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Synthetic Study on Chiral Building Block of Vicinal Diol, Chiron Approach to the Precursors of All Sphingosine Stereoisomers

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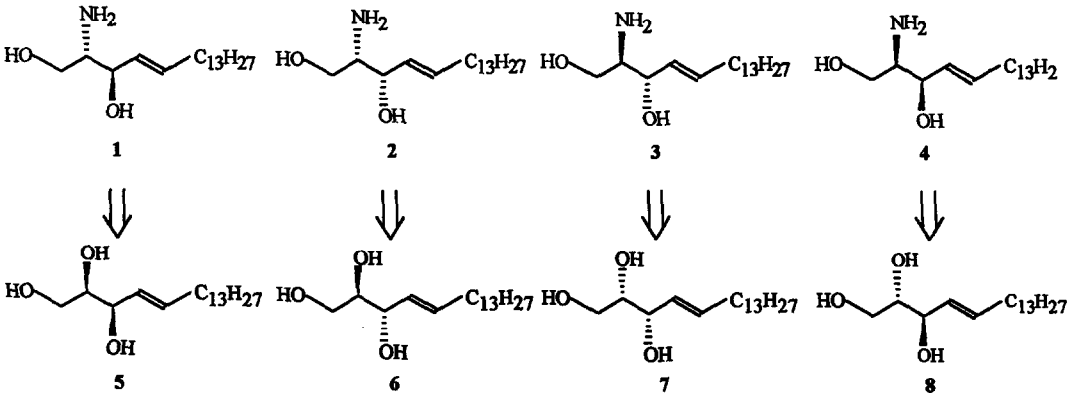
Abstract: All enantiomeric stereoisomers of 1,2,3-trihydroxy-4E-octadecene, key intermediates for the syntheses of sphingosines, were prepared using sugar as chiral pool

Chiral vicinal diols, aminoalcohols or their derivatives are major moiety of many biologically active compounds such as arachidonic acid metabolites, sphingosine. In order to synthesize these compounds many synthetic methods have been reported,[1] and more efforts are still being taken in the search of a more efficient and versatile approach. Herein we wish to describe the preparation of these moieties using sugars as chiral pool substrates, and its application to the syntheses of four stereoisomers of 1,2,3-trihydroxy-4E-octadecene (**5, 6, 7, 8**), key intermediates for the syntheses of sphingosines (Scheme 1).

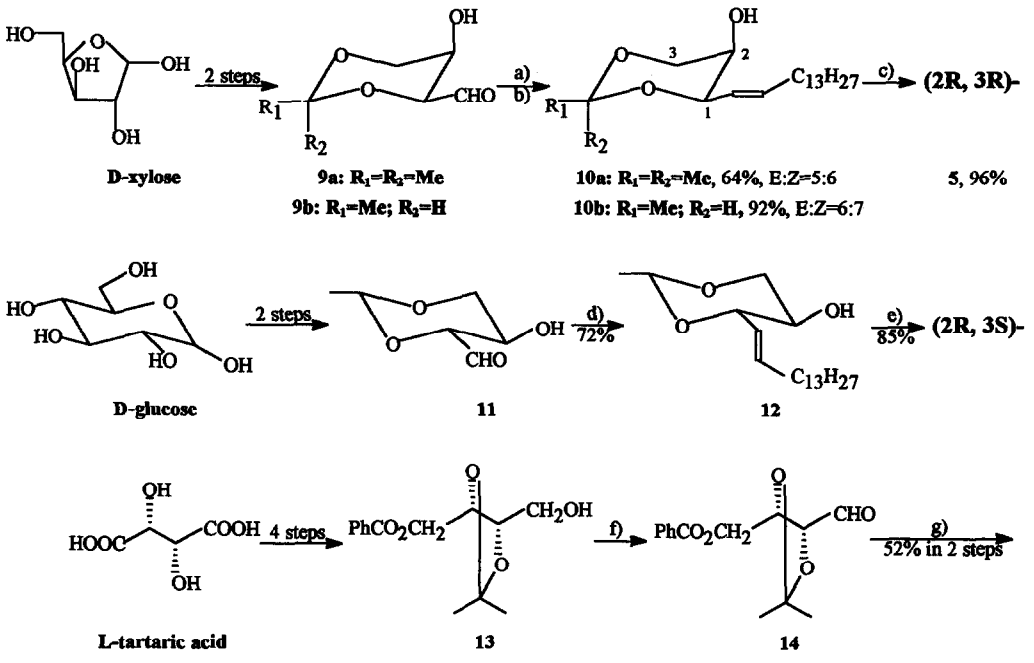
Scheme 1:

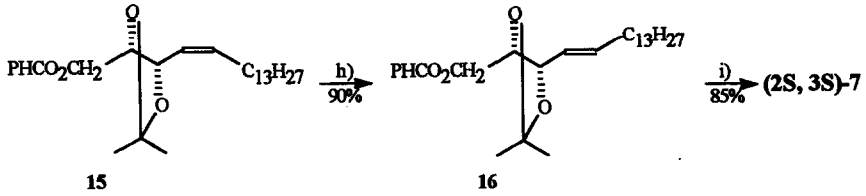


Sphingomyelin derived from sphingosine (**1**) is a major constituent of cell membrane and appears to be important in biological processes on cell surfaces.[2] Recently sphingosine itself has also attracted considerable interest as a potent inhibitor of protein kinase C (PKC), an essential enzyme in cell regulation and signal transduction.[3,4] Moreover, it was reported that all four stereoisomers of sphingosine (**1, 2, 3, 4**) have effective abilities to inhibit PKC.[4] For further biological studies, all sphingosine stereoisomers are needed. Therefore we elaborated the 'chiron' approaches for the synthesis of them.

For syntheses of compounds **5, 6, 7,** aldehydes **9a, 11, 14** were prepared from D-xylose,[5] D-glucose[6] and L-tartaric acid[7] respectively according to known procedures. These aldehydes were then subjected to Wittig reaction with tetradecylenetriphenylphosphorane to provide alkenes **10a, 12, 15** accordingly. The ratio between (E)- and (Z)-configuration were determined as 5:6 for **10a** and 6:1 for **12**. While in the case of **15**, mainly (Z)-isomer was obtained. Thus, an isomerization reaction was brought about for the latter by irradiation in the presence of phenyl sulfide,[8] leading to a 10:1 (E)- and (Z)-isomer mixture from which the desired (E)-isomer was separated. Finally, deprotection of **10a, 12** and **16** gave corresponding trihydroxy compounds (2R, 3R)-**5**, (2R, 3S)-**6**, (2S, 3S)-7 (Scheme 2).

Scheme 2:

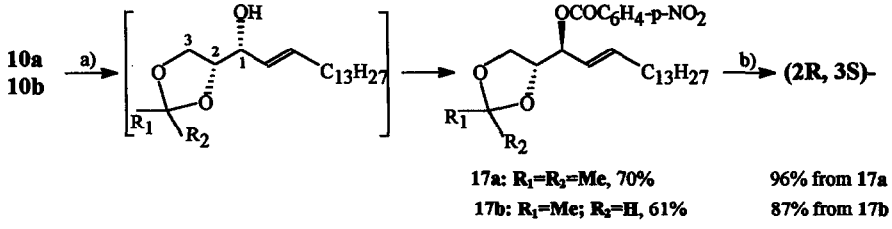




Reagents and conditions: a) $PPh_3C_{14}H_{29}Br$, n-BuLi, THF; b) separation of isomers; c) 80% HOAc-H_2O, 60°C; d) $PPh_3C_{14}H_{29}Br$, LDA, THF; e) PPTS, t-BuOH, 60°C; f) Collin's regent; g) $PPh_3C_{14}H_{29}Br$, LDA, THF; h) PhSSPh, hv; i) K_2CO_3, H_2O, then 80% HOAc-H_2O, 60°C

With compound **10a** in hand, we tried to prepare (2S, 3R)-isomer **8** using a Mitsunobu reaction[9]. However, after deprotection of p-nitrobenzoyl and acetal, the trihydroxy compound obtained showed a -3.3 value of $[\alpha]_D$, which is similar to that of (2R, 3S)-isomer **6** prepared from D-glucose. In view of the fact that the 1,3-isopropylidene acetal is relatively unstable under acid condition, we proposed that a rearrangement reaction perhaps occurred on 1,3-isopropylidene acetal group under Mitsunobu reaction conditions (Scheme 3). This rearrangement might be avoided by using the relatively stable 1,3-ethylene acetal instead of 1,3- isopropylidene acetal.[10]

Scheme 3:

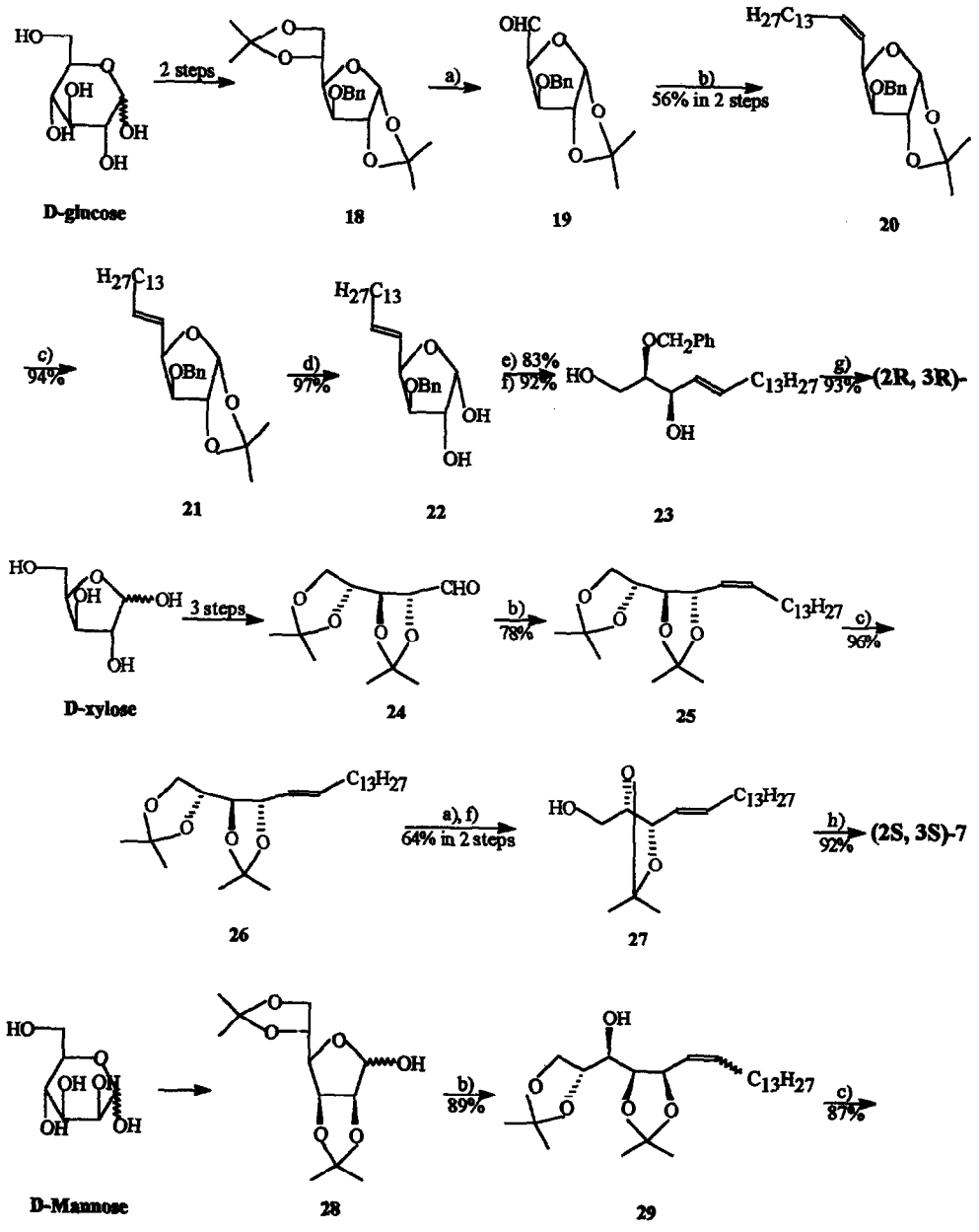


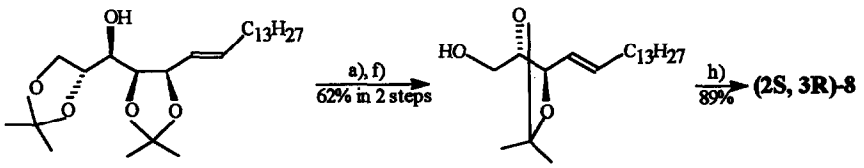
Reagents and conditions: a) p-$NO_2C_6H_4COOH$, PPh_3, $EtO_2CN{=}NCO_2Et$, PhH; b) K_2CO_3, H_2O, then 80% HoAc-H_2O, 60°C

Thus β-hydroxyaldehyde **9b** was therefore prepared by known method from D-galactose,[11] and transformed to alkene **10b** in 92% isolated yield as a 6:7 ratio of (E)- and (Z)-isomer mixture determined by 300 MHz ^1H NMR spectra, from which pure (E)-isomer could be separated by flash chromatography. Unfortunately, there was a rearrangement reaction occurred on **10b** under the Mitsunobu reaction condition as well. The trihydroxy compound provided was once again identified as (2R, 3S)-**6**.

So far we synthesized all stereoisomers of 1, 2, 3-trihydroxy-4-octadecene except the (2S, 3R)-one (**8**), then we turned our attention to the one-pot terminal isopropylidene acetal hydrolysis and subsequent glycol cleavage reaction reported recently by us.[12] Using this efficient reaction as the key step, the synthesis of (2S, 3R)-isomer **8** was reached from D-mannose. We have also developed alternative routes to synthesize (2R, 3R)- and (2S, 3S)- isomers **5**, **7** starting from D-glucose and D-xylose respectively, as shown in Scheme 4.

Scheme 4:


D-glucose
2 steps
18
a)
19
b)
56% in 2 steps
20
c)
94%
21
d)
97%
22
e) 83%
f) 92%
23
g)
93%
(2R, 3R)-
D-xylose
3 steps
24
b)
78%
25
c)
96%
26
a), f)
64% in 2 steps
27
b)
92%
(2S, 3S)-7
D-Mannose
28
b)
89%
29
c)
87%



30 **31**

Bn = $PhCH_2$

Reagents and conditions: a) H_5IO_6, Et_2O; b) $PPh_3C_{14}H_{29}Br$, n-BuLi, THF; c) PhSSPh, hv; d) 1N H_2SO_4, dioxane, reflux; e) $NaIO_4$, $NaHCO_3$, MeOH; f) $NaBH_4$, i-PrOH; g) Li, NH_3(l); h) 80% HOAc-H_2O, 60°C

The known compound **18** prepared from D-glucose[13] was exposed to periodic acid in diethyl ether to furnish aldehyde **19**. Compound **19** was then treated with tetradecylenetriphenylphosphorane, and isomerized to give **21.** Subsequent hydrolysis of isopropylidene acetal, cleavage of glycol followed reduction of the resulting aldehyde led to **23,** which was converted to (2R, 3R)-isomer **5** using Li/liq. NH_3 reduction.

For the syntheses of compound **7, 8,** compounds **24**[14] and **28**[15] were subjected to the above mentioned Wittig reaction and isomerization reaction sequence to yield the corresponding alkene **26** and **30**. Cleavage of the terminal isopropylidene of **26, 30** by exposure them to periodic acid in diethyl ether and subsequently reduction of the resulted aldehydes with sodium borohydride afforded **27** and **31**. Compounds **27** and **31** were deprotected in the usual way to provide (2S, 3S)-**7** and (2S, 3R)-**8** respectively.

In conclusion, we have developed efficient methods for the preparation of four stereoisomers of 1,2,3-trihydroxy-4E-octadencene. Their physical data were shown in Table 1. The syntheses of D-*erythro*-sphingosine (**1**) and L-*threo*-sphingosine (**2**) from compound **5, 6** respectively have already been reported.[16,1d] Thus, the formal syntheses of D-*erythro*-sphingosine (**1**) and L-*threo*-sphingosine (**2**) were reached, and the syntheses of the stereoisomers **3, 4** were also possible by similar methods. The strategy of building the chiral vicinal diol moiety, developed herewith, would be also useful to the syntheses of other biologically active compounds. Some further applications of this strategy for the syntheses of unsaturated fatty acids and new sphingosine type compounds are under investigation in this laboratory and will be reported in due time.

Table 1 The Physical Data of *erythro*- and *threo*-vicinal diol 5, 6, 7, 8

Compound	5	6	7	8
Absolute configuration	2R, 3R	2R, 3S	2S, 3S	2S, 3R
$[\alpha]_D$ (EtOH)	+3.75 (c 0.23)	-3.48 (c 0.78)	-3.84 (c 0.69)	+3.58 (c 0.17)
mp (°C)	60~62	59~60.5	59~61	61~62

Experimental

General: Melting points were uncorrected. IR spectra were recorded with a Shimadzu IR-440 spectrometer. ^{1}H NMR were recorded with TMS as an internal standard on a EM-360A, FX90Q, Varian XL-200, AMX-300, or AMX-600 spectrometer. MS spectra were obtained on a Finnigan 4021 or HP5989A spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MS Autopol polarimeter. Flash column chromatography was performed on silica gel H (10-40 μm) and with petroleum ether-ethyl acetate system as eluent.

Wittig reaction of aldehyde 9a:

A solution of n-BuLi (1 mL of 2.5 N solution in hexane, 2.5 mmol) was added dropwise to a magnetically stirred suspension of tetradecyltriphenylphosphonium bromide (3.19 g, 5.92 mmol) in THF (30 mL) under nitrogen at -40°C. The reaction mixture was stirred for 30 min, and aldehyde **9a**[17] (80 mg, 0.5 mmol) in THF (5 mL) was added. After being stirred at -40°C for 1 hr, the mixture was slowly warmed to rt and stirred for additional 2 hrs. Then it was poured into a stirred ice water, extracted with ether. The organic layer was washed with brine, and dried. The cis/trans isomers were separated by flash chromatography to afford the cis-isomer (60 mg) and trans-isomer (50 mg) of **10a**, total yield 64%: **(E)-isomer**: $[\alpha]_D$= -23.1 (c 0.44, $CHCl_3$) [lit: $[\alpha]_D$= -26 (c 0.7)][5]; ^{1}H NMR ($CDCl_3$, 600MHz) δ 0.88(t, 3H), 1.26(m, 22H), 1.41,1.51(2s, 6H), 2.06(m, 2H), 3.31(s, 1H), 3.81(dd, J=12.2 and 1.9Hz, 1H), 4.06(dd, J=12.2 and 7.0Hz. 1H), 4.31(d, J=6.2Hz, 1H), 5.61(dd, J=15.4 and 7.0Hz, 1H), 5.74(dt, J=15.4 and 8.6Hz, 1H); MS (m/z) 341(M^++1), 322(M^+-H_2O), 183($C_{13}H_{27}$). **(Z)-isomer**: ^{1}H NMR ($CDCl_3$, 600MHz) δ 0.88(t, 3H), 1.26(m, 22H), 1.46,1.48(2s, 6H), 2.06(m, 2H), 3.28(s, 1H), 3.81(dd, J=12.18 and 1.86Hz, 1H), 4.06(dd, J=12.18 and 1.50Hz, 1H), 4.65(d, J=6.6Hz, 1H), 5.55-5.65(m, 2H).

Preparation of compound (2R, 3R)-5:

A solution of the acetal **10a** (20 mg, 0.059 mmol) dissolved in 2 mL of 80% HoAc-H_2O was heated at 60°C for 1 hr under nitrogen. Then the mixture was cooled, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic layer separated was washed with brine and dried with Na_2SO_4. Chromatography on silica gel yielded (2R, 3R)-**5** (17 mg, 96%): $[\alpha]_D$= +3.75 (c 0.23, EtOH); MS (m/z) 239(M^+-$HOCH_2CHOH$), 209($CH{=}CHC_{13}H_{27}$), 183($C_{13}H_{27}$), 61($HOCH_2CHO$).

Wittig reaction of aldehyde 11:

LDA (20 mL, 3.2 mmol) was added dropwise to a stirred solution of tetradecyltriphenylphosphonium bromide (3.29 g, 6.1 mmol) in 5 mL of dry THF at -30°C under nitrogen. The reaction mixture was stirred at -30°C for 30 min and then the aldehyde **11** (222 mg, 1.5 mmol) in 3 mL of dry THF was added. The resulted solution was stirred at -30°C for 20 min, then allowed to warm to rt and stirred for additional 2.5 hrs. The mixture was cooled to -30°C before quenched with 20 mL of ice water, and extracted with EtOAc. Evaporation and purification of the residue by flash chromatography gave 358 mg (72%) of **12** as a wax solid. The ratio between (Z)- and (E)-configuration was determined as *ca.* 1:6 by GC analysis: $[\alpha]_D$ = -7.8 (c 0.24, $CHCl_3$); IR (film) 3400, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.90(t, J=7.4Hz, 3H), 1.25(m, 2H), 1.35(d, J=5.1Hz, 3H), 1.74(br s, 1H), 2.10(t, J=6.3Hz, 2H), 3.46(m, 2H), 3.73(t, J=8.1Hz, 1H), 4.17(m, 1H), 4.71(q, J=5.1Hz, 1H),

5.47(dd, J=15.4 and 7.6Hz, 1H), 5.88(dt, J=15.4 and 6.3Hz, 1H); MS (m/z) 325(M^+-1), 309(M^++1-H_2O), 283(M^++1-CH_3CHO), 265(M^++1-H_2O-CH_3CHO). Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.70; H, 12.03.

Cleavage of acetal 12:

To a stirred solution of the acetal **12** (328 mg, 1 mmol) in t-BuOH (20 mL), p-TsOH (503 mg, 2 mmol) was added. The mixture was stirred at 80°C for 6 hrs under nitrogen, then neutralized with solid K_2CO_3 and extracted with EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel to give 252 mg (85%) of (2R, 3S)-**6**: $[\alpha]_D$= -3.48 (c 0.78, EtOH); MS (m/z) 301(M^++1), 283(M^++1-H_2O), 239(HOCHCH=$CHC_{13}H_{27}$), 91($HOCH_2CHOHCHOH$).

Preparation of compound 15:

A solution of alcohol **13** (1.5 g, 5.68 mmol) in CH_2Cl_2 (20 mL) was added rapidly to a solution of pyridine (5.4 mL, 66.77 mmol) and CrO_3 (2.57 g, 25.7 mmol) in anhydrous CH_2Cl_2 (150 mL) under nitrogen. After stirring for 1 hr at rt, the mixture was diluted with Et_2O, and the solution was filtered through celite, and concentrated. The crude product was directly used in the next Wittig reaction. An analytic sample was obtained by chromatography: ^{1}H NMR ($CDCl_3$, 90MHz) δ 1.41(d, J=4.3Hz, 6H), 4.16(m, 1H), 4.53(m,3H), 7.3-8.1(m, 5H), 9.7(s, 1H); MS (m/z) 265(M^++1), 235(M^+-CHO), 105(PhCO).

To a solution of the phosphonium salt (18.5 g, 34.34 mmol) in THF (50 mL) at -78°C, was added n-BuLi (1.67 M 20 mL, 33.40 mmol), and the resulting carmine solution was stirred at -78°C for 1 hr before the crude aldehyde **14** in THF (25 mL) was added. The temperature was slowly raised to rt. Benzoyl chloride (0.2 mL, 1.72 mmol) was added, and the mixture was stirred for an additional 4 hrs at rt. Then, the mixture was poured into cold brine and extracted with ether. After drying over $MgSO_4$ and evaporation in vacuo, the crude product was purified by chromatography to give 1.30 g (52 % in 2 steps) of alkene **15**: ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.90(t, 3H), 1.24(m, 22H), 1.58(s, 3H), 2.12(m, 2H), 4.00(m, 1H), 4.32(dd, J=12.0 and 4.9Hz, 1H), 4.55(dd, J=12.0 and 4.9Hz, 1H), 4.76(dd, J=8.0 and 6.8Hz, 1H), 5.43(dd, J=11.4 and 8.0Hz, 1H), 5.76(dt, J=11.4 and 8.3Hz, 1H), 7.4-8.4(m, 5H); MS (m/z) 444(M^+), 429(M^+-CH_3), 387(M^++1-Me_2CO).

Isomerization of compound 15:

A 19:1 cyclohexane-dioxane solution (120 mL) of compound **15** (1.0 g, 2.25 mmol) and phenyl sulfide (490 mg, 2.25 mmol) was irradiated with a 125-W high pressure mercury lamp under nitrogen for 6 hrs. The solution was concentrated and chromatographed to yield 0.9 g (90%) of the trans-isomer **16**: $[\alpha]_D$= -4.80 (c 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.88(t, 3H), 1.24(m, 22H), 1.44(s, 3H), 1.47(s, 3H), 2.05(m, 2H), 4.02(dd, J=8.0 and 4.0Hz, 1H), 4.35(d, J=12.0Hz, 1H), 4.37(d, J=12.0Hz, 1H), 4.50(dd, J=12.0 and 4.0Hz, 1H), 5.50(dd, J=16.0 and 8.0Hz, 1H), 5.83(dt, J=16.0 and 6.6Hz, 1H), 7.30-8.10(m, 5H).

Deprotection of compound 16:

To a stirred solution of **16** (1.0 g, 2.25 mmol) in MeOH (20 mL) at rt was added solid K_2CO_3 (0.1 g, 2.5 mmol). After being stirred at rt for 1 hr, the mixture was acidified with 80% HOAc, and stirred for 1 hr at 60°C. The reaction mixture cooled was neutralized with solid $NaHCO_3$ and diluted with EtOAc, washed with brine and

dried. Purification by flash chromatography gave (2S, 3S)-7 (0.57 g, 85%): $[\alpha]_D$= -3.84 (c 0.69, EtOH); MS (m/z) 301(M^++1), 283(M^++1-H_2O), 239(HOCHCH=$CHC_{13}H_{27}$), 91($HOCH_2CHOHCHOH$).

Mitsunobu reaction of compound 10a:

A mixture of **10a** (34 mg, 0.1 mmol), triphenylphosphine (133 mg, 0.5 mmol), p-nitrobenzoic acid (73.5 mg, 0.44 mmol), and dry benzene (2 mL) was stirred at rt for 15 min. After the addition of diethyl azodicarboxylate (0.08 mL, 0.5 mmol), the mixture was stirred at rt overnight. The solution was then evaporated and flash chromatographed to provide **17a** (34.4 mg, 70%): $[\alpha]_D$= +28.33 (C 0.66, $CHCl_3$), ^1H NMR ($CDCl_3$, 600MHz) δ 0.87(t, 3H), 1.25(m, 22H), 1.45,1.56(2S, 6H), 2.02(m, 2H), 3.79(dd, J=11.5 and *ca.*0Hz, 1H), 4.11(m, 1H), 4.29(t, J=7.8Hz, 1H), 4.98(m,1H), 5.42(dd, J=15.4 and 7.9Hz, 1H), 5.74(dt, J=15.4 and 7.9Hz, 1H), 8.15-8.31(m, 4H); MS (m/z) 474(M^+-CH_3), 339(M^+-p-$NO_2C_6H_4CO$), 183($C_{13}H_{27}$), 150(p-$NO_2C_6H_4CO$).

Deprotection of compound 17a:

Following the deprotection procedure of compound **16**, compound **6** was obtained from **17a** (25 mg, 0.05 mmol) in 96% yield (14.7 mg): $[\alpha]_D$= -3.32 (c 0.34, EtOH); MS (m/z) 301(M^++1), 283(M^++1-H_2O), 239(HOCHCH=$CHC_{13}H_{27}$), 91($HOCH_2CHOHCHOH$).

Wittig reaction of aldehyde 9b:

This reaction was carried out according to the procedure for **9a**. Thus, from 380 mg (2.6 mmol) of aldehyde **9b**[17] was isolated 782 mg (92%) of alkene **10b** as a mixture of (E)- and (Z)-isomer. The ratio between (E)- and (Z)-isomer was determined as *ca.* 6:7 by ^1H NMR and the pure (E)-isomer was obtained by flash chromatography: mp 54-56°C; $[\alpha]_D$= -29.23 (c 0.51, $CHCl_3$), IR (KBr) 3450, 1460, 1120, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz), δ 0.88(t, J=6.6Hz, 3H), 1.26-1.37(m, 25H), 2.10(m, 2H), 2.42(br s, 1H), 3.39(dd, J=11.6 and 1.0Hz, 1H), 3.86(m, 1H), 4.05(m, 1H), 4.16(br d, J=5.6Hz, 1H), 4.80(q, J=4.7Hz, 1H), 5.60(dd, J=15.9 and 5.6Hz, 1H), 5.81(dt, J=15.9 and 6.5Hz, 1H); MS (m/z) 326(M^+), 311(M^+-CH_3), 309(M^++1-H_2O), 283(M^+-$CH_2CH_2CH_3$). Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.56; H, 11.75.

Mitsunobu reaction of compound 10b:

Following the Mitsunobu reaction procedure of compound **10a**, compound **17b** was obtained from **10b** (720 mg, 2.21 mmol) in 61% yield (640 mg): mp 61-63°C; $[\alpha]_D$= +36.05 (c 0.4 $CHCl_3$); IR (KBr) 1720, 1600, 1350, 1260, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=7.0Hz, 3H), 1.26(m, 22H), 1.39(d, J=5.0Hz, 3H), 2.00(m, 2H), 3.64(m, 1H), 4.10(m, 1H), 4.34(dd, J=10.5 and 5.3Hz, 1H), 4.81(q, J=5.0Hz, 1H), 4.97(m, 1H), 5.47(dd, J=15.3 and 6.9Hz, 1H), 5.82(dt, J=15.3 and 6.9Hz, 1H), 8.30-8.13(m, 4H); FAB MS (m/z) 514 (M^++39), 150(p-$NO_2C_6H_4CO$). Anal. Calcd for $C_{27}H_{41}NO_6$: C, 68.18; H, 8.69; N, 2.95. Found: C, 67.86; H, 8.40; N, 2.65.

Deprotection of compound 17b:

Following the deprotection procedure of compound **16**, compound **6** was obtained from **17b** (100 mg, 0.21 mmol) in 87% yield (55 mg): mp 59-60.5°C; $[\alpha]_D$= -3.2 (c 0.03 EtOH); IR (film) 3400, 1620, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.9Hz, 3H), 1.30(m, 22H), 2.08(m, 2H), 3.65-3.82(m, 3H),

4.23(m, 1H), 5.52(dd, J=15.4 and 6.9Hz, 1H), 5.79(dt, J=15.3 and 8.3Hz, 1H); MS (m/z) 283(M^++1-H_2O), 239(CHOHCH=$CHC_{13}H_{27}$), 183($C_{13}H_{27}$), 91 ($HOCH_2CHOHCHOH$), 61($HOCH_2CHO$). Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.37.

Reaction of Acetal 18 with periodic acid in ether:

Acetal **18** (2.9 g, 8.3 mmol) in 10 mL of Et_2O was added at rt under nitrogen atmosphere to a well-stirred suspension of periodic acid (2.92 g, 12.81mmol) in dry ether (100 mL). Stirring was continued for 10 hrs, and the reaction mixture was filtered and evaporated. The residue was used directly in the next Wittig reaction. An analytic sample was obtained by chromatography: $[\alpha]_D$= -81.6 (c 0.85, $CHCl_3$) [lit: $[\alpha]_D$= -86.5 (c)][12]; ^1H NMR ($CDCl_3$, 60MHz) δ 1.30,1.46(2s, 6H), 4.03-4.35(m, 3H), 4.56(s, 2H), 6.10(d, 1H), 7.30(m, 5H), 9.65(s, 1H).

Wittig reaction of aldehyde 19:

This reaction was carried out according to the procedure for **9a**. Thus from the crude aldehyde **19** was isolated 2.13g (56% in 2 steps) of alkene **20**: mp 40-42°C; $[\alpha]_D$= -68.5 (c 0.8 $CHCl_3$); IR (KBr) 1470, 1450, 1090, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.9Hz, 3H), 1.26(m, 22H), 1.32,1.51(2s, 6H), 2.08(m, 2H), 3.82(m, 1H), 4.60(m, 3H), 4.95(m, 1H), 5.67(m, J=11.1Hz, 2H), 5.95(d, J=3.8Hz, 1H), 7.29(m, 5H); FAB MS (m/z) 459(M^++1), 458(M^+). Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.02; H, 10.38.

Isomerization of alkene 20:

Following the isomerization reaction procedure of compound **15**, compound **21** was obtained from **21** (1.35 g, 2.95 mmol) in 94% yield (1.27 g): mp 40.5-41.4°C; $[\alpha]_D$= -32.6 (c 0.3 $CHCl_3$); IR (film) 1500, 1450, 1380, 1080, 1020, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.87(t, J=6.8Hz, 3H), 1.27(m, 22H), 1.33,1.51(2s, 6H), 2.12(m, 2H), 3.83(d, J=3.1Hz, 1H), 4.62(m, 4H), 5.68(dd, J=15.5 and 7.9Hz, 1H), 5.87(dt, J=15.5 and 6.55Hz, 1H), 5.95(d, J=3.8Hz, 1H), 7.32(m, 5H); MS (m/z) 459(M^++1), 413, 91($PhCH_2$). Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.09; H, 10.19.

Hydrolysis of acetal 21:

To a solution of acetal **21** (1.2 g, 2.62 mmol) in dioxane (15 mL) was added 5 mL of 1N H_2SO_4. After refluxing for 4 hrs, the solvent was removed by rotatory evaporator. The residue was diluted with EtOAc, neutralized with saturated $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with EtOAc. Concentration and chromatography gave 1.06 g (97%) of the product **22** as a solid: mp 70-72°C; $[\alpha]_D$= +6.05 (c 0.97, $CHCl_3$); IR (KBr) 3350, 1500, 1460, 1450, 1110, 1010, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=7.0Hz, 3H), 1.26(m, 22H), 2.04(m, 2H), 2.53(br s, 2H), 4.12(m, 2H), 4.23(m, 1H), 4.56-4.70(m, 3H), 5.63(dd, J=15.5 and 8.0Hz, 1H), 5.77(dt, J=15.5 and 6.6Hz, 1H), 7.32(m, 5H); MS (m/z) 419(M^++1), 418(M^+), 342(M^+-C_6H_4), 340(M^+-C_6H_6). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.61; H, 10.38.

Cleavage of glycol 22 and reduction of the resulted aldehyde:

Glycol **22** (0.67 g, 1.6 mmol) was dissolved in 20 mL of MeOH containing sodium metaperiodate (0.74 g, 3.46 mmol) and $NaHCO_3$ (0.29 g, 3.46mmol). After stirring overnight at rt, the mixture was evaporated. The

residue was suspended in Et_2O and filted. Flash chromatography to yield 0.514 g (83%) of the aldehyde, which was used immediately in the next reduction step: IR (film) 3450, 1720, 1500, 1460, 1450, 1080, 1020, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 60MHz) δ 0.96(t, 3H), 1.4(m, 22H), 2.2(m, 2H), 3.6(br s, 1H), 4.85(m, 3H), 5.45(m, 1H), 5.8(m, 2H), 7.5(m, 5H), 9.75(d, 1H).

To a suspension of sodium borohydride (11 mg, 0.29 mmol) in i-PrOH (1 mL), a solution of the aldehyde (93 mg, 0.24 mmol) in 1 mL of i-PrOH was added at 0°C. After stirring for an additional 30 min at 0°C, the mixture was allowed warming to rt and stirred overnight. The mixture was poured into cold 5% HOAc solution, extracted with ether. The extract was dried and concentrated. The residue was chromatographed to give 86 mg (92%) of the product as a solid: mp 43-44°C; $[\alpha]_D$= -12.32 (c 0.36, $CHCl_3$); IR (KBr) 3400, 1460, 1040, 960 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz) δ 0.88(t, J=7.0Hz, 3H), 1.26(m, 22H), 2.03(m, 2H), 2.69(br s, 1H), 3.42(dd, J=5.5 and 4.6Hz, 1H), 3.63(dd, J=11.9 and 4.5Hz, 1H), 3.78(dd, J=11.6 and 4.3Hz, 1H), 4.20(dd, J=6.49 and 6.3Hz, 1H), 4.67(dd, J=18.6 and 11.5Hz, 2H), 5.48(dd J=15.3 and 7.1Hz, 1H), 5.77(dt, J=15.3 and 8.4Hz, 1H), 7.35(m, 5H); MS (m/z) 390(M^+), 372(M^+-H_2O), 259(M^+-CH_2OH). Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84. Found: C, 76.67; H, 10.88.

Reductive cleavage of benzyl ether 23:

To ammonia (*ca.* 40 mL) cooled in dry ice-acetone bath, lithium (250 mg, 35.7 mmol) was added and stirred until dissolved. Then a solution of benzyl ether **23** (0.4 g, 1.03 mmol) in 5 mL of dry Et_2O was added dropwise. After being stirred for 15 min, the cooling bath was removed, and ammonia was evaporated by continuous stirring overnight. The residue was diluted with brine and extracted with EtOAc. After drying over $MgSO_4$, the combined organic layer was concentrated and chromatographed to provide (2R, 3R)-**5** (0.286 g, 93%) as a solid: mp 60-62°C; $[\alpha]_D$= +4.05 (c 0.15, $CHCl_3$); IR (KBr) 3400, 1080, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=7.1Hz, 3H), 1.26(m, 22H), 2.06(m, 2H), 3.57-3.77(m, 4H), 4.11(dd, J=6.3 and 6.3Hz, 1H), 5.50(dd, J=15.4 and 7.1Hz, 1H), 5.80(dt, J=15.4 and 6.7Hz, 1H); MS (m/z) 283(M^+-H_2O+1), 239(M^+-$HOCH_2CHOH$), 183($C_{13}H_{27}$). Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.86; H, 12.33.

Wittig reaction of aldehyde 24:

This reaction was carried out according to the procedure for **9a**. Thus from aldehyde **24** (1.28g, 5.57mmol) was isolated 1.78g (78%) of alkene **25**: $[\alpha]_D$= +0.94 (c 0.96, $CHCl_3$); IR (film) 1460, 1240, 1220, 1060, 880, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, 3H), 1.26(m, 22H), 1.38,1.43(2s, 6H), 1.44(s, 6H), 2.16(m, 2H), 3.26-4.12(m, 4H), 4.65(m, 1H), 5.37(dd, J=10.9 and 7.4Hz, 1H), 5.72(dt, J=10.9 and 7.4Hz, 1H); MS (m/z) 410(M^+), 101; Anal. Calcd for $C_{25}H_{46}O_4$: C, 73.12; H, 11.29. Found: C, 73.74; H, 11.78.

Isomerization of alkene 25:

Following the isomerization reaction procedure of compound **15**, compound **26** was obtained from **25** (1.28 g, 3.12 mmol) in 96% yield (1.23 g): $[\alpha]_D$= -1.7 (c 0.2, $CHCl_3$); IR (film) 1380, 1220, 1070, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=7.0Hz, 3H), 1.26(m, 22H), 1.43(s, 12H), 2.06(m, 2H), 3.62-4.12(m, 4H), 4.20(dd, J=8.3 and 8.3Hz, 1H), 5.41(dd, J=15.2 and 7.0Hz, 1H), 5.83(dt, J=15.2 and 5.8Hz, 1H); FAB MS (m/z) 395(M^+-CH_3). Anal. Calcd for $C_{25}H_{46}O_4$: C, 73.12; H, 11.29. Found: C, 73.10; H, 11.18.

Cleavage of terminal glycol acetal 26 and reduction of the resulted aldehyde:

The cleavage of terminal glycol acetal **26** (1.729 g, 4.2 mmol) was carried out according to the procedure of the reaction of acetal **18** with periodic acid in ether: IR (film) 1700, 1580, 1460, 1380, 1210, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 60MHz) δ 0.9(t, 3H), 1.27(m, 22H), 1.45(s, 6H), 2.18(m, 2H), 4.9(m, 2H), 5.6(m, 2H), 9.7(d, 1H).

The crude aldehyde was subjected to reduction according to the procedure for the preparation of compound **23** to yield **27** (0.918 g, 64% in 2 steps): $[\alpha]_D$= -1.5 (c 0.2, $CHCl_3$); IR (film) 3400, 1580, 1440, 1020, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.9Hz, 3H), 1.26(m, 22H), 1.43,1.44(2s, 6H), 2.04(m, 2H), 3.55-3.85(m, 3H), 4.10(dd, J=6.0 and 5.2Hz, 1H), 5.44(dd, J=15.3 and 8.0Hz, 1H), 5.83(dt, J=15.3 and 6.7Hz, 1H); MS (m/z) 340(M^+), 325(M^+-CH_3), 323(M^++1-H_2O), 183($C_{13}H_{27}$). Anal. Calcd for $C_{21}H_{40}O_3$: C, 74.06; H, 11.84. Found: C, 74.40; H, 11.51.

Hydrolysis of acetal 27:

Following the hydrolysis procedure of acetal **10a** in the preparation of (2R, 3R)-**5**, compound (2S, 3S)-7 was obtained from **27** (825 mg, 2.43 mmol) in 92% yield (668 mg): mp 59-61°C; $[\alpha]_D$= -3.67 (c 0.47, $CHCl_3$); IR (KBr) 3400, 1460, 1080, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.8Hz, 3H), 1.26(m, 22H), 2.04(m, 2H), 2.51(br s, 3H), 3.55-3.76(m, 3H), 4.09(dd, J=6.4 and 5.6Hz, 1H), 5.47(dd, J=15.5 and 7.2Hz, 1H), 5.81(dt, J=15.5 and 6.6Hz, 1H); MS (m/z) 283(M^++1-H_2O), 239(M^+-$HOCH_2CH_2OH$). Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.84; H, 12.42.

Wittig reaction of compound 28:

This reaction was carried out according to the procedure for **9a**. Thus from compound **28** (2.0g, 7.7mmol) was isolated 2.05g of cis-isomer and 1.03g of trans-isomer of **29**, total yield 89%: **Z-isomer**: $[\alpha]_D$= -42.5 (c 1.1, $CHCl_3$); IR (film) 3450, 1460, 1380, 1210, 1040, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.87(t, J=6.4Hz, 3H), 1.25(m, 22H), 1.34,1.37,1.41,1.52(4s, 12H), 2.10(m, 2H), 3.42-4.36(m, 5H), 5.07(dd, J=7.4 and 7.3Hz, 1H), 5.72-5.67(m, $J_{6,7}$=10.6Hz, 2H); MS (m/z) 440(M^+), 425(M^+-CH_3), 423(M^+-H_2O+1). Anal. Calcd for $C_{26}H_{48}O_5$: C, 70.87; H, 10.98. Found: C, 71.03; H, 11.44.

Isomerization of alkene 29:

Following the isomerization reaction procedure of compound **15**, compound **30** was obtained from **29** (2.55 g, 5.8 mmol) in 87% yield (2.219 g): $[\alpha]_D$= -19.4 (c1.2, $CHCl_3$); IR (film) 3450, 1460, 1380, 1370, 1210, 1120, 1070, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.9Hz, 3H), 1.26(m, 22H), 1.34,1.38,1.39,1.51(4s, 12H), 2.07(m, 2H), 3.40-4.32(m, 5H), 4.66(dd, J=7.7 and 7.6Hz, 1H), 5.70(dd, J=15.4 and 8.0Hz, 1H), 5.82(dt, J=15.4 and 6.5Hz, 1H); MS (m/z) 440(M^+), 439(M^+-1). Anal. Calcd for $C_{26}H_{48}O_5$: C, 70.87; H, 10.98. Found: C, 70.72; H, 11.09.

Cleavage of terminal glycol acetal 30 and reduction of the resulted aldehyde:

The cleavage of terminal glycal acetal **30** (590 mg, 1.34 mmol) was carried out according to the procedure for acetal **18**: IR (film) 1700, 1470, 1380, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 90MHz) δ 0.86(t, 3H), 1.31(m, 2H), 1.43,1.60(2s, 6H), 2.06(m, 2H), 4.83(m, 2H), 5.88(m, 2H), 9.50(d, 1H); MS (m/z) 323(M^+-CH_3).

The crude aldehyde was subjected to reduction according to the procedure for the preparation of compound **23** to yield **31** (283 mg, 62% in 2 steps): $[\alpha]_D$= -19.2 (c 1.8, $CHCl_3$); IR (film) 3400, 1370, 1210, 1030, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=6.8Hz, 3H), 1.26(m, 22H), 1.48(s, 6H), 2.05(m, 2H), 2.56(br s, 1H), 3.92(m, 3H), 4.23(m, 1H), 5.42(m, 1H), 5.80(m, 1H); FAB MS (m/z) 341(M^++1), 322(M^+-H_2O).

Hydrolysis of acetal 31:

Following the hydrolysis procedure of acetal **10a** in the preparation of (2R, 3R)-**5**, compound (2S, 3R)-**8** was obtained in 89% yield (143 mg): mp 61-62°C; $[\alpha]_D$= +4.5 (c 0.06, $CHCl_3$), $[\alpha]_D$= +3.58 (c 0.2, EtOH); IR (KBr) 3400, 1080, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88(t, J=7.0Hz, 3H), 1.26(m, 22H), 2.04(m, 2H), 3.66-3.75(m, 3H), 4.22(m, 1H), 5.52(dd, J=15.5 and 6.9Hz, 1H), 5.79(dt, J=15.6 and 8.5Hz, 1H); MS (m/z) 283(M^++1-H_2)), 239(M^+-$HOCH_2CH_2OH$), 91($HOCH_2CHOHCHOH$), 61($HOCH_2CHO$). Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.33.

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