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Asymmetric Isopropylation of Steroidal 24-Aldehydes for the Synthesis of 24(*R*)-Hydroxycholesterol

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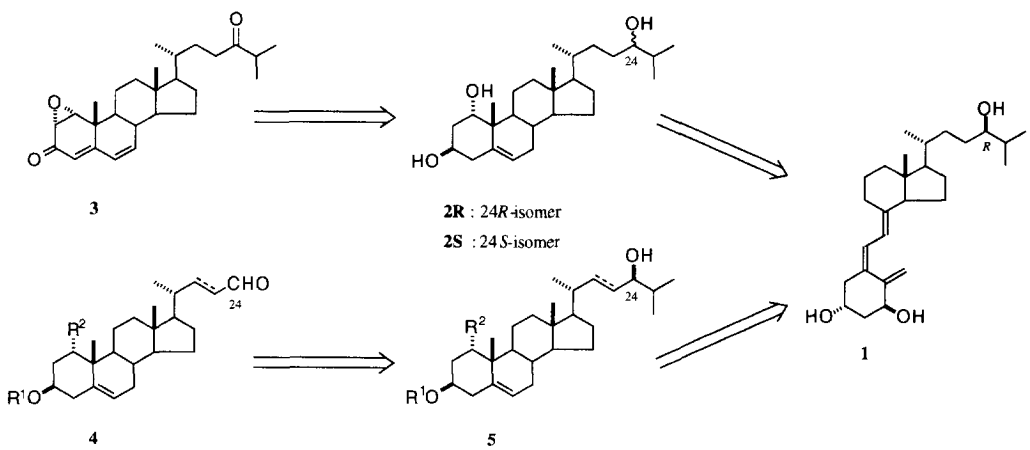
Abstract: The chiral β-amino alcohols-catalyzed addition of diisopropylzinc to steroidal 24-aldehydes successfully provided 24(*R*)-hydroxycholesterols in good yields with high diastereoselectivities, which are synthetic intermediates of 1α,24(*R*)-dihydroxyvitamin D_3 (**1**). α,β-Unsaturated steroidal aldehydes were found to give the corresponding isopropylated adducts in much higher yields (up to 91%) than those of saturated steroidal aldehydes.

INTRODUCTION

1α,24(*R*)-Dihydroxyvitamin D_3[1] (**1**), an active analogue of vitamin D_3, inhibits the growth of keratinocyte and induces keratinocyte differentiation[2] with less hypercalcemic activity, and was approved to be a therapeutic drug for psoriasis. The 1α,24(*R*)-dihydroxyvitamin D_3 **1** was effectively synthesized from 1α,24(*R*)-dihydroxycholesterol (**2R**), obtained by chromatographic separation of a diastereomeric mixture, which was prepared from the 24-epoxydienone precursor (**3**) using the Birch reduction.[1] The separated diastereoisomer **2S** was known to be converted efficiently into the desired intermediate **2R**.[3] Although other syntheses of 1α,24(*R*)- and 1α,24(*S*)-hydroxycholesterol derivatives have been reported,[4] no catalytic stereoselective synthesis is known.

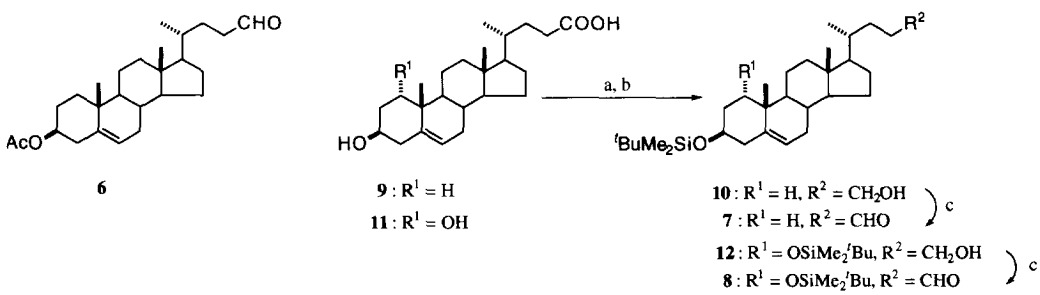


Recently, dialkylzincs have been reported to react with aldehydes in the presence of a catalytic amount of some chiral β-amino alcohols to afford the corresponding optically active secondary alcohols.[5] Thus, we attempted the asymmetric addition of diisopropylzinc to steroidal 24-aldehydes (**4**) to construct the side chain framework of 1α,24(*R*)-dihydroxycholesterol (**5**). We report here the successful results of the asymmetric isopropylation using diisopropylzinc.

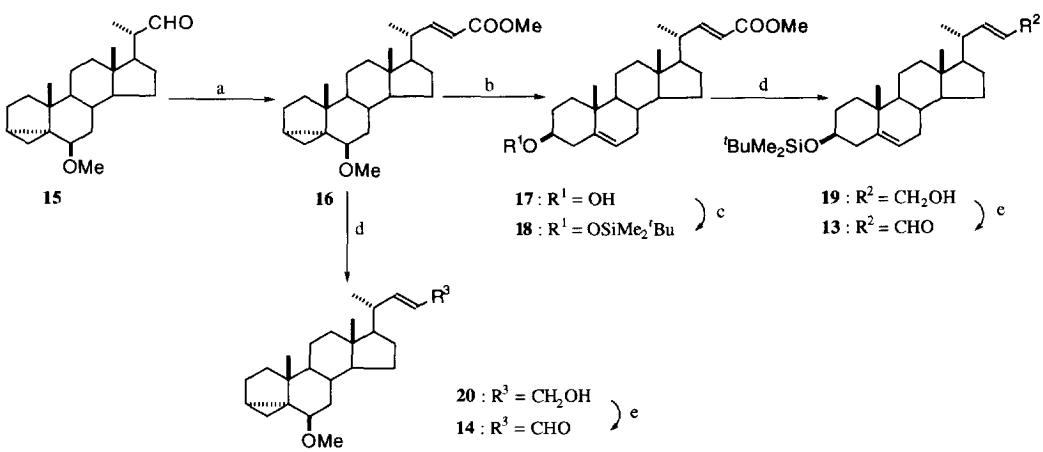
RESULTS AND DISCUSSION

Preparation of starting steroidal aldehydes

The starting steroidal 3-acetylated 24-aldehyde **6** was obtained from 3β-acetoxycholenic acid according to the cited reference.[6a] The 3-silylated aldehyde **7** was easily available from cholenic acid[6] (**9**) in 3 steps as follows: (1) silylation of the alcohol **9**; (2) reduction of the resulting silylated ester; and (3) oxidation of the hydroxyl group of the reduced silylated alcohol **10** to give the aldehyde **7** (Scheme 1). The 1α-hydroxylated aldehyde **8** was similarly prepared from the corresponding 1α-hydroxycholenic acid[7] (**11**) through the bis-silylated alcohol **12**.



Scheme 1. Reagents: a) $^tBuMe_2SiCl$; b) LAH ; c) $(COCl)_2$, DMSO , NEt_3

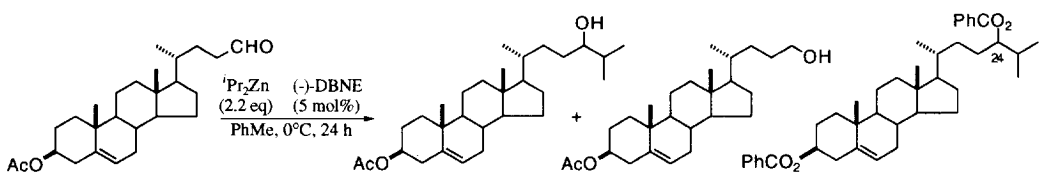


Scheme 2. Reagents: a) Ph_3P=CHCOOMe ; b) *p*-TsOH ; c) $^tBuMe_2SiCl$; d) DIBAH ; e) $(COCl)_2$, DMSO, NEt_3

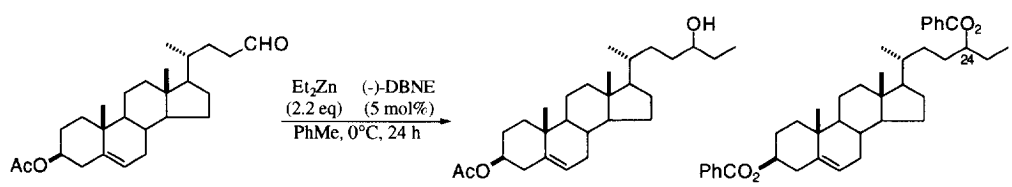
The α,β-unsaturated 24-aldehydes, substrates **13** and **14**, were prepared by the sequence shown in Scheme 2. The α,β-unsaturated aldehyde **13** was prepared from the starting 22-aldehyde **15**, which was easily obtained from stigmasterol,[8] in 5 steps as follows: (1) Wittig reaction of the 22-aldehyde **15**; (2) protic isomerization of the *i*-methyl ether[9] **16**; (3) silylation of the resulting alcohol **17**; (4) reduction of the ester **18**; and (5) oxidation of the alcohol **19** to the aldehyde **13**. Reduction of the *i*-methyl ether **16** followed by oxidation of the resulting alcohol **20** provided the other α,β-unsaturated aldehyde **14**.

*Reaction of the saturated aldehyde **6** with diisopropylzinc*

Concerning the reaction of aldehydes with diisopropylzinc, few examples are known except for K. Soai's work.[5b,5g] According to this paper, the asymmetric addition reaction of the steroidal aldehyde **6** with diisopropylzinc was performed in the presence of 5 mol% (-)-(*N*,*N*)-di-*n*-butylamino-1-phenylpropane-1-ol ((-)-DBNE) as a chiral β-amino alcohol, which was reported to be an effective catalyst for the addition reaction of aliphatic aldehydes with several dialkylzincs,[5b] to give the isopropylated adduct[10] **21** only in 29% yield (entry 1, Table 1). The diastereomeric ratio of the product **21** was determined after the conversion into the corresponding dibenzoate[11] **23** *via* hydrolysis and benzoylation to be **23R**:**23S** = 95.0:5.0 by HPLC analysis. The lower yield of the adduct **21** was attributed to the formation of the reduction product **22** in 48% yield.



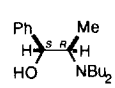
Other than diisopropylzincs, diethylzinc was easily available and widely investigated in order to test the reactivity of the aldehyde **6**. In the presence of (-)-DBNE (5 mol%), the steroidal aldehyde **6** was allowed to react with diethylzinc to adequately provide the ethylated adduct **24** in 77% yield. The diastereomeric ratio of the product **24** was determined by HPLC analysis of the corresponding dibenzoate **25** obtained through hydrolysis and benzoylation to be **25S**:**25R** = 93.5:6.5. This result disclosed that diisopropylzinc was less reactive to aldehydes than diethylzinc, and predominantly acted as a reducing agent under the tested reaction conditions.

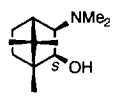


To improve the product yield by both an acceleration of the isopropylation reaction and a suppression of the reduction reaction, the amount of chiral catalyst, (-)-DBNE, was increased to 20 mol% (entry 2) and 50 mol% (entry 3). The use of 20 mol% (-)-DBNE resulted in the formation of the product **21** in higher yield (63%) with a diastereomeric ratio of 98.5:1.5 together with the reduced product **22** (33%), whereas the use of 50 mol% (-)-DBNE gave a 54% yield. A mixture of toluene and hexane (1:1) instead of toluene only as the reaction solvent, resulted in the lower formation of the product **21** (35%) even using a 20 mol% amount of (-)-DBNE (entry 4). A decrease (1.3 eq) in the amount of diisopropylzinc also led to a lower yield of the adduct **21** along with an increase in the reduced product **22** (entry 5). In the presence of 20 mol% (-)-3-*exo*-(dimethylamino)isoborneol[5e] ((-)-DAIB), in the place of (-)-DBNE, the yield of the product **21** was not improved but the diastereomeric ratio of the product was the highest in this studies (**23R**:**23S** = 99.4:0.6, entry 6). Instead of (-)-DBNE, (+)-DBNE was used to study the effect of the substrate chirality on the diastereoselectivity to furnish the product **21** (63%) with a diastereomeric ratio of 6.5:93.5. This result showed that the chirality of the substrate **6** is preferable to construct the desired 24(*R*)-isomer **21R** from the viewpoint of the chiral double recognition (entry 7). In the presence of 95 mol% (-)-DBNE with 21% ee corresponding to 20 mol% enantiomerically pure (-)-DBNE, the isopropylated adduct **21** was also obtained in 61% yield with a similar diastereomeric ratio (98.5:1.5) to the case of enantiomerically pure (-)-DBNE, thus showing a asymmetric amplification[5d] (entry 8).

Table 1. Reaction of Aldehyde **6** with $^{i}Pr_2Zn$

entry	chiral β-amino alcohol		solvent	$^{i}Pr_2Zn$ (eq)	**21** (%)	**22** (%)	R : S[*5]
1	(-)-DBNE[*1]	5 mol%	toluene	2.2 eq	29%	48%	95.0 : 5.0
2	(-)-DBNE	20 mol%	toluene	2.2 eq	63%	33%	98.5 : 1.5
3	(-)-DBNE	50 mol%	toluene	2.2 eq	54%	38%	98.5 : 1.5
4	(-)-DBNE	20 mol%	[*4]	2.2 eq	35%	47%	98.5 : 1.5
5	(-)-DBNE	20 mol%	toluene	1.3 eq	29%	49%	98.5 : 1.5
6	(-)-DAIB[*2]	20 mol%	toluene	2.2 eq	61%	14%	99.4 : 0.6
7	(+)-DBNE	20 mol%	toluene	2.2 eq	63%	35%	6.5 : 93.5
8	(-)-DBNE (21 %ee)	95 mol%[*3]	toluene	2.2 eq	61%	16%	98.5 : 1.5

[*1] 

[*2] 

[*3] corresponding to 20 mol% of (-)-DBNE (100%ee)

[*4] toluene / hexane = 1 / 1

[*5] estimated by the corressponding dibenzoate **23**

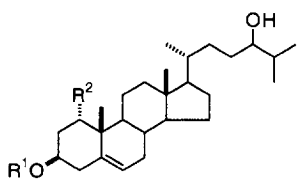
Reaction of other saturated aldehydes with diisopropylzinc

To examine the influence of protection groups of the hydroxy group at the C-3 position, as well as the substituent group at the C-1 position, other saturated aldehydes **7** and **8** were subjected to the reaction with diisopropylzinc. The results are summarized in Table 2. The 3-silylated aldehyde **7** also provided the isopropylated adduct **26** in similar yields in the presence of both 5 mol% and 20 mol%, with similar diastereoselectivities by HPLC measurement of the analogously derived dibenzoate **23** (entries 1 and 2, Table 2). These results indicated that the protecting group of the hydroxy group at the C-3 position did not

significantly affect the reaction manner. On the other hand, in the presence of 20 mol% of (-)-DBNE, the substrate **8** possessing a silylated hydroxy group at the C-1 position reacted with diisopropylzinc to afford the isopropylated adduct **27** in much higher yield (80%) along with a sufficient diastereomeric ratio (93.5 : 6.5), which was determined by HPLC measurement of the diol **28** after desilylation (entries 3 and 4).

Table 2. Reaction of Other Saturated Aldehydes with $^{i}Pr_2Zn$

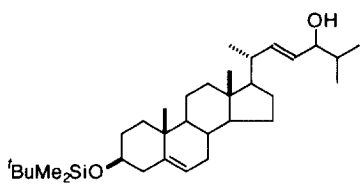
entry	aldehyde	chiral β-amino alcohol		isopropylated adduct (%)	reduced product (%)	R : S
1	**7**	(-)-DBNE	5 mol%	30%	25%	92.7 : 7.3
2	**7**	(-)-DBNE	20 mol%	63%	6%	98.4 : 1.6
3	**8**	(-)-DBNE	5 mol%	30%	15%	98.0 : 2.0
4	**8**	(-)-DBNE	20 mol%	80%	3%	93.5 : 6.5



26 : $R^1 = OSiMe_2{}^{t}Bu$, $R^2 = H$

27 : $R^1 = OSiMe_2{}^{t}Bu$, $R^2 = OSiMe_2{}^{t}Bu$

28 : $R^1 = H$, $R^2 = OH$



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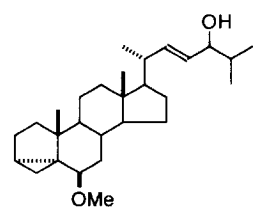

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Reaction of α,β–unsaturated aldehydes with diisopropylzinc

During the addition reaction of aldehydes with diethylzinc, α,β-unsaturated aldehydes were more reactive than saturated aldehydes.[5f] This result suggested that the addition reaction of α,β-unsaturated aldehydes with diisopropylzinc was expected to be accelerated by suppressing the reduction reaction. Therefore, we studied the catalytic diastereoselective addition of diisopropylzinc to steroidal α,β-unsaturated aldehydes, **13** and **14**. The aldehyde **13** was allowed to react with diisopropylzinc in the presence of 20 mol% (-)-DBNE to afford the isopropylated adduct **29** in 90% yield accompanied by the reduced product **19** (3%). The yield of the adduct **29** was found to be much higher as expected than those in the case of saturated aldehydes. The diastereomeric ratio (24*R*-isomer:24*S*-isomer) of the adduct **29** was determined to be 4.4:95.6 by HPLC analysis of the dibenzoate **23** derived from the product **29** using a sequence of hydrolysis, dibenzoylation, and hydrogenation (entry 1, Table 3). Even in the presence of 5 mol% (-)-DBNE, a similar

Table 3. Reaction of α,β-Unsaturated Aldehydes with $^{i}Pr_2Zn$

entry	aldehyde	chiral β-amino alcohol		isopropylated adduct (%)	reduced product (%)	R : S
1	**13**	(-)-DBNE	5 mol%	91%	3%	5.4 : 94.6
2	**13**	(-)-DBNE	20 mol%	90%	3%	4.4 : 95.6
3	**14**	(-)-DBNE	20 mol%	86%	5%	2.9 : 97.1

addition to the aldehyde **13** afforded the adduct **29** in 91% yield with a satisfactory diastereomeric ratio of 5.4:94.6 (entry 2). The aldehyde **14** also reacted with diisopropylzinc to give the isopropylated adduct **30** in 86% yield with a high diastereoselectivity (2.9:97.1, entry 3), which was also estimated by HPLC analysis of the derivative **23** through hydrogenation, acidic isomerization and dibenzoylation. These results demonstrated that the isopropylation reaction of α,β-unsaturated aldehydes with diisopropylzinc to be much faster than that of saturated aldehydes overcoming the reduction of the starting α,β-unsaturated aldehydes.

CONCLUSION

In conclusion, it was found that the addition reactions of steroidal saturated aldehydes with diisopropylzinc in the presence of 20 mol% chiral β-amino alcohols successfully provided 24(*R*)-hydroxycholesterol derivatives in good yields with high diastereoselectivities. It was also found that the steroidal α,β-unsaturated aldehydes with diisopropylzinc in the presence of 5 mol% chiral β-amino alcohols produced Δ^{22}-24(*S*)-hydroxycholesterol derivatives in much higher yields and with sufficiently high diastereoselectivities. These obtained 24-hydroxycholesterol derivatives with high optical purities can be used as key intermediates for the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 by the known procedure.[12] These results also opened a new route to 1α,24(*R*)-dihydroxyvitamin D_3.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 8100M spectrometer. NMR spectra were obtained using a VARIAN GEMINI 200 (200 MHz) spectrometer with $CDCl_3$. Chemical shifts and coupling constants (*J*) are given in ppm relative to internal tetramethylsilane and Hz, respectively. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). Mass spectra (MS) were taken at 70 eV using a HP 5971 mass spectrometer. For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector (254 nm) and a Shimadzu C-R3A chromatopac was employed. Melting points were taken with a Mettler FP 81 and are uncorrected. A toluene solution of diisopropylzinc was purchased from Trichemical Inc.

Preparation of starting steroidal aldehydes.

3β-(*tert*-Butyldimethylsilyloxy)chol-5-en-24-al (7).

To a solution of 3β-hydroxychol-5-en-24-oic acid[6] (**9**, 10.39 g, 27.8 mmol) in DMF (155 ml) was added *tert*-butyldimethylchlorosilane (13.62 g, 90.0 mmol), imidazole (15.21 g, 225.0 mmol), and 4-dimethylaminopyridine (7.30 g, 60.0 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 6 h. Water (100 ml) was added and the resulting mixture was extracted with EtOAc (300 ml). The extract was washed with water (200 ml) and brine (200 ml). Drying ($MgSO_4$), filtration, and evaporation of the solvent gave a crude silylated product which was allowed to react with $LiAlH_4$ (4.56 g, 120 mmol) in THF (200 ml) at 0°C. After stirring for 18 h at room temperature, a saturated aqueous Na_2SO_4 solution was added dropwise. Drying (Na_2SO_4 and $MgSO_4$), filtration, and evaporation of the solvent gave a crude product which was chromatographed on silica gel (700 g) eluting with hexane and EtOAc (20:1 up to 1:1) to yield 3β-(*tert*-butyldimethylsilyloxy)chol-5-en-24-ol (**10**, 9.43 g, 19.9 mmol, 72%); mp: 146.5-152.0°C (hexane-ethyl

acetate); IR (KBr): 3350, 2930, 1458, 1377, 1248, 1092 cm^{-1}; ^1H NMR: δ 0.06 (s, 6H), 0.68 (s, 3H), 0.89 (s, 9H), 0.94 (d, 3H, *J* = 6 Hz), 0.99 (s, 3H), 0.90-2.40 (m, 23H), 3.40-3.60 (m, 1H), 3.55-3.70 (m, 2H), 5.25-5.35 (m, 1H); MS (m/z): 459 $(M-15)^+$; Found: C, 75.66; H, 11.70; $C_{30}H_{54}O_2Si$ requires C, 75.88; H, 11.46.

Dimethylsulfoxide (5.67 ml, 80.0 mmol) was added dropwise at -50°C to a solution of oxalyl chloride (3.43 ml, 40.0 mmol) in dichloromethane (100 ml). The resulting mixture was stirred for 1 h at -50°C. A solution of **8** (4.67 g, 9.85 mmol) in dichloromethane (70 ml) was added dropwise and the reaction mixture was stirred at -50°C for 30 min. Triethylamine (13.9 ml, 100 mmol) was added and the resulting mixture was stirred at 0-25°C for 1 h. A saturated aqueous NH_4Cl solution (20 ml) was poured into the mixture, which was then extracted with dichloromethane (200 ml). The extract was washed with a saturated aqueous $NaHCO_3$ solution (200 ml) and then brine (200 ml). Drying ($MgSO_4$), filtration, and evaporation of the solvent gave a crude product which was chromatographed on silica gel (250 g) with hexane and EtOAc (40:1 up to 20:1) to give **5** (4.27 g, 9.06 mmol, 92%); mp: 132.0-137.0°C (hexane-ethyl acetate); $[\alpha]_D^{20}$= -12 (*c* 0.05, EtOH); IR (KBr): 2925, 2870, 2845, 1725, 1456, 1380, 1250, 1082 cm^{-1}; ^1H NMR: δ 0.06 (s, 6H), 0.68 (s, 3H), 0.88 (s, 9H), 0.90 (d, 3H, *J* = 6 Hz), 0.99 (s, 3H), 0.90-2.55 (m, 23H), 3.40-3.60 (m, 1H), 3.55-3.70 (m, 2H), 5.25-5.40 (m, 1H), 9.78 (t, 1H, *J* = 3 Hz); MS (m/z): 457 $(M-15)^+$; Found: C, 76.14; H, 11.40; $C_{30}H_{52}O_2Si$ requires C, 76.21; H, 11.08.

1α,3β-Bis(*tert*-butyldimethylsilyloxy)chol-5-en-24-al (8).

1α,3β-Bis(*tert*-butyldimethylsilyloxy)chol-5-en-24-ol (**12**) was obtained from 1α,3β-dihydroxychol-5-en-24-oic acid[7] (**11**) by a procedure similar to the monosilylated alcohol **9** in 57% yield; mp: 166.0-170.0°C (hexane-ethyl acetate); IR (KBr): 3400, 2920, 1457, 1373, 1246, 1075 cm^{-1}; ^1H NMR: δ 0.04 (s, 12H), 0.68 (s, 3H), 0.86 (s, 18H), 0.91 (d, 3H, *J* = 6 Hz), 0.95 (s, 3H), 0.90-2.50 (m, 23H), 3.50-3.70 (m, 1H), 3.70-3.80 (b, 1H), 3.90-4.10 (m, 2H), 5.40-5.50 (m, 1H); MS (m/z): 604 (M^+); High-resolution MS for $C_{32}H_{59}O_3Si_2$ $(M-{}^tBu)^+$: Calcd m/z; 547.4003; Found: 547.3969.

The aldehyde **8** was obtained from the above alcohol **12** by a procedure similar to the monosilylated aldehyde **7** in 84% yield; mp: 152.0-157.0°C (hexane-ethyl acetate); $[\alpha]_D^{20}$= +40 (*c* 0.05, EtOH); IR (KBr): 2940, 1752, 1458, 1380, 1254, 1077 cm^{-1}; ^1H NMR: δ 0.02 (s, 12H), 0.68 (s, 3H), 0.88 (s, 18H), 0.92 (d, 3H, *J* = 6 Hz), 0.95 (s, 3H), 0.90-2.50 (m, 23H), 3.70-3.80 (b, 1H), 3.90-4.10 (m, 2H), 5.40-5.50 (m, 1H), 9.79 (t, 1H, *J* = 3 Hz); MS (m/z): 470 $(M-132)^+$; Found: C, 71.49; H, 11.26; $C_{36}H_{64}O_3Si_2$ requires C, 71.70; H, 11.03.

(22*E*)-3β-(*tert*-Butyldimethylsilyloxy)chol-5,22-dien-24-al (13).

A mixture of 6β-methoxy-3α,5α-cyclo-23,24-bisnorcholan-22-al[8] (**15**, 6.05 g, 17.5 mmol) and methyl (triphenylphosphoranylidene)acetate (14.06 g, 42.1 mmol) in toluene (75 ml) was heated at 80°C for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (300 g) using hexane and ether (20:1 up to 5:1) to provide methyl (*E*)-6β-methoxy-3α,5α-cyclochol-22-en-24-oate (**16**, 5.86 g, 14.8 mmol); mp: 46.0-48.0°C (hexane-ether); IR (KBr): 1730, 1441, 1331, 1273, 1169, 1100 cm^{-1}; ^1H NMR: δ 0.78 (s, 3H), 1.01 (s, 3H), 1.08 (d, 3H, *J* = 6 Hz), 0.35-2.05 (m, 21H), 2.05-2.35 (m, 1H), 2.77 (t, 1H, *J* = 3 Hz), 3.31 (s, 1H), 3.71 (s, 3H), 5.74 (d, 1H, *J* = 14 Hz), 6.84 (dd, 1H, *J* = 6, 14 Hz); MS (m/z): 400 (M^+).

The above product **16** (2.06 g, 5.19 mmol) was treated at 80°C for 2 h with *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in dioxane (30 ml) and water (20 ml). Water (300 ml) was added to the reaction mixture which was extracted with EtOAc (300 ml). The separated organic layer was washed with a saturated aqueous $NaHCO_3$ solution (200 ml) and brine (200 ml) and then dried over $MgSO_4$. After filtration and evaporation of the solvent, the chromatographic separation of the crude residue on silica gel (80 g) with hexane and EtOAc (20:1 up to 4:1) yielded methyl (22*E*)-3β-hydroxychol-5,22-dien-24-oate (**16,** 1.78 g, 4.65 mmol, 90%) ; mp: 139.5-140.5°C (hexane-ethyl acetate); IR (KBr): 3445, 2934, 1725, 1460, 1331, 1282, 1059 cm^{-1}; ^1H NMR: δ 0.70 (s, 3H), 1.00 (s, 3H), 1.08 (d, 3H, *J* = 6 Hz), 0.90-2.40 (m, 21H), 3.30-3.60 (m, 1H), 3.70 (s, 3H), 5.75 (d, 1H, *J* = 14 Hz), 6.82 (dd, 1H, *J* = 6, 14 Hz); MS (m/z): 386 (M^+).

To a solution of **17** (1.65 g, 4.31 mmol) in DMF (12 ml) was added *tert*-butyldimethylchlorosilane (3.24 g, 21.53 mmol) and imidazole (2.94 g, 42.94 mmol), and the mixture was stirred at 80°C for 1 h. Brine (200 ml) was added and then extracted with EtOAc (300 ml). The extract was washed with 1N HCl solution (200 ml), brine (200ml) and then dried over $MgSO_4$. After filtration and evaporation of the solvent, the residual product was chromatographed on silica gel (100 g) eluting with hexane and EtOAc (60:1) to give methyl (22*E*)-3β-(*tert*-butyldimethylsilyloxy)chol-5,22-dien-24-oate (**18**, 2.12 g, 4.27 mmol, 99%); mp: 119.0-121.0°C (hexane-ethyl acetate); IR (KBr): 1730, 1280, 1255, 1100 cm^{-1}; ^1H NMR: δ 0.02 (s, 6H), 0.69 (s, 3H), 0.85 (s, 9H), 0.96 (s, 3H), 1.06 (d, 3H, *J* = 6 Hz), 0.90-2.35 (m, 21H), 3.30-3.60 (m, 1H), 3.69 (s, 3H), 5.35-5.45 (m, 1H), 5.70 (d, 1H, *J* = 14 Hz), 6.81 (dd, 1H, *J* = 6, 14 Hz); MS (m/z): 485 $(M-15)^+$; Found: C, 74.35; H, 10.70; $C_{31}H_{52}O_2Si$ requires C, 74.34; H, 10.46.

To a solution of **18** (2.00 g, 4.02 mmol) in toluene (100 ml) at -78°C was added a 1.0 M solution of $^iBu_2AlH$ (17 ml, 17 mmol). After stirring at -78°C for 3 h, a 1N HCl solution (100 ml) was added, and the resulting mixture was extracted with EtOAc (150 ml). The extract was washed with a 1N HCl solution (200 ml), a saturated aqueous $NaHCO_3$ (200 ml), and then brine (200 ml). After drying ($MgSO_4$), filtration and evaporation of the solvent, the obtained crude product was chromatographed on silica gel (120 g) using hexane and EtOAc (20:1 up to 8:1) to give (22*E*)-3β-(*tert*-butyldimethylsilyloxy)chol-5, 22-dien-24-ol (**19**, 1.77 g, 3.77 mmol, 94%); mp: 83.5-84.0°C (hexane-ethyl acetate); IR (KBr): 2936, 1458, 1333, 1273, 1100 cm^{-1}; ^1H NMR: δ 0.05 (s, 6H), 0.70 (s, 3H), 0.89 (s, 9H), 1.00 (s, 3H), 1.04 (d, 3H, *J* = 6 Hz), 0.90-2.35 (m, 21H), 3.30-3.60 (m, 1H), 4.00-4.10 (m, 2H), 5.25-5.35 (m, 1H), 5.50-5.60 (m, 2H); MS (m/z); 472 (M^+).

The titled aldehyde **13** was obtained from the above alcohol **19** by a procedure similar to the aldehyde **5** in 83% yield; mp: 137.5-138.0°C (hexane-ethyl acetate); $[\alpha]_D^{20}$= -26 (*c* 0.05, EtOH); IR (KBr): 1636, 1471, 1383, 1255, 1088 cm^{-1}; ^1H NMR: δ 0.65 (s, 6H), 0.73 (s, 3H), 0.89 (s, 9H), 1.00 (s, 3H), 1.13 (d, 3H, *J* = 6 Hz), 0.90-2.50 (m, 21H), 3.40-3.60 (m, 1H), 5.35-5.45 (m, 1H), 6.05 (d, 1H, *J* = 14 Hz), 6.72 (dd, 1H, *J* = 6, 14 Hz), 9.48 (d, 1H, *J* = 6 Hz); MS (m/z): 455 $(M-15)^+$; Found: C, 76.51; H, 10.97; $C_{30}H_{50}O_2Si$ requires C, 76.53; H, 10.70.

(*E*)-6β-Methoxy-3α, 5α-cyclochol-22-en-24-al (14).

(*E*)-6β-Methoxy-3α,5α-cyclochol-22-en-24-ol (**20**) was obtained from the ester **16** by a procedure similar to the alcohol **19** in 89% yield; mp: 69.5-71.0°C (hexane-ethyl acetate); IR (KBr): 3420, 1471, 1098 cm^{-1}; ^1H NMR: δ 0.73 (s, 3H), 1.01 (s, 3H), 1.03 (d, 3H, *J* = 6 Hz), 0.35-2.20 (m, 22H), 2.77 (t, 1H, *J* = 3 Hz), 3.31 (s, 3H), 4.05 (b, 2H), 5.45-5.65 (m, 2H); MS (m/z): 372 (M^+); Found: C, 80.40; H, 11.09; $C_{25}H_{40}O_2$ requires C, 80.59 H, 10.82.

The titled aldehyde **14** was obtained from the above alcohol **20** by a procedure similar to the aldehyde **7** in 84% yield; mp: 131.0-134.0°C (hexane-ethyl acetate); $[\alpha]_D^{20}$= +58 (*c* 0.05, EtOH); IR (KBr): 1698, 1471, 1381, 1096 cm^{-1}; ^1H NMR: δ 0.73 (s, 3H), 1.01 (s, 3H), 1.13 (d, 3H, *J* = 6 Hz), 0.35-2.05 (m, 21H), 2.30-2.50 (m, 1H), 2.78 (t, 1H, *J* =3 Hz), 3.31 (s, 3H), 4.05 (b, 2H), 6.04 (d, 1H, *J* = 14 Hz), 6.72 (dd, 1H, *J* = 6, 14 Hz), 9.50 (d, 1H, *J* = 6 Hz); MS (m/z): 370 $(M)^+$; Found: C, 80.82; H, 10.50; $C_{25}H_{38}O_2$ requires C, 81.02; H, 10.34.

General procedure for the asymmetric addition of diisopropylzinc to aldehydes

To a solution of **an aldehyde** (1.00 mmol) and (*1S,2R*)-(-)-2-(*N,N*-dibutylamino)-1-phenyl-1-propanol ((-)-DBNE, 52 mg, 0.20 mmol) in toluene (8 ml) was added at 0°C a 0.87 M toluene solution of diisopropylzinc (2.5 ml, 2.2 mmol), and the resulting mixture was stirred for 24 h. After a 0.5 N HCl solution was added, the mixture was extracted with EtOAc (20 ml). The separated extract was washed with a saturated aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml). Drying over $MgSO_4$, filtration followed by evaporation of the solvent gave a crude product, which was subjected to silica gel chromatography (20 g) with hexane and EtOAc (50:1 up to 1:1) providing **the corresponding isopropylated adduct** as a diastereomeric mixture together with the reduced product.

24-Hydroxycholesterol 3-acetate[10] **(21)** was obtained from the aldehyde **4** in 63% yield accompanied by 3β-(*O*)-acetoxychol-5-en-24-ol (**22**) as the reduced product (33%); **21**; IR (KBr): 3400, 1720, 1440, 1360, 1235, 1025 cm^{-1}; ^1H NMR: δ 0.67 (s, 3H), 0.85-0.95 (m, 9H), 1.00 (s, 3H), 1.1-2.0 (m, 25H), 2.03 (s, 3H), 2.25-2.4 (m, 2H), 3.32 (bs, 1H), 4.5-4.7 (m, 1H), 5.35-5.4 (m, 1H); MS (m/z): 444 (M^+); **22**; mp; 84-107°C (hexane-ethyl acetate); IR (KBr): 3300, 1720, 1440, 1362, 1238, 1036 cm^{-1}; ^1H NMR: δ 0.69 (s, 3H), 0.88 (s, 3H), 0.93 (d, 3H, *J* = 6 Hz), 1.02 (s, 3H), 0.90-2.00 (m, 21H), 2.01 (s, 3H), 2.25-2.35 (m, 2H), 3.61 (t, 2H, *J* = 6 Hz), 4.50-4.70 (m, 1H), 5.30-5.40 (m, 1H) ; MS (m/z): 342 $(M-60)^+$; Found: C, 77.18; H, 10.77; $C_{26}H_{42}O_3$ requires C, 77.56; H, 10.51.

The results of other isopropylation reactions of the aldehyde **6** with diisopropylzinc under various conditions are summarized in Table 1.

24-Hydroxycholesterol 3-(*O*)-*tert*-butyldimethylsilyl ether (26) was similarly obtained from the aldehyde **7** in 63% yield together with the reduced alcohol **10** (6%); IR (KBr): 2959, 2857, 1256, 1088 cm^{-1}; ^1H NMR: δ 0.03 (s, 6H), 0.67 (s, 3H), 0.90 (s, 9H), 0.85-0.95 (m, 6H), 1.00 (s, 3H), 1.10-2.00 (m, 25H), 2.25-2.40 (m, 2H), 3.33 (b, 1H), 3.80-4.10 (m, 1H), 5.35-5.40 (m, 1H); MS (m/z): 501 $(M-15)^+$; Found: C, 76.35; H, 11.70; $C_{33}H_{60}O_2Si$ requires C, 76.68; H, 11.70.

1α, 24-Dihydroxycholesterol 3,24-bis(*tert*-butyldimethylsilyl) ether (27) was also obtained from the aldehyde **8** in 80% yield along with the reduced alcohol **12** (3%); IR (KBr): 3420, 1460, 1375, 1250, 1090, 1070 cm^{-1}; ^1H NMR: δ 0.00-0.01 (m, 12H), 0.68 (s, 3H), 0.90 (s, 18H), 0.90-1.00 (m, 9H), 1.00-2.10 (m, 25H), 1.55 (s, 3H), 2.10-2.40 (m, 2H), 3.33 (b, 1H), 3.77 (b, 1H), 3.90-4.10 (m, 1H), 5.35-5.40 (m, 1H); MS (m/z): 646 (M^+); High-resolution MS for $C_{35}H_{65}O_3Si_2$ $(M-^tBu)^+$: Calcd m/z; 589.4472 ; Found; 589. 4527.

(22*E*)-3β-*tert*-Butyldimethylsilyloxy-24-hydroxycholest-5,22-diene (29) was analogously obtained from the aldehyde **13** in 91% yield accompanied by the reduced alcohol **19** (3%); IR (KBr): 2959, 2857, 1256, 1088 cm^{-1}; ^1H NMR: δ 0.04 (s, 6H), 0.69 (s, 3H), 0.85-0.95 (m, 6H), 0.88 (s, 9H), 1.00 (s, 3H), 1.04 (d, 3H, J = 6 Hz), 1.05-2.4 (m, 23H), 3.35-3.55 (m, 1H), 3.70-3.80 (m, 1H), 5.25-5.55 (m, 3H); MS (m/z): 496 $(M-18)^+$.

(22*E*)-6β-Methoxy-3α,5α-cyclocholest-5,22-dien-24-ol[4b] **(30)** was obtained from the aldehyde **14** in a similar manner in 86% yield together with the reduced alcohol **20** (5%); IR (KBr): 2960, 2850, 1475, 1455, 1095 cm^{-1}; ^1H NMR: δ 0.04 (s, 6H), 0.72 (s, 3H), 0.85-0.95 (m, 6H), 1.00 (s, 3H), 1.03 (d, 3H, J = 6 Hz), 0.35-2.40 (m, 23H), 2.70-2.80 (m, 1H), 3.31 (s, 3H), 3.55-3.70 (m, 1H), 5.25-5.55 (m, 3H); MS (m/z): 414 (M^+).

Determination of the diastereomeric ratio of the isopropylated adducts

A typical procedure for the determination of the diastereomertc ratios of the isopropylated adducts is as follows. After deprotection of the isopropylated adducts such as hydrolysis or desilylation, the obtained alcohols were acylated with benzoyl chloride in pyridine to provide the corresponding benzoate. The obtained benzoate was subjected to HPLC analysis to estimate the diastereomeric ratio by comparison of the peak areas of the 24R- and 24S-benzoates.

Determination of the diastereomeric ratios of the isopropylated adduct 21.

To determine the diastereomeric ratio of **21**, a 10% aqueous sodium hydroxide solution (13 ml) was added at room temperature to a solution of the diastereomeric **21** (*ca.* 300 mg) in THF (20 ml) and methanol (9 ml). After stirring at room temperature for 2 h, a 1N HCl solution was added and the mixture was extracted with EtOAc (200 ml). The separated organic layer was successively washed with a saturated aqueous $KHSO_4$ solution (100 ml), a saturated aqueous $NaHCO_3$ solution (100 ml), and then brine (100 ml). Drying over $MgSO_4$, filtration and evaporation of the solvent gave the crude product. To a solution of the resulting crude product (*ca.* 10 mg) and pyridine (0.1 ml) in dichloromethane (0.5 ml) was added benzoyl chloride (0.05 ml) at room temprature. After stirring at room temperature for 1 h, the reaction mixture was concentrated *in vacuo* to leave the crude product, which was separated by column chromatography on silica gel (10 g) using hexane and EtOAc (40:1) yielding the corresponding dibenzoate **23** as a diastereomeric mixture. The dibenzoate **23** was subjected to HPLC analysis (Zorbax sil 25 cm x 4.6 mm I.D.) using hexane-dichloromethane-ethanol (90:10:0.1) as the mobile phase at 2.0 ml/min to estimate the ratio of the 24*R*- and 24*S*-dibenzoates (24*R*; 14.5 min, 24*S*; 16.5 min). The results are listed in Table 1; **23**; IR (KBr): 3600, 3450, 1715 cm^{-1}; ^1H NMR: δ 0.64 (s, 3H), 0.85-1.05 (m, 9H), 1.06 (s, 3H), 1.10-2.10 (m, 24H), 2.40-2.50 (m, 2H), 4.75-5.05 (m, 2H), 5.35-5.45 (m, 1H), 7.37-7.65 (m, 6H), 8.00-8.10 (m, 4H); MS (m/z): 488 $(M-122)^+$.

Determination of the diastereomeric ratios of the isopropylated adduct 26.

Pyridinium-hydrogen fluoride (0.6 ml) was added at room temprature to a solution of the diastereomeric mixture of **26** (50 mg) in acetonitrile (6 ml) and pyridine (0.2 ml). After stirring at room temperature for 4 h, a saturated aqueous $NaHCO_3$ solution (20 ml) was added and the resulting mixture was extacted with EtOAc (20 ml). The organic layer was washed with a saturated aqueous $KHSO_4$ solution (20 ml), a saturated

aqueous $NaHCO_3$ solution (20 ml), and then brine (20 ml). The usual work up gave the crude alcohol, which was similarly converted into the dibenzoate **23** by the benzoylation with benzoyl chloride and pyridine. The diastereomeric ratios were evaluated by a similar HPLC analysis of the obtained dibenzoate **23** (Table 2).

Determination of the diastereomeric ratios of the isopropylated adduct 27.

The isopropylated adduct **27** was desilylated in a manner similar to the above **25** to afford a crude 1α,24-dihydroxycholesterol (**28**), which was subjected to HPLC analysis (YMC A-303 25 cm x 4.6 mm I.D.) using acetonitrile-water (6:4) at 1.0 ml/min. The diastereomeric ratio of **28** was estimated by comparison of the peak areas of the 24*R*- and 24*S*-triols (24*R*; 34 min, 24*S*; 28 min) (Table 2); **28**; IR (KBr): 3400, 1460, 1370, 1050 cm^{-1}; ^1H NMR: δ 0.65 (s, 3H), 0.85-1.00 (m, 9H), 1.07 (s, 3H), 1.00-2.20 (m, 25H), 2.20-2.40 (m, 2H), 3,28 (m, 1H), 3.83 (m, 1H), 3.90-4.10 (m, 1H), 5.60 (m, 1H); MS (m/z): 418 (M^+) .

Determination of the diastereomeric ratios of the isopropylated adduct 29.

The isopropylated adduct **29** was similarly subjected to desilylation followed by dibenzoylation like the isopropylated adduct **25** to give (22*E*)-3β,24-bis(benzoyloxy)cholest-5,22-diene. A 10% Pd/C was added to a solution of the resulting Δ^{22}-dibenzoate in EtOAc (1 ml). The resulting mixture was stirred at room temperature for 2 h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated to leave the dibenzoate **23**. The analytical samples were subjected to HPLC analysis as previously mentioned to determine the diastereomeric ratios of **29** (Table 3).

Determination of the diastereomeric ratio of the isopropylated adduct 30.

A mixture of the isopropylated adduct **30** (10 mg) and a 5% Pt/C (2mg) in ethanol (1 ml) was stirred at room temperature for 2 h under a hydrogen atmosphere. The catalyst was filtered off and the resulting filtrate was evaporated. The obtained residue was treated at 80°C for 1 h with *p*-toluenesulfonic acid monohydrate (5 mg) in dioxane (1 ml) and water (1 ml). The usual work up gave a crude 24-hydroxycholesterol, which was similarly benzoylated to yield the dibenzoate **23**. The analytical sample was subjected to HPLC analysis as previously mentioned to estimate the diastereomeric ratio of **30** (Table 3).

Asymmetric addition of diethylzinc to aldehyde ***6***

To a solution of the aldehyde **6** (400 mg, 1.00 mmol) and (-)-DBNE (52 mg, 0.20 mmol) in toluene (8 ml) was added at 0°C a 1.0 M toluene solution of diethylzinc (2.2 ml, 2.2 mmol), and the resulting mixture was stirred for 24 h. The usual work up and purification similar to the isopropylated product **21** provided the corresponding ethylated adduct **24** (331 mg, 0.77 mmol, 77%) as a diastereomeric mixture. The ethylated adduct **24** was converted to 24-hydroxy-27-norcholesterol 3, 24-dibenzoate (**25**) by a manner (hydrolysis and benzoylation) similar to the case of the isopropylated product **24**. An analytical sample was subjected to HPLC analysis (Zorbax sil 25 cm x 4.6 mm I.D.) using a mixture of hexane-dichloromethane-ethanol (90:10:0.1) as the mobile phase at 0.7 ml/min. The diastereomeric ratio was estimated by comparison of the peak areas of the 24*S*- and 24*R*-dibenzoates of **25** (24*R*; 26.5 min, 24*S*; 28.0 min) to be 24*S* : 24*R* = 93.5 : 6.5.

24-Hydroxy-27-norcholesterol 3-acetate (24); IR (KBr): 3300, 1782, 1466, 1442, 1375, 1250, 1034 cm^{-1}; ^1H NMR: δ 0.67 (s, 3H), 0.85-0.95 (m, 6H), 1.02 (s, 3H), 1.10-2.00 (m, 26H), 2.03 (s, 3H), 2.25-2.35 (m, 2H), 3.37 (bs, 1H), 4.50-4.70 (m, 1H), 5.35-5.4 (m, 1H); MS (m/z): 370 $(M-60)^+$.

24-Hydroxy-27-norcholesterol 3, 24-dibenzoate (25); IR (KBr): 1717, 1451, 1277, 1113 cm^{-1}; ^1H NMR: δ 0.66 (s, 3H), 0.85-1.05 (m, 6H), 1.06 (s, 3H), 1.10-2.10 (m, 25H), 2.40-2.55 (m, 2H), 4.75-4.95 (m, 1H), 4.95-5.10 (m, 1H), 5.35-5.45 (m, 1H), 7.35-7.60 (m, 6H), 8.00-8.10 (m, 4H).

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