes a formal synthesis of brassinolide (**1**). Based on these results, the stereochemistry of the C-22 position of **16** was deduced to be the R configuration, and hence the tetronate **14** to be the Z isomer.

On the other hand, the dehydration reaction of **12a** with thionyl chloride and pyridine at 0 °C gave rise to the exo olefin **23** and **14** in 83% yield in the ratio of 91:9. Catalytic hydrogenation of **23** over rhodium–alumina again provided the key intermediate **16** as the sole product in 91% yield. This result led to the determination of the stereochemistry of **11a** to have 22-R configuration. The stereoselectivity exhibited in the predominant formation of **11a** can be rationalized by assuming that the addition reaction of **9** to **10** would proceed via the expected chelation intermediate.

Furthermore, isomerization of the double bond of **23** by treatment with 1.1 equimolar amount of DBU in refluxing benzene for 15 min furnished **14** and **15** in 24.2 and 68.8% yields, respectively (Scheme III). Hydrogenation of the major E isomer (**15**) gave the γ-lactone **24** in 92% yield, whose primary alcohol was then converted into the methyl group by three steps in 80% yield. Transformation of **26** into the triol **28** was achieved in four steps via **27** as described before in 86% overall yield. In order to accomplish the synthesis of (22*S*,23*S*,24*R*)-24-epibrassinolide,

Scheme III[a]



[a] (a) DBU, benzene, reflux, 15 min. (b) 5% Rh–Al_2O_3, H_2, EtOAc, 7 atm, 13 h. (c) $LiAlH_4$, THF, room temperature, 0.5 h. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min. (e) $LiAlH_4$, Et_2O, room temp., 0.5 h; (f) Ac_2O, py, DMAP, room temp., 6 h; (g) *p*-TsOH, dioxane–H_2O, 80 °C, 1 h; (h) Ac_2O, py, DMAP, room temp., 8 h; (i) 5% KOH–MeOH, reflux, 1 h; (j) *p*-TsOH, acetone, room temp., 2 h; (5) MsCl, py, room temp., 1 h; (l) B_2H_6, THF, 2 h; then 2 M NaOH, 30% H_2O_2, room temp., 20 min; (m) PCC, CH_2Cl_2, room temp., 2 h; (n) LiBr, DMF, reflux, 1 h; (o) OsO_4, *N*-methylmorpholine *N*-oxide, *'BuOH*–THF–H_2O, room temp., 3 h; (p) AcOH–H_2O, reflux, 3 h.

the glycol on the side chain of **28** was protected as the acetonide according to Ikekawa's procedure[5j] in 95% yield. After mesylation of the remaining alcohol of **29**, the mesylate was converted into the 6-oxo derivative **30** by the usual method in 80% yield from **29**. Elimination of the mesyl group (**30**) with lithium bromide afforded the olefin **31**. Osmylation of **31** followed by acidic hydrolysis furnished the desired tetraol **32**. Conversion of **32** into (22*S*,23*S*,24*R*)-24-epibrassinolide (**33**) has already been achieved by Baeyer–Villiger oxidation.[13-15]

Thus, we could develop a novel stereoselective construction of steroidal side chain bearing polyhydroxy groups, whose stereochemistry could be controlled by manipulation of dehydration reaction of **11**, followed by stereoselective hydrogenation of the resulting 5-ylidenetetronates.

Experimental Section

(20*Z*)-3β-Acetoxy-25-homochol-5,20(22),23-trieno-25,22-lactone (4) and (20*E*)-3β-Acetoxy-25-homochol-5,20(22),23-trieno-25,22-lactone (5). A solution of pregnenolone (**2**) (5.0 g, 15.8 mmol) in anhydrous tetrahydrofuran (50 mL) was added to a stirred solution of 5-lithio-2-

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methoxyfuran [prepared from 2-methoxyfuran (4.4 mL, 94.8 mmol) in anhydrous tetrahydrofuran (80 mL) and 2.6 M *n*-butyllithium (22 mL, 94.8 mmol)] at −78 °C under a current of nitrogen. The reaction mixture was stirred for 1 h at the same temperature. After the reaction was quenched with aqueous ammonium chloride solution (30 mL), the product was isolated by extraction with ethyl acetate to give the crude furylcarbinol (**3**) (5.95 g), whose solution in acetone (80 mL), was treated with a catalytic amount of *p*-toluenesulfonic acid (50 mg) for 5 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL); the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the product which was acetylated with acetic anhydride (15 mL) and pyridine (80 mL) for 6 h at room temperature. The reaction mixture was poured into water (200 mL); isolation of the product by extraction with ethyl acetate gave two products which were separated by chromatography on silica gel (250 g) using benzene containing 40% hexane as the eluant to give the 20E compound **5** (less polar; 1.69 g, 25%) as a colorless plates [mp 235–236 °C (benzene–hexane); $[\alpha]_D$ −29.8° (*c* = 0.62, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (100 MHz) δ 0.70 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 2.03 (6 H, s, 21-H_3 and acetyl), 4.40–4.80 (1 H, m, 3-H), 5.28–5.44 (1 H, m, 6-H), 6.05 (1 H, d, *J* = 5 Hz, 24-H), 7.60 (1 H, d, *J* = 5 Hz, 23-H); MS *m/z* 424 (M^+). Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 75.99; H, 8.52.] and the 20Z compound **4** (more polar; 4.23 g, 63%) as colorless needles [mp 217–218 °C (benzene–hexane); $[\alpha]_D$ −293.2° (*c* = 1.00, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (100 MHz) δ 0.70 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.95 (3 H, s, 21-H_3), 2.03 (3 H, s, acetyl), 4.40–4.80 (1 H, m, 3-H), 5.28–5.44 (1 H, m, 6-H), 6.08 (1 H, d, *J* = 5 Hz, 24-H), 7.65 (1 H, d, *J* = 5 Hz, 23-H); MS *m/z* 424 (M^+). Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.40; H, 8.58].

Hydrogenation of 4. A mixture of 10% palladium–carbon (100 mg) and the 20Z compound **4** (1.0 g, 2.36 mmol) in ethyl acetate (30 mL) was stirred for 6 h under a current of hydrogen. The catalyst was filtered off and the filtrate was concentrated to afford (20*S*,22*S*)-3β-acetoxy-25-homochol-5-eno-25,22-lactone (**6**) (0.99 g, 98%) as colorless needles (from benzene–hexane) which was identical with an authentic sample.[9]

Hydrogenation of 5. The same procedure as for the 20Z compound **4** was applied to the 20E compound **5** (1.0 g, 2.36 mmol) to afford (20*S*,22*R*)-3β-acetoxy-25-homochol-5-eno-25,22-lactone (**7**) (0.98 g, 97%) as colorless needles (from benzene–hexane), which was identical with an authentic sample.[9]

3-Isopropyltetronic Acid (9). Bromine (107 g, 0.67 mol) in chloroform (100 mL) was added to a stirred solution of ethyl α-isopropylacetoacetate (**8**) (105 g, 0.61 mol) in chloroform (350 mL) at 0 °C; the reaction mixture was further stirred for 1 h at room temperature. Evaporation of the solvent gave the residue, which was heated for 2 h at 130 °C. After cooling, the residue was diluted with hot 10% aqueous potassium carbonate solution (150 mL), washed with dichloromethane, and acidified with 10% hydrochloric acid. The acidic solution was extracted with chloroform; the extract was washed with water and brine and dried over Na_2SO_4. Removal of the solvent gave the pale yellow solid which was recrystallized from benzene to give the tetronic acid **9** (45.0 g, 52%) as colorless needles: mp 120–123 °C; IR ($CHCl_3$) 3300, 1740, 1680, 1660 cm^{-1}; ^1H NMR (60 MHz) δ 1.22 (6 H, d, *J* = 7 Hz, isopropyl), 2.50–3.10 (1 H, m, $CH(CH_3)_2$), 4.70 (2 H, s, C_5-H_2); MS *m/z* 142 (M^+). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.13; H, 7.14.

(20*R*,22*R*)- (12a) and (20*R*,22*S*)-20-hydroxy-23-methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergost-23-eno-28,22-lactone (12b). A solution of 6β-methoxy-3α,5-cyclopregnan-20-one (**10**) (10.0 g, 30.4 mmol) in anhydrous tetrahydrofuran (300 mL) was added to a stirred solution of the dianion [prepared from 3-isopropyltetronic acid (**9**) (20.0 g, 140.8 mmol) in anhydrous tetrahydrofuran (150 mL) and lithium diisopropylamide (281.6 mmol) in anhydrous tetrahydrofuran (150 mL)] at −78 °C under a current of nitrogen; the reaction mixture was then stirred for 1 h at the same temperature. After being quenched with aqueous ammonium chloride solution (100 mL), the mixture was extracted with ethyl acetate; the extract was washed with aqueous sodium bicarbonate solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a pale yellow solid (14.3 g), whose solution in dry *N*,*N*-dimethylformamide (200 mL) was treated with potassium carbonate (9.40 g, 68.0 mmol) for 2 h at 100 °C, and then chloromethyl methyl ether (3.0 mL, 37.2 mmol) was added at 50 °C. The reaction mixture was stirred for 10 min at the same temperature and diluted with ethyl acetate (400 mL). The organic layer was washed with aqueous potassium hydrogen sulfate solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave two products which were separated by chromatography on silica gel (300 g) using dichloromethane as the eluant to give the 20R,22R compound **12a** (less polar; 12.1 g, 77%) as colorless prisms [mp 154–156 °C (MeOH); $[\alpha]_D$ +28.9° (*c* = 1.24, $CHCl_3$); IR ($CHCl_3$) 1750, 1660 cm^{-1}; ^1H NMR (100 MHz) δ 0.93 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.20 (3 H, s, 21-H_3), 1.23 (6 H, d, *J* = 7 Hz, 26-H_3 and 27-H_3), 2.76 (1 H, t, *J* = 2.5 Hz, 6-H), 2.70–3.04 (1 H, m, 25-H), 3.32 (3 H, s, 6-OMe), 3.52 (3 H, s, OCH_2OCH_3), 4.66 (1 H, s, 22-H), 5.03 and 5.46 (each 1 H, each d, *J* = 6 Hz, OCH_2OCH_3); MS *m/z* 516 (M^+). Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.36; H, 9.56] and the 20R,25S compound **12b** (more polar; 1.2 g, 7%) as colorless prisms [mp 157.5–159 °C (MeOH); $[\alpha]_D$ +28.7° (*c* = 2.98, $CHCl_3$); IR ($CHCl_3$) 1750, 1660 cm^{-1}; ^1H NMR (100 MHz) δ 0.93 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.22 (3 H, s, 21-H_3), 1.25 (6 H, d, *J* = 7 Hz, 26-H_3 and 27-H_3), 2.76 (1 H, t, *J* = 2.5 Hz, 6-H), 2.75–3.10 (1 H, m, 25-H), 3.32 (3 H, s, 6-OMe), 3.55 (3 H, s, OCH_2OCH_3), 4.55 (1 H, s, 22-H), 5.11 and 5.35 (each 1 H, each d, *J* = 6 Hz, OCH_2OCH_3); MS *m/z* 516 (M^+). Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 71.90; H, 9.58.

(20*Z*)- (14) and (20*E*)-23-Methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergost-20(22),23-dieno-28,22-lactone (15). Trifluoroacetic anhydride (4.2 mL, 29.1 mmol) was added dropwise to a stirred solution of the alcohol **12a** (5.0 g, 9.7 mmol), triethylamine (4.1 mL, 29.1 mmol); and 4-pyrrolidinopyridine (0.44 g, 2.9 mmol) in anhydrous dichloromethane (50 mL) at room temperature under a current of nitrogen; the reaction mixture was then stirred for 1 h and poured into water (30 mL). Isolation of the product by extraction with ethyl acetate gave the trifluoroacetate **13a** (5.2 g, 88%): IR ($CHCl_3$) 1780, 1760, 1650 cm^{-1}; ^1H NMR (100 MHz) δ 1.03 (3 H, s, 18-H_3), 1.17 (3 H, s, 19-H_3), 1.39 (6 H, d, *J* = 7 Hz, 26-H_3 and 27-H_3), 1.90 (3 H, s, 21-H_3), 2.93 (1 H, t, *J* = 2.5 Hz, 6-H), 3.04–3.32 (1 H, m, 25-H), 3.47 (3 H, s, 6-OMe), 3.69 (3 H, s, OCH_2OCH_3), 5.27 and 5.35 (each 1 H, each d, *J* = 6 Hz, OCH_2OCH_3), 5.31 (1 H, s, 22-H); MS *m/z* 612 (M^+). Anal. Calcd for $C_{33}H_{47}O_7F_3$: 612.3273. Found: 612.3308. A solution of the trifluoroacetate **13a** (5.2 g, 8.5 mmol) in anhydrous benzene (80 mL) containing DBU (1.4 mL, 9.4 mmol) was refluxed for 20 min. After cooling, the mixture was washed with aqueous potassium hydrogen sulfate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave two products which were separated by chromatography on silica gel (100 g) using benzene as the eluant to give the 20Z compound **14** (less polar; 2.9 g, 68%) as colorless plates [mp 171–172 °C (MeOH); $[\alpha]_D$ −126.8° (*c* = 1.34, $CHCl_3$); IR ($CHCl_3$) 1730, 1600 cm^{-1}; ^1H NMR (100 MHz) δ 0.72 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.26 and 1.29 (each 3 H, each d, *J* = 7 Hz, 26-H_3 and 27-H_3), 2.05 (3 H, s, 21-H_3), 2.79 (1 H, t, *J* = 2.5 Hz, 6-H), 2.83–3.18 (1 H, m, 25-H), 3.34 (3 H, s, 6-OMe), 3.57 (3 H, s, OCH_2OCH_3), 5.13 and 5.18 (each 1 H, each d, *J* = 6 Hz, OCH_2OCH_3); MS *m/z* 498 (M^+). Anal. Calcd for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.39; H, 9.51] and the 20E compound **15** (more polar; 0.63 g, 15%) as colorless needles [mp 147–147.5 °C (MeOH); $[\alpha]_D$ +12.3° (*c* = 0.57, $CHCl_3$); IR ($CHCl_3$) 1730, 1610 cm^{-1}; ^1H NMR (100 MHz) δ 0.75 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 1.27 (6 H, d, *J* = 7 Hz, 26-H_3 and 27-H_3), 1.95 (3 H, s, 21-H_3), 2.80 (1 H, t, *J* = 2.5 Hz, 6-H), 2.72–3.10 (1 H, m, 25-H), 3.34 (3 H, s, 6-OMe), 3.56 (3 H, s, OCH_2OCH_3), 5.13 and 5.23 (each 1 H, each d, *J* = 6 Hz, OCH_2OCH_3); MS *m/z* 498 (M^+). Anal. Calcd for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.60; H, 9.50].

(22*R*,23*R*,24*S*)-23-Methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostano-28,22-lactone (16). A solution of the 20Z compound **14** (1.2 g, 2.4 mmol) in ethyl acetate (20 mL) was hydrogenated over 5% rhodium on alumina (1.0 g) for 13 h under medium pressure (7.0 atm) of hydrogen. The catalyst was filtered off and the filtrate was evaporated to afford a white solid, which was recrystallized from methanol to give the lactone **16** (1.09 g, 90%) as colorless needles: mp 133.5–135 °C (MeOH); $[\alpha]_D$ +67.1° (*c* = 1.46, $CHCl_3$); Ir ($CHCl_3$) 1770 cm^{-1}; ^1H NMR (400 MHz) δ 0.76 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.08 (3 H, d, *J* = 7 Hz, Me), 1.15 (3 H, d, *J* = 7 Hz, Me), 1.25 (3 H, d, *J* = 7 Hz, Me), 2.08–2.18 (1 H, m, 25-H), 2.29 (1 H, dd, *J* = 8, 5 Hz, 24-H), 2.78 (1 H, t, *J* = 2.5 Hz, 6-H), 3.33 (3 H, s, 6-OMe), 3.41 (3 H, s, OCH_2OCH_3), 4.23 (1 H, dd, *J* = 3.5, 1.5 Hz, 23-H), 4.33 (1 H, dd, *J* = 5, 3.5 Hz, 22-H), 4.6, and 4.74 (each d, *J* = 6 Hz, OCH_2OCH_3); MS *m/z* 502 (M^+). Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.30; H, 10.40.

(22*R*,23*R*,24*R*)-22,28-Dihydroxy-23-methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostane (17). Lithium aluminum hydride (390 mg, 10 mmol) was added in small portions to a stirred solution of the lactone **16** (1.7 g, 3.4 mmol) in anhydrous tetrahydrofuran (130 mL) under nitrogen at room temperature. After the mixture was stirred for 30 min, 25% aqueous sodium hydroxide solution (10 mL) was added; the reaction mixture was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the diol **17** (1.7 g, 98%) as a colorless amorphous powder: IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.71 (3 H, s, 18-H_3), 0.87 (3 H, d, *J* = 7 Hz, Me), 1.00 (3 H, d, *J* = 7 Hz, Me), 1.02 (3 H, s, 19-H_3), 1.06 (3 H, d, *J* = 7 Hz, Me), 1.96–2.04 (1 H, m, 25-H), 2.77 (1 H, t, *J* = 2.5 Hz, 6-H), 3.33 (3 H, s, 6-OMe), 3.45 (3 H, s, OCH_2OCH_3), 3.72–3.86 (4

H, m, 22-H, 23-H, and 28-H_2), 4.68 and 4.81 (each 1 H, each d, J = 6 Hz, OCH_2OCH_3); MS m/z 505 (M^+ −1). Anal. Calcd for $C_{31}H_{53}O_5$: 505.3893. Found: 505.3870.

(22*R*,23*R*,24*S*)-22-Hydroxy-23-methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostane (18). Methanesulfonyl chloride (0.17 mL, 2.2 mmol) was added slowly to a stirred solution of the diol **17** (1.0 g, 2.0 mmol) in anhydrous dichloromethane (30 mL) containing triethylamine (0.3 mL, 2.2 mmol) under nitrogen at 0 °C. After the mixture was stirred for 10 min at the same temperature, aqueous sodium bicarbonate solution (10 mL) was added; isolation of the product by ethyl acetate extraction gave the mesylate (1.2 g) whose solution in anhydrous ether (50 mL) was treated with lithium aluminum hydride (500 mg, 13.2 mmol) under nitrogen for 30 min at room temperature. To the reaction mixture was added 25% aqueous sodium hydroxide solution (5.0 mL); extraction with ethyl acetate followed. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a white solid which was purified by chromatography on silica gel (20 g) using dichloromethane containing 30% chloroform as the eluant to give the alcohol **18** (810 mg, 84%) as colorless plates: mp 117.5–119 °C (MeOH); $[\alpha]_D$ +12.1° (c = 1.19, $CHCl_3$); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.73 (3 H, s, 18-H_3), 0.87 (3 H, d, J = 7 Hz, Me), 0.89 (3 H, d, J = 7 Hz, Me), 0.93 (3 H, d, J = 7 Hz, Me), 0.94 (3 H, d, J = 7 Hz, Me), 1.03 (3 H, s, 19-H_3), 1.95–2.03 (1 H, m, 25-H), 2.77 (1 H, t, J = 2.5 Hz, 6-H), 3.33 (3 H, s, 6-OMe), 3.43 (3 H, s, OCH_2OCH_3), 3.56 (1 H, d, J = 9 Hz, 22-H or 23-H), 3.59 (1 H, d, J = 9 Hz, 22-H or 23-H), 4.70 and 4.72 (each 1 H, each d, J = 6 Hz, OCH_2OCH_3); MS m/z 490 (M^+). Anal. Calcd for $C_{31}H_{54}O_4$: C, 75.87; H, 11.09. Found: C, 75.65; H, 11.39.

(22*R*,23*R*,24*S*)-3β,22,23-Triacetoxyergost-5-ene (20). The alcohol **18** (500 mg, 1.0 mmol) was acetylated with acetic anhydride (2.0 mL) and pyridine (10 mL) containing a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (50 mg) for 12 h at room temperature. The reaction mixture was poured into water (20 mL); isolation of the product by ether extraction gave a pale yellow solid, which was recrystallized from methanol to give the acetate **19** (510 mg, 96%) as colorless needles: mp 160–160.5 °C (MeOH); $[\alpha]_D$ +62.7°(c = 0.82, $CHCl_3$); IR ($CHCl_3$) 1720 (cm^{-1}; ^1H NMR (400 MHz) δ 0.73 (3 H, s, 18-H_3), 0.94 (3 H, d, J = 7 Hz, Me), 0.95 (3 H, d, J = 7 Hz, Me), 0.96 (3 H, d, J = 7 Hz, Me), 0.98 (3 H, d, J = 7 Hz, Me), 1.02 (3 H, s, 19-H_3), 1.85–1.98 (1 H, m, 25-H), 2.07 (3 H, s, acetyl), 2.76 (1 H, t, J = 2.5 Hz, 6-H), 3.32 (3 H, s, 6-OMe), 3.34 (3 H, s, OCH_2OCH_3), 3.74 (1 H, d, J = 9 Hz, 23-H), 4.55 and 4.68 (each 1 H, each d, J = 6.5 Hz, OCH_2OCH_3), 5.16 (1 H, d, J = 9 Hz, 22-H); MS m/z 532 (M^+). Anal. Calcd for $C_{33}H_{56}O_5$: C, 74.39; H 10.59. Found: C, 74.33; H, 10.89. The acetate **19** (510 mg, 0.96 mmol) in dioxane (15 mL) and water (2.3 mL) was treated with *p*-toluenesulfonic acid (90 mg) for 1 h at 80 °C. The reaction mixture was diluted with ethyl acetate (50 mL), and the organic layer was washed with aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the 3β,22-diol (410 mg), whose solution in pyridine (10 mL) containing 4-(*N*,*N*-dimethylamino)pyridine (20 mg) was treated with acetic anhydride (2 mL) for 15 h at room temperature. The reaction mixture was poured into water (20 mL) and isolation of the product by ether extraction gave a white solid, which was recrystallized from methanol to give the triacetate **20** (463 mg, 85%) as colorless prisms: mp 141–142 °C (MeOH), (lit.[5j] mp 140–141 °C). Its spectroscopic data were identical with those reported.

(22*R*,23*R*,24*S*)-3β,22,23-Trihydroxyergost-5-ene (21). A solution of the triacetate **20** (300 mg, 0.54 mmol) in 5% KOH–MeOH (10 mL) was refluxed for 1 h. The reaction mixture was diluted with ethyl acetate (50 mL), and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a white solid, which was recrystallized from methanol to give the triol **21** (225 mg, 97%) as colorless prisms, mp 206–208 °C (lit.[5j] 205–208 °C). Its spectroscopic data were identical with those reported.

(22*R*)-23-Methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergost-20(21),23-dieno-28,22-lactone (23). Thionyl chloride (7.1 mL, 96.9 mmol) was added slowly to a stirred solution of the alcohol **12a** (10.0 g, 19.4 mmol) in anhydrous pyridine (150 mL) at 0 °C under a current of nitrogen. After being stirred for 10 min at the same temperature, the reaction mixture was poured into water (200 mL); isolation of the product by ether extraction gave two products, which were separated by chromatography on silica gel (200 g) using benzene as the eluant to give the 20Z compound **14** (less polar; 0.72 g, 7%) as colorless plates, mp 171–172 °C (MeOH), having physical and spectroscopic properties identical with those of the compound described above, and the exo olefin **23** (more polar; 7.3 g, 76%) as colorless prisms: mp 166–167.5 °C (MeOH–CH_2Cl_2); $[\alpha]_D$ +92.6° (c = 1.59, $CHCl_3$); IR ($CHCl_3$) 1740, 1660 cm^{-1}; ^1H NMR (100 MHz) δ 0.71 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.22 and 1.24 (each 3 H, each d, J = 7 Hz, 26-H_3 and 27-H_3), 2.76 (1 H, t, J = 2.5 Hz, 6-H), 2.60–3.00 (1 H, m, 25-H), 3.33 (3 H, s, 6-OMe), 3.47 (3 H, s, OCH_2OCH_3), 4.86 and 5.22 (each 1 H, each d, J = 4 Hz, OCH_2OCH_3), 5.17, 5.26, and 5.28 (each 1 H, each s, 21-H_2 and 22-H): MS m/z 498 (M^+). Anal. Calcd for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.43; H, 9.55.

Isomerization of the Exo Olefin 23 with DBU. A solution of the exo olefin **23** (7.0 g, 14.1 mmol) in anhydrous benzene (100 mL) containing DBU (2.4 mL, 15.5 mmol) was refluxed for 15 min. After cooling, the mixture was washed with aqueous potassium hydrogen sulfate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave two products which were separated by chromatography on silica gel (150 g) using benzene as the eluant to give the 20Z compound **14** (less polar; 1.7 g, 24%) as colorless plates [mp 171–172 °C (MeOH), having physical and spectroscopic properties identical with those of the compound described above] and the 20E compound **15** (more polar; 4.8 g, 69%) as colorless needles [mp 147–148 °C (MeOH), having physical and spectroscopic properties identical with those of the compound described above].

(22*S*,23*S*,24*R*)-23-Methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostano-28,22-lactone (24). The same procedure followed for the lactone **16** was applied to the 20E compound **15** (1.2 g, 2.4 mmol) to afford the lactone **24** (1.1 g, 92%) as a colorless powder: $[\alpha]_D$ +24.7° (c = 2.02, $CHCl_3$); IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR (400 MHz) δ 0.79 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.05 (3 H, d, J = 7 Hz, Me), 1.07 (3 H, d, J = 7 Hz, Me), 1.27 (3 H, d, J = 7 Hz, Me), 2.08–2.14 (1 H, m, 25-H), 2.18 (1 H, dd, J = 8, 4 Hz, 24-H), 2.77 (1 H, t, J = 2.5 Hz, 6-H), 3.32 (3 H, s, 6-OMe), 3.41 (3 H, s, OCH_2OCH_3), 3.93 (1 H, dd, J = 8, 2 Hz, 23-H), 4.36 (1 H, dd, J = 4, 2.5 Hz, 22-H), 4.71 and 4.73 (each 1 H, each d, J = 7 Hz, OCH_2OCH_3); MS m/z 502 (M^+). Anal. Calcd for $C_{31}H_{50}O_5$: 502.3657. Found: 502.3656.

(22*S*,23*S*,24*S*)-22,28-Dihydroxy-23-methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostane (25). The same procedure as for the diol **17** was applied to the lactone **24** (1.1 g, 2.2 mmol) to afford the diol **25** (1.1 g, 99%) as a colorless amorphous powder: IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.75 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.03 (9 H, d, J = 7 Hz, 21-H_3, 26-H_3, and 27-H_3), 1.96–2.04 (1 H, m, 25-H), 2.77 (1 H, t, J = 2.5 Hz, 6-H), 3.32 (3 H, s, 6-OMe), 3.45 (3 H, s, OCH_2OCH_3), 3.64–3.92 (4 H, m, 22-H, 23-H, and 28-H_2), 4.70 and 4.77 (each 1 H, each d, J = 6 Hz, OCH_2OCH_3); MS m/z 505 (M^+ − 1). Anal. Calcd for $C_{31}H_{53}O_5$: 505.3893. Found: 505.3914.

(22*S*,23*S*,24*R*)-22-Hydroxy-23-methoxymethoxy-6β-methoxy-3α,5-cyclo-5α-ergostane (26). The same procedure as for the alcohol **18** was applied to the diol **25** (1.1 g, 2.2 mmol) to afford the alcohol **26** (863 mg, 81%) as a colorless amorphous powder: $[\alpha]_D$ +29.5° (c = 1.06, $CHCl_3$); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.75 (3 H, s, 18-H_3), 0.89 (3 H, d, J = 7 Hz, Me), 0.91 (3 H, d, J = 7 Hz, Me), 0.96 (3 H, d, J = 7 Hz, Me), 1.02 (3 H, s, 19-H_3), 1.03 (3 H, d, J = 7 Hz, Me), 1.98–2.04 (1 H, m, 25-H), 2.77 (1 H, t, J = 2.5 Hz, 6-H), 3.32 (3 H, s, 6-OMe), 3.43 (3 H, s, OCH_2OCH_3), 3.52–3.56 (1 H, m, 23-H), 3.64 (1 H, dd, J = 6, 2.5 Hz, 22-H), 4.67 and 4.73 (each 1 H, each d, J = 6 Hz, OCH_2OCH_3); MS m/z 489 (M^+ − 1).

(22*S*,23*S*,24*R*)-3β,22,23-Triacetoxyergost-5-ene (27). The same procedure as for the alcohol **18** was applied to the alcohol **26** (863 mg, 1.8 mmol) to afford the triacetate **27** (835 mg, 85%) as a colorless amorphous powder: $[\alpha]_D$ −44.2° (c = 0.98, $CHCl_3$); IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (400 MHz) δ 0.67 (3 H, s, 18-H_3), 0.77 (3 H, d, J = 7 Hz, Me), 0.84 (3 H, d, J = 7 Hz, Me), 0.91 (3 H, s, Me), 0.96 (3 H, s, Me), 1.00 (3 H, s, 19-H_3), 2.03 (3 H, s, acetyl), 2.06 (3 H, s, acetyl), 2.10 (3 H, s, acetyl), 4.55–4.64 (1 H, m 3-H), 5.09 (1 H, dd, J = 3.5, 3.5 Hz, 22-H), 5.23 (1 H, dd, J = 7, 3.5 Hz, 23-H), 5.35–5.39 (1 H, m, 6-H); MS m/z 498 (M^+ - CH_3CO_2H). Anal. Calcd for $C_{32}H_{50}O_4$: 498.3708. Found: 498.3693.

(22*S*,23*S*,24*R*)-3β,22,23-Trihydroxyergost-5-ene (28). The same procedure as for the triol **21** was applied to the triacetate **27** (860 mg, 1.5 mmol) to afford the triol **28** (646 mg, 97%) as colorless needles: mp 165.5–167 °C (benzene–hexane); $[\alpha]_D$ −44.6° (c = 0.69, $CHCl_3$); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.71 (3 H, s, 18-H_3), 0.88 (3 H, d, J = 7 Hz, Me), 0.91 (3 H, d, J = 7 Hz, Me), 0.97 (3 H, d, J = 7 Hz, Me), 1.01 (3 H, s, 19-H_3), 1.02 (3 H, d, J = 7 Hz, Me), 3.48–3.58 (1 H, m, 3-H), 3.60 (1 H, dd, J = 3, 3 Hz, 22-H), 3.73 (1 H, dd, J = 4, 3 Hz, 23-H), 5.33–5.37 (1 H, m, 6-H); MS m/z 432 (M^+). Anal. Calcd for $C_{28}H_{48}O_3$: C, 77.72; H, 11.18. Found C, 77.36; H, 11.28.

(22*S*,23*S*,24*R*)-22,23-Isopropylidenedioxy-5α-ergost-2-en-6-one (31). The triol **28** (160 mg, 0.37 mmol) in acetone (2 mL) was treated with *p*-toluenesulfonic acid (20 mg) for 2 h at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL), and the organic layer was washed with aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the acetonide **29** (170 mg). Methanesulfonyl chloride (0.06 mL, 0.72 mmol) was added to a stirred solution of the acetonide **29** (170 mg) in pyridne (2 mL) at

room temperature under a current of nitrogen. The reaction mixture was then stirred for 1 h and poured into water (10 mL); isolation of the product by ether extraction gave the mesylate (186 mg). BH_3–THF complex (1.0 mL, 1.0 mmol) was added dropwise to a stirred solution of the mesylate in anhydrous tetrahydrofuran (3 mL) under a current of nitrogen at room temperature. After the reaction mixture was stirred for 2 h, 10% aqueous sodium hydroxide (0.5 mL) and 30% hydrogen peroxide (0.7 mL) were added; the resulting solution was further stirred for 20 min at the same temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the 6-hydroxy compound (190 mg) whose solution in dichloromethane (8 mL) was treated with pyridinium chlorochromate (150 mg, 0.8 mmol) for 2 h at room temperature. The reaction mixture was diluted with ether (20 mL), and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the 6-oxo compound **30** (153 mg), whose solution in *N,N*-dimethylformamide (3 mL) was treated with lithium bromide (54 mg, 0.51 mmol) for 1 h at 130 °C. The reaction mixture was poured into water (10 mL) and isolation of the product by ether extraction gave the residue which was purified by chromatography on silica gel (4 g) using dichloromethane as the eluant to give the 2-en-6-oxo compound **31** (95 mg, 63%) as colorless needles: mp 181–182 °C (MeOH), $[\alpha]_D$ +0.9° (c = 0.21, $CHCl_3$), IR ($CHCl_3$) 1710 cm^{-1}, ^1H NMR (100 MHz) δ 0.70 (3 H, s, 18-H_3), 0.71 (3 H, s, 19-H_3), 1.34 (3 H, s, acetonide), 1.37 (3 H, s, acetonide), 3.73–4.08 (2 H, m, 22-H and 23-H), 5.40–5.80 (2 H, m, 2-H and 3-H). MS m/z 470 (M^+). Anal. Calcd for $C_{30}H_{46}O_4$: 470.3759. Found: 470.3754.

(22*S*,23*S*,24*R*)-2α,3α,22,23-Tetrahydroxy-5α-ergostan-6-one (32). Osmium tetraoxide (7.5 mg, 0.03 mmol) in tetrahydrofuran (0.075 mL) was added dropwise to a stirred solution of the 2-ene-6-oxo compound **31** (75 mg, 0.16 mmol) in *tert*-butyl alcohol–tetrahydrofuran–water (10:8:1 v/v) (5 mL) containing *N*-methylmorpholine *N*-oxide (56.3 mg, 0.48 mmol) at room temperature. After 3 h at the same temperature, saturated aqueous sodium hydrogen sulfide (5 mL) was added to the reaction mixture and isolation of the product by ethyl acetate gave the diol (78 mg), whose solution in 80% aqueous acetic acid (2.7 mL) was refluxed for 3 h. After cooling, the reaction mixture was diluted with ethyl acetate (10 mL); and organic layer was washed with aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a white solid, which was purified by chromatography on silica gel (2 g) using chloroform containing 5% methanol as the eluant to give the tetraol **32** (62 mg, 84%) as colorless needles: mp 184–185 °C (EtOAc) (lit.[13,14] 184–185 °C; lit.[15] 182–183 °C). Its spectroscopic data were identical with those reported.

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Registry No. 2, 145-13-1; **3**, 104336-29-0; **3** (Ts salt), 104336-30-3; **4**, 104336-32-5; **5**, 104336-31-4; **6**, 95042-54-9; **7**, 95042-55-0; **8**, 1522-46-9; **9**, 104336-33-6; **10**, 32249-55-1; **11a**, 104336-34-7; **11b**, 104336-35-8; **12a**, 104336-36-9; **12b**, 104336-37-0; **13a**, 104336-38-1; **13b**, 104336-39-2; **14**, 104336-40-5; **15**, 104336-41-6; **16**, 104336-42-7; **17**, 104336-43-8; **17** (mesylate), 104336-44-9; **18**, 104336-45-0; **19**, 104336-46-1; **19** (3β,22-diol), 104336-47-2; **20**, 90095-32-2; **21**, 85707-12-6; **23**, 104336-48-3; **24**, 104418-95-3; **25**, 104418-96-4; **26**, 104418-97-5; **27**, 104418-98-6; **28**, 104418-99-7; **29**, 104419-00-3; **29** (mesylate), 104419-01-4; **29** (6-hydroxymesylate), 104419-02-5; **30**, 104419-60-5; **31**, 104419-03-6; **31** (diol), 104336-49-4; **32**, 72050-69-2; 5-lithio-2-methoxyfuran, 104336-28-9.

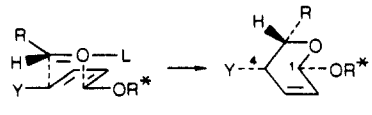
Interactivity of Chiral Catalysts and Chiral Auxiliaries in the Cycloaddition of Activated Dienes with Aldehydes: A Synthesis of L-Glucose

Mark Bednarski and Samuel Danishefsky*

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received January 27, 1986*

Abstract: $Eu(fod)_3$ and $Eu(hfc)_3$ catalyze the cycloaddition of a variety of aldehydes with oxygenated highly substituted butadienes. With achiral dienes, (+)-$Eu(hfc)_3$ shows only modest enantiofacial selectivities. Similarly, modest selectivities were observed in the reactions of several chiral dienes with aldehydes in the presence of the achiral $Eu(fod)_3$. However, the combination of chiral dienes with chiral (+)-$Eu(hfc)_3$ catalyst exhibited striking interactivities, resulting in some instances in diastereofacial excesses of 95%. Of the systems examined, only those dienes whose intrinsic facial selectivities are small and opposite in direction to that of the (+)-$Eu(hfc)_3$ catalyst exhibit useful interactivity of the two chiral components. Thus, the diastereomeric excesses observed here do not arise from strictly numerical factoring of componental preferences (simple double diastereoselectivity) but are a consequence of a "specific interactivity", inherent in the process itself. Application of these findings to the synthesis of optically pure substituted pyrans, L-glycolipids, and L-glucose is described.

The Lewis acid catalyzed aldehyde–diene cyclocondensation reaction (eq 1) has emerged as a useful implement in organic synthesis.[1] It has been successfully applied to reach various targets of interest in the carbohydrate[2a] and polypropionate[2b] areas. The



(1)

range of aldehydes and dienes which have participated in the process and the high levels of topographic and diastereofacial control which can be realized by careful management of variables (substrates, solvents, catalysts, temperatures) add to the utility of the method. Another feature of the reaction, when it operates in the pericyclic pathway,[3] is its suprafacial character. If the

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