Tetrahedron Vol. 43, No. 16, pp. 3803 to 3816, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00
Pergamon Journals Ltd.

PLATELET ACTIVATING FACTOR SYNTHETIC STUDIES[1]

Ulrike Peters [a], Wassja Bankova [b], and Peter Welzel* [a]

[a] Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum

[b] Bulgarian Academy of Sciences, Institute of Organic Chemistry
1113 Sofia (Bulgaria)

(*Received in Germany* 23 *May* 1987)

Abstract - From the mannitol derivatives **8** and **37** both enantiomeric series of optically active glycerol derivatives are easily available as exemplified by the synthesis of known precursors of PAF (**6**) and ent-**6**.

Introduction

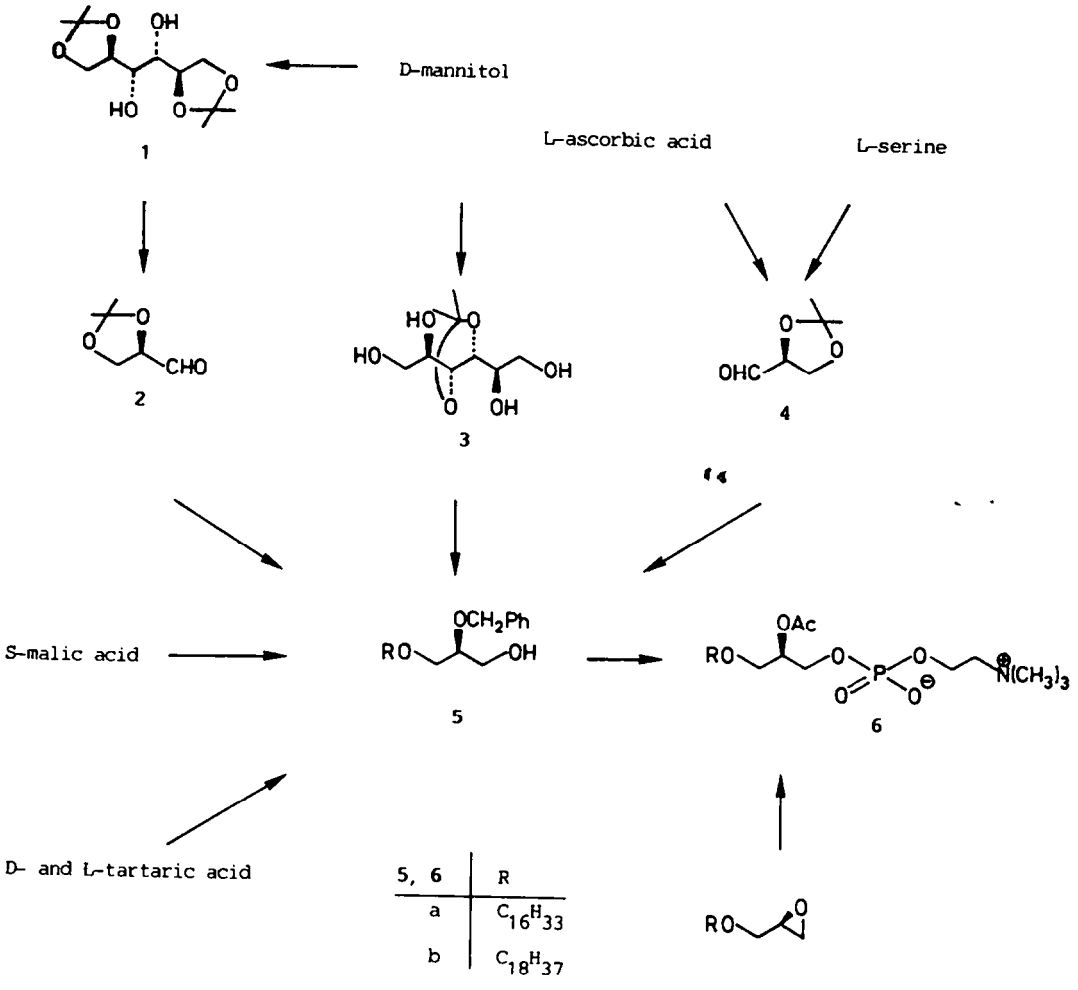
Optically active glycerol derivatives play an important role in organic synthesis as "chiral C_3 building blocks".[2-4] They are available by degradation of carbohydrates,[2-8] from L-serine,[9] (S)-(-)malic acid,[10] D- and L-tartaric acid,[11] from glycerol or an achiral glycerol derivative by enantioselective acylation,[12] by enantio- or diastereoselective reduction of 1-hydroxypropanone derivatives,[13-15] by Sharpless epoxidation of allyl alcohol,[16] via diastereoselective reduction of homochiral ß-keto sulfoxides,[17] and by enzyme-catalyzed ester hydrolysis of 1,3-bis-acetoxy-2-benzyloxy-propane.[18-20] The most popular glycerol derived chiral C_3 building blocks[21] are **2** and **4** which are readily available from the mannitol derivative **1**[2,3] and L-ascorbic acid,[8] respectively. However, it has been pointed out, that for certain optically active compounds with an unsymmetrically substituted glycerol unit, such as simple glycerol esters and ethers, phospholipids,[6] or glycolipids[22] (many of which are important cell-wall and membrane constituents), **2** and **4**, respectively, may not be the starting materials of choice because extensive functional group manipulations are sometimes required.[5,7] A case in question is the platelet activating factor (PAF, **6**), a mediator of many physiological responses, such as anaphylaxis, inflammation, platelet aggregation, and hypotension.[23] Besides **2** (from which straightforwardly only ent-**6** is available, for the synthesis of **6** inversion of configuration at C-2 is necessary)[23-28] and **4**,[27]

(S)-malic acid[10], D- and L-tartaric acid,[11]
the 3,4-acetonide of D-mannitol (**3**),[6] and epoxide **7**[29]

have been used as starting materials. In most cases the 2-benzyl compound **5** was the precursor to **6**. In the very last steps the benzyl group was removed hydrogenolytically and the acetyl group was introduced. This methodology avoids complicating acetyl migrations.
Some time ago, we have shown that **8** is a very convenient precursor of certain optically active glycerol derivatives.[7,30,31] It is the purpose of the present paper to demonstrate, that **5** and related compounds are readily available in both enantiomeric forms from **8** and **37**.

Synthesis of ent-6a and 6a from 8

Alkylation of **8** with benzyl bromide and allyl bromide provided **9** and **10**, respectively, which on acid-catalyzed acetal cleavage furnished **12** and **18**. Selective reactions in the 1- and 6-position of **12** with pivaloyl chloride, benzoyl chloride, tert-butyldiphenylsilyl chloride, trityl chloride and tosyl chloride proceeded smoothly to give **13**, **14**, **15**, **16**, and **17** in good to excellent yields. Diol cleavage was performed either with sodium periodate (**13**, **14**, **15**, and **17**) or with lead tetraacetate (**16**). After immediate reduction of the intermediate glyceraldehyde derivatives with sodium borohydride **24** - **28** were obtained in yields ranging from 69% to 94%.
In the case of **24**, **25**, and **26** the optical purity was examined. The diastereomeric Mosher esters[32] derived from racemic **25**/ent-**25** displayed two well-separated methoxy signals in the 400 MHz ^{1}H NMR spectrum. The sample of **25** derived from **14** was shown to have an e.e. of 43 ± 2% (determined by Mosher ester analysis). The $[\alpha]_D^{20}$ value of this sample of **25** was



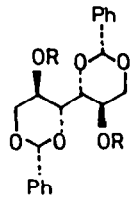
Scheme 1

-6.1 ± 0.2, corresponding to an $[\alpha]_D^{20} = -14.3 \pm 0.7$[33] for optically pure **25**. The loss of optical purity can be attributed to benzoyl group migration under the conditions of the borohydride reduction of the intermediate glyceraldehyde derivative. Thus (see Scheme 3), cleavage of **14** with $NaIO_4$ and subsequent reduction with $NaBD_4$ provided a 66 ($\pm$ 2) : 34 ($\pm$ 1) mixture of [1-D_1]-**25** and [3-D_1]-ent-**25** ($[\alpha]_D^{20} = -4.5$), as determined by ^2H NMR analysis. Assuming that the optical rotation is practically uneffected by the ^2H substitution, an $[\alpha]_D^{20} = -13.9 \pm 0.7$ of optically pure **25** can be estimated from this experiment.

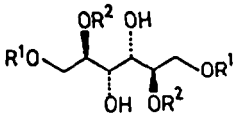
Using the same type of analysis (in this case the nicely separated tert-butyl signals of the diastereomeric Mosher esters were used) a sample of **24** which was obtained from **13** ($NaBH_4$ reduction: 45 min at 20°C) was shown to have an e.e. of 78%. In a second experiment ($NaBH_4$ reduction: 1.5 h at 20°C) a sample of **24** was obtained from **13** which had an e.e. of 57%. In this case, too, racemization had its origin in acyl group migration: Reduction of the intermediate glyceraldehyde derivative with $NaBD_4$ (45 min at 20°C) gave a 90 : 10 mixture of [1-D_1]-**24** and [3-D_1]-ent-**24** (^2H NMR analysis).

The diastereomeric Mosher esters[32] of the racemate **26**/ent-**26** displaced two tert-butyl signals in the 400 MHz ^1H NMR spectrum and many double signals in the ^{13}C NMR spectrum. On the other hand, the Mosher ester derived from a sample of **26** (obtained from **15**) furnished only one tert-butyl ^1H NMR signal and a single set of carbon resonances in the ^{13}C NMR spectrum. No trace of the second diastereoisomer could be detected in this case.

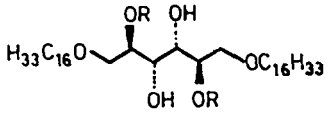
The alkylation of the silyl ether **16** with hexadecyl bromide and tosylate, respectively, was accompanied by extensive silyl group migration. Besides **31**, the disilyl ether **32**, the dialkylated compound **33** were isolated as well as **5a** which turned out to be racemic. **31** was



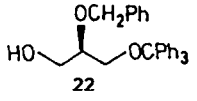
	R
8	H
9	CH_2Ph
10	All
11	$CHPh_2$



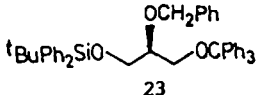
	R^1	R^2
12	H	CH_2Ph
13	$COC(CH_3)_3$	CH_2Ph
14	COPh	CH_2Ph
15	Si^tBuPh_2	CH_2Ph
16	CPh_3	CH_2Ph
17	Tos	CH_2Ph
18	H	All
19	H	$CHPh_2$



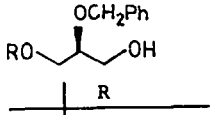
	R
20	CH_2Ph
21	$CHPh_2$



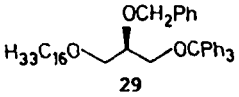
22



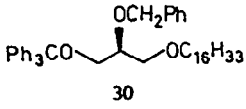
23



	R
24	$COC(CH_3)_3$
25	COPh
26	Si^tBuPh_2
27	CPh_3
28	Tos



29



30

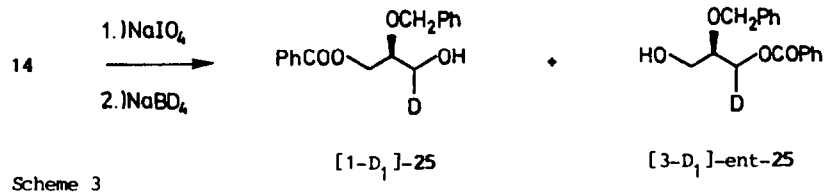
5a

ent-5a

6a

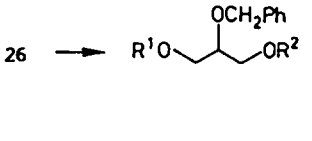
ent-6a

Scheme 2

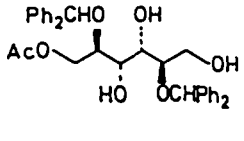


Scheme 3

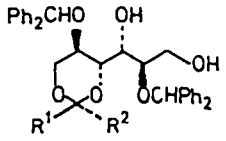
desilylated to give **5a**, which was also racemic.[34]
Alkylation of the trityl compound **27** proceeded uneventfully to give **30** in 86% yield. **30** can be converted to ent-**6a** by methods reported in the enantiomeric series.[11] To reach the PAF series itself, **26** was tritylated to give **23** (96%). Desilylation of **23** provided **22** (91%), which has already been converted to **6a**.[11]
We have also considered the possibility to obtain **6a** from **12** by a more direct route. In principle, this can be achieved by direct alkylation in the 1- and 6-position with a hexadecyl derivative. Unfortunately, until now we have been unable to find a satisfactory solution to this problem. Reaction of **12** with hexadecyl mesylate in the presence of sodium hydride furnished the desired **20** in poor 14% yield along with mono-, isomeric di- and the trialkylated products.[35] The same result was obtained under phase-transfer conditions (15% of **20**). Oxidative cleavage of **20** ($PbOAc_4$) followed by $NaBH_4$ reduction provided the PAF precursor **5a** in 72% yield.



	R^1	R^2
31	Si^tBuPh_2	$C_{16}H_{33}$
32	Si^tBuPh_2	Si^tBuPh_2
33	$C_{16}H_{33}$	$C_{16}H_{33}$



34



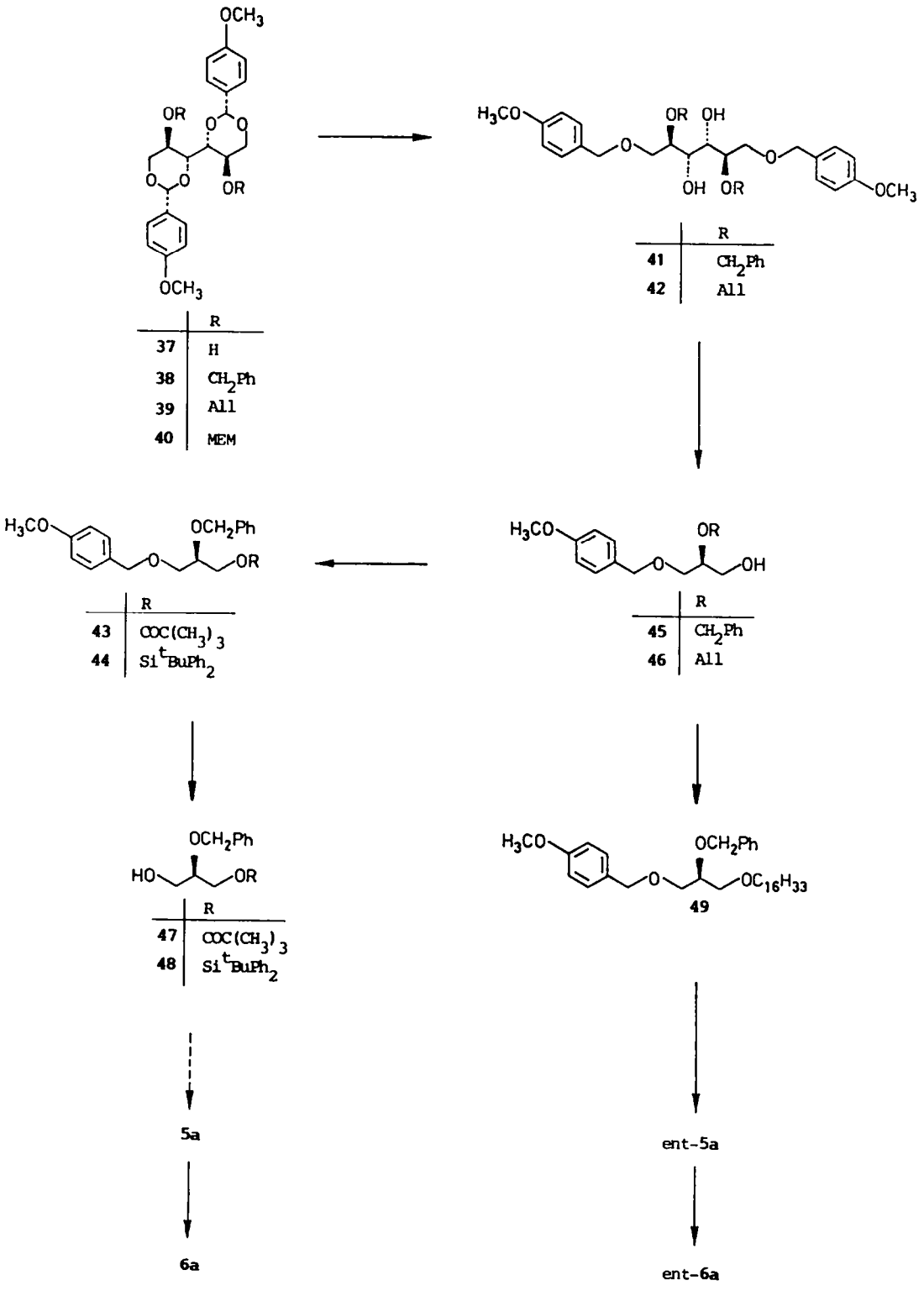
	R^1	R^2
35	Ph	H
36	H	Ph

Scheme 4

With the idea of shielding the 3- and 4-positions in compounds of type **12** from alkylation, the bis-diphenylmethyl ether **11** was prepared from **8**. Here exists the problem of two protecting groups with similar sensitivity towards acidic conditions. In the event, cleavage of **11** in 80% acetic acid led to a mixture of products from which **19** was isolated in 41% yield along with the acetate **34** (23%), and a 1:3 mixture of the monoacetals **35** and **36** (15%). The alkylation of **19** proceeded as disappointing as that of **12**. Under phase-transfer conditions a mixture of products was formed from which the desired **21** was obtained in 26% yield.[35]

Synthesis of optically active glycerol derivatives from **37**.

We also investigated the chemistry of the bis-methoxy analogue **37** of 1,3:4,6-di-O-benzylidene-D-mannitol (**8**) because it is known that 6-membered acetals of 4-methoxybenzaldehyde can be reductively cleaved under very mild conditions to give 4-methoxybenzyl ethers.[36] **37** was dialkylated to give **38** (91%), **39** (83%), and **40** (70%). Reductive acetal cleavage in **38** and **39** with sodium cyanoborohydride - trifluoroacetic acid led to the formation of the 1,6-di-O-methoxybenzylated compounds **41** (78%) and **42** (76%), respectively. $NaIO_4$ cleavage followed by sodium borohydride reduction provided the glycerol derivative **45** (86%) and **46** (67%). Alkylation of **45** with hexadecyl bromide gave **49** in 90% yield. The methoxybenzyl protecting group was then oxidatively removed with cerium(IV) ammonium nitrate in acetonitrile-water to provide ent-**5a**, a known precursor to ent-**6a**, in 82% yield. This seems to be the most direct and efficient access to compounds of the ent-PAF type, starting from D-mannitol.
From compounds such as **45** the PAF series can be reached by two functional group manipulations. Along this line we prepared (via **43** and **44**, respectively) the (R)-compounds **47** and **48** which are the enantiomers of **24** and **26**, described above.



	R
37	H
38	CH_2Ph
39	All
40	MEM

	R
41	CH_2Ph
42	All

	R
43	$COC(CH_3)_3$
44	Si^tBuPh_2

	R
45	CH_2Ph
46	All

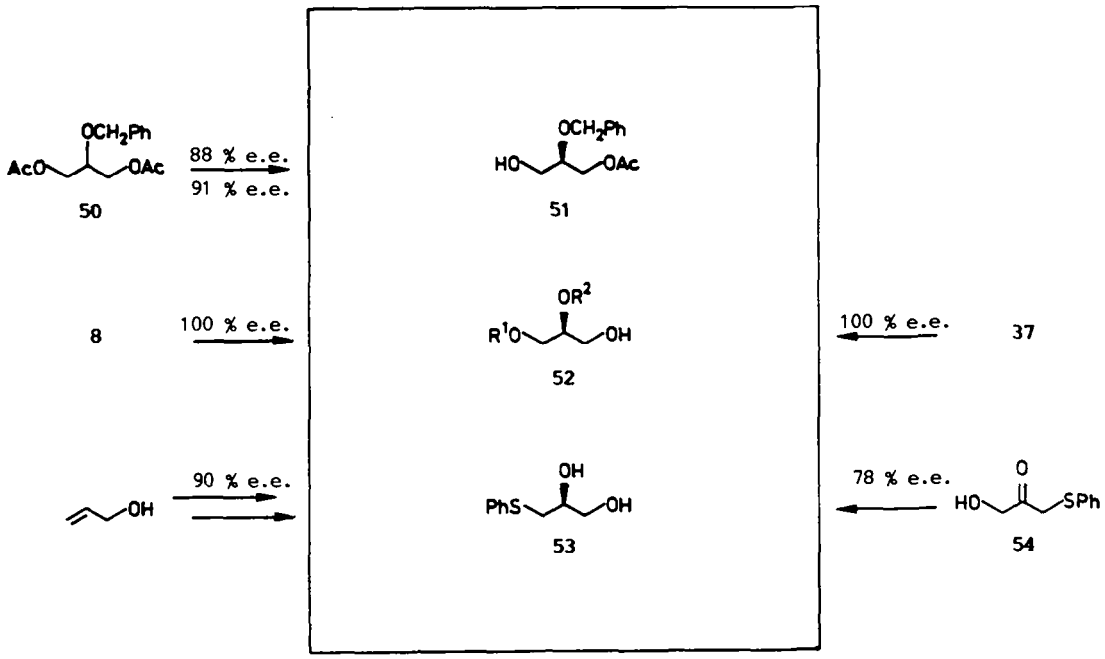
	R
47	$COC(CH_3)_3$
48	Si^tBuPh_2

49

Scheme 5

Conclusions.

In Scheme 6 the processes are summarized which recently have been demonstrated to lead from a single precursor readily to both enantiomeric series of chiral glycerol derivatives. Probably, the most efficient route includes a Sharpless epoxidation of allyl alcohol followed by $Ti(O^iPr)_4$-mediated epoxide opening with thiols, secondary amines and phenols to give compounds such as 53,[16] a glycerol derivative which is also available by yeast reduction of 54.[13]



Scheme 6

The most flexible route (concerning the nature of R^1 and R^2) towards compounds of type 52 appears to be the one that we have developed starting from the mannitol derivatives 8 and 37.

A drawback of the elegant enzyme-catalyzed ester hydrolysis method seems to be at present that only 50 (which has to be prepared from glycerol in 4 steps) is cleaved with high enantioselectivity.[18-20] In view of the very ready acyl group migration described above one may ask wether the incomplete enantioselectivity reported both by Schneider[18] and by Kreiser[19] has its origin in a less than 100% enantioselectivity of the enzyme or is caused by acyl group migration.

EXPERIMENTAL

General

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminium caps with open top and Teflon-faced septum (Aldrich). Usual work-up means partitioning the reaction mixture between water and an organic solvent (given in parenthesis), drying the combined organic solutions in vacuo at 40°C using a rotatory evaporator. The instrumentation used was: ^1H NMR: WP 80 (Bruker), AM 400 (Bruker); IR: Perkin Elmer 257 and 1310; EI MS: MAT-731 and MAT-CH-5 (Varian); FIB MS: MAT-CH-5, Cs ion source; CD: Jobin-Yvon-ISA dichrograph Mark III connected online to a PDP-8/e; $[\alpha]_D$: Polarimeter 141 (Perkin-Elmer); MPLC: medium-pressure liquid chromatography using 31.0 cm x 2.5 cm (column B) or 37.0 cm x 1.5 cm

(column A), 50 µm silica gel (Grace) Duramat pump (CfG), Thomachrom UV detector (Reichelt); reversed-phase MPLC: column A, 40-63 µm LiChroprep RP-18 (Merck).

2,5-Di-O-benzyl-1,3(R):4,6(R)-di-O-benzylidene-D-mannitol (9).[31]
To a solution of **8** (496.3 mg, 1.39 mmol) in DMF (2.8 ml) was added at 0°C NaH (55-60% suspension in oil, 169.7 mg, 3.89 mmol) and after 15 min benzyl bromide (415 µl, 3.49 mmol). The reaction mixture was stirred 45 min at 0°C and 1.75 h at 20°C. Work-up (CH_2Cl_2) and MPLC (hexanes-ethylacetate 12:1) furnished **9** (588.8 mg, 78%).- M.p. 106-107° (from hexanes).- $[\alpha]_D^{20}$ = -35.9 (c 1.6, $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ= 3.35-4.39 (8H), 4.53 (s, benzyl. H's), 5.34 (s, acetal. H's), 7.15-7.40 (Ar-H).- MS: m/z(%)= 538 (5, M^+), 447 (3), 91 (100).

2,5-Di-O-allyl-1,3(R):4,6(R)-di-O-benzylidene-D-mannitol (10).
To a solution of **8** (73.1 mg, 0.202 mmol) in DMF (3 ml) was added NaH (55-60% suspension in oil, 25.0 mg, 0.573 mmol). After 1.25 h at 20°C, tetra-n-butylammonium iodide (38.9 mg, 0.105 mmol), dissolved in DMF (1 ml), and allyl bromide (70 µl, 0.817 mmol) were added. The reaction mixture was stirred at 50°C for 1.5 h. Work-up (CH_2Cl_2) and MPLC (hexanes-ethyl acetate 6:1) provided **10** (89.4 mg, 100%).- M.p. 59-60°C (from acetone-hexanes).- $[\alpha]_D^{20}$ = -40.9 (c 4.7, $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ= 3.50-4.60 (12H), 5.00-5.35 (m, H_2C=CH-), 5.48 (s, acetal. H's), 5.62-6.15 (m, H_2C=CH-), 7.25-7.60 (Ar-H).- MS: m/z(%) = 438 (11, M^+), 437 (5), 397 (6), 219(50), 41 (100).- (Found: 438.2041 (MS). Calc for $C_{26}H_{30}O_6$: 438.2042).

1,3(R):4,6(R)-Di-O-benzylidene-2,5-bis-O-diphenylmethyl-D-mannitol (11).
A solution of **8** (0.53 g, 1.47 mmol) in THF (15 ml), containing NaH (55-60% suspension in oil, 0.69 g, 15.71 mmol), was stirred at 20°C for 45 min. Solid tetra-n-butylammonium iodide (1.08 g, 2.93 mmol) and bromodiphenylmethane (1.33 g, 5.37 mmol) were added and the reaction mixture was stirred 3.5 h at 50°C. Filtration over silica gel and MPLC (hexanes-ethyl acetate 30:1) gave **11** (86%).- ^1H NMR (80 MHz, $CDCl_3$): δ= 3.53-4.32 (8H), 5.32 (s, acetal. H's), 5.48 (s, benzyl. H's), 7.00-7.60 (Ar-H).- MS: m/z (%)= 690 (2, M^+), 523.2122 (7, $(M-CHPh_2)^+$, Calc for $C_{33}H_{31}O_6^+$: 523.2120), 167 (100).- CD (CH_3CN, c 0.252 mmol/l): λ_{max} ($\Delta\varepsilon$) = 269 (-0.30), 262 (-0.30), 256 (-0.16), 250 (-0.05), 223 nm (9.61).

2,5-Di-O-benzyl-D-mannitol (12).
From **8** (9.96 g) **9** was prepared as described above. The crude reaction product was hydrolyzed with H_2O (300 ml), ethanol (100 ml) and conc. HCl (17.8 ml) at 100°C for 17 h. Neutralization with $NaHCO_3$ and usual work-up (ethyl acetate), followed by crystallization ($CHCl_3$-hexanes) gave **12** (3.49 g). The mother liquor (after solvent evaporation) was again hydrolyzed to give a second crop of **12** (3.60 g).- Total yield: 71%.- M.p. 118-119°C (from $CHCl_3$-hexanes)(lit.,[37] 119-120°C (from ethanol), lit.,[38] 115°C).- $[\alpha]_D^{20}$ = -7.7 (c 1.4, ethanol)(lit.,[37] -7 (c 0.6, ethanol), lit.,[38] -8.5 (abs. ethanol)).- ^1H NMR (80 MHz, pyridine-d_5): δ = 4.15-4.85 (8H), 4.86 and 5.01 (J_{AB}= 11.2 Hz, benzyl. H's), 5.00-6.00 (OH), 7.20-7.60 (Ar-H).- FIB-MS (glycerol): m/z = 363 ($(M+H)^+$), 181.

2,5-Di-O-benzyl-1,6-bis-O-(2,2-dimethyl-propionyl)-D-mannitol (13).
To a solution of **12** (29.4 mg, 0.081 mmol) in pyridine (115 µl), pivaloyl chloride (20 µl, 0.163 mmol) was added at - 17°C. After 1.5 h at -17°C usual work-up (CH_2Cl_2) gave pure **13** (43.0 mg, 100%).- $[\alpha]_D^{20}$ = -19.3 (c 1.0, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ= 1.17 (s, $C(CH_3)_3$), 2.66-2.80 (OH), 3.71-3.78 (2-H, 5-H), 3.88 (3-H, 4-H), 3.97 (1-H, 6-H), 4.48 (1-H', 6-H'), 4.51 and 4.71 (J_{AB}= 11.1 Hz, benzyl. H's), 7.25-7.35 (Ar-H); $J_{1,1'}=J_{6,6'}$= 11.6 Hz, $J_{1,2}=J_{5,6}$= 4.7 Hz, $J_{1',2}=J_{5,6'}$= 3.7 Hz, $J_{2,3}=J_{4,5}$= 7.0 Hz.- IR (CCl_4): 1720 cm^{-1} (C=O).- MS: m/z (%)= 422 (1, $(M-108)^+$), 91 (100).- FIB-MS (triethyl citrate): m/z = 663 ($(M+Cs)^+$), 531 ($(M+H)^+$), 423.- (Found: C, 67.79; H, 7.95. $C_{30}H_{42}O_8$ (530.7) requires C, 67.90; H, 7.98).

1,6-Di-O-benzoyl-2,5-di-O-benzyl-D-mannitol (14).
A solution of **12** (30.6 mg, 0.985 mmol) and benzoyl chloride (20 µl, 0.172 mmol) in pyridine (115 µl) was left at -17°C for 1.5 h. Usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 3:1) furnished **14** (36.2 mg, 75%).- M.p. 89-90°C (from $CHCl_3$-ethyl acetate-hexanes).- $[\alpha]_D^{20}$ = - 17.0 (c 1.1, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ= 2.83-2.90 (OH), 3.86-3.92 (2-H, 5-H), 4.05 (3-H, 4-H), 4.52 (1-H, 6-H), 4.57 and 4.76 (J_{AB}= 11.5 Hz, benzyl. H's), 4.72 (1-H', 6-H'), 7.22-8.03 (Ar-H); $J_{1,1'}=J_{6,6'}$= 12.0 Hz, $J_{1,2}=J_{5,6}$= 4.5 Hz, $J_{1',2}=J_{5,6'}$= 3.3 Hz, $J_{2,3}=J_{4,5}$= 7.5 Hz, $J_{3,OH}=J_{4,OH}$= 7.5 Hz.- IR (CCl_4): 1715 cm^{-1} (C=O).- FIB-MS (glycerol): m/z = 571 ($(M+H)^+$), 553.- (Found: C, 71.44; H, 6.09. $C_{34}H_{34}O_8$ (570.6)

requires C, 71.56; H, 6.01).

2,5-Di-O-benzyl-1,6-bis-O-tert-butyldiphenylsilanyl-D-mannitol (15).
To a suspension of **12** (49.6 mg, 0.137 mmol) in CH_2Cl_2 were added NEt_3 (43 µl, 0.308 mmol), 4-dimethylaminopyridine (4-DMAP)[39] (1.3 mg, 0.011 mmol in 1.1 ml CH_2Cl_2) and $^tBuPh_2SiCl$ (145 µl, 0.558 mmol), and the reaction mixture was left at 20°C for 4 d. Usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 20:1) provided **15** (111.5 mg, 97%).- $[\alpha]_D^{20}$= -10.6 (c 1.1, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.04 (s, $SiC(CH_3)_3$), 2.95-3.15 (OH), 3.55-4.20 (8H), 4.52 and 4.65 (J_{AB}= 11.0 Hz, benzyl. H's), 7.20-7.80 (Ar-H). After addition of trichloroacetyl isocyanate:[40] ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.04 (s, $SiC(CH_3)_3$), 3.50-4.14 (6H), 4.31 and 4.48 (J_{AB}= 11.6 Hz, benzyl. H's), 5.77 (d, $J_{2,3}$=$J_{4,5}$= 5 Hz, 3-H, 4-H), 7.00-7.70 (Ar-H), 8.20 (NH).- (Found: C, 74.50; H, 7.48. $C_{52}H_{62}O_6Si_2$ (839.2) requires C, 74.42; H, 7.45).

2,5-Di-O-benzyl-1,6-di-O-trityl-D-mannitol (16).
To a suspension of **12** (99.8 mg, 0.276 mmol) in CH_2Cl_2 (2 ml) were added 4-DMAP (135.7 mg, 1.111 mmol) and trityl chloride (340.7 mg, 1.222 mmol). The reaction mixture was stirred for 50.5 h at 30°C. After usual work-up (ether), MPLC (hexanes- ethyl acetate 5:1) gave **16** (216.2 mg, 93%).- $[\alpha]_D^{20}$ = -20.9 (c 1.0, $CHCl_3$).- ^{1}H NMR (80MHz, $CDCl_3$): δ= 2.75-2.93 (OH), 3.20-4.12 (8H), 4.57 and 4.72 (J_{AB}= 12.0 Hz, benzyl. H's), 7.10-7.55 (Ar-H).- MS: m/z (%)= 333 (5), 243 (100), Ph_3C^+), 91 (57).- (Found: C, 82.20; H, 6.45. $C_{58}H_{54}O_6$ (847.1) requires C, 82.24; H, 6.43).

2,5-Di-O-Benzyl-1,6-bis-O-(toluene-4-sulfonyl)-D-mannitol (17).
To a suspension of **12** (100.0 mg, 0.276 mmol), 4-DMAP (2.5 mg, 0.020 mmol) and 4-toluenesulfonyl chloride (108.9 mg, 0.571 mmol) in CH_2Cl_2 (2 ml), triethylamine (80 µl, 0.574 mmol) was added. After 10 h at 20°C again 4-toluenesulfonyl chloride (27.1 mg, 0.143 mmol) was added and the reaction mixture was left at 20°C for another 14 h. Solvent evaporation and SC (hexanes-ethyl acetate 2:1) provided **17** (126.1 mg, 68%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 2.18-2.38 (OH), 2.40 (s, 6H, Ar-CH_3), 3.52-3.88 (4H), 4.02-4.40 (m, CH_2-1, CH_2-6), 4.43 and 4.59 (J_{AB}= 11.2 Hz, benzyl. H's), 7.12-7.76 (Ar-H).- IR ($CHCl_3$): 1360, 1175 cm^{-1} (SO_2).- FIB-MS (triethanolamine-glycerol-LiCl): m/z = 677 ($(M+Li)^+$).- (Found: C, 60.89; H, 5.75. $C_{34}H_{38}O_{10}S_2$ (670.8) requires C, 60.88; H, 5.71).

2,5-Di-O-allyl-D-mannitol (18).
A solution of **10** (65.0 mg, 0.148 mmol) in H_2O (1.0 ml) and ethanol (3.2 ml) was stirred in the presence of Dowex-W50 (H^+, 1.0 g in 0.5 ml H_2O) for 1 h at 100°C. After neutralization ($NaHCO_3$), filtration and solvent evaporation which was three times repeated after addition of toluene, SC (hexanes-ethyl acetate-ethanol 15:15:1) furnished **18** (31.7 mg, 82%).- M.p. 77-78°C (from acetone-hexanes).- $[\alpha]_D^{20}$ = -25.4 (c 0.8, ethanol).- ^{1}H NMR (80 MHz, acetone-d_6): δ= 3.40-4.04 (8H), 4.05-4.25 (m, H_2C=CHCH_2), 5.00-5.45 (m, H_2C=CHCH_2), 5.70-6.25 (m, H_2C=CHCH$_2$).- FIB-MS (glycerol): m/z = 285 ($(M+Na)^+$), 263 ($(M+H)^+$), 205.- (Found: C, 55.00; H, 8.53. $C_{12}H_{22}O_6$ (262.3) requires C, 54.95; 8.45).

Acid hydrolysis of 11.
A solution of **11** (48.7 mg, 0.071 mmol) in 80% aqueous acetic acid (13 ml) was stirred 34 h at 40°C and 66 h at 20°C. After neutralization ($NaHCO_3$) and usual work-up (CH_2Cl_2, ethyl acetate), SC (hexanes-ethyl acetate 1:1) provided **19** (14.7 mg, 41%), **34** (9.1 mg, 23%) and a 1:3 mixture (^{1}H NMR) of **35** and **36** (6.5 mg, 15%). The mixture of **35** and **36** was separated by reversed-phase MPLC (methanol-H_2O 5:1).

2,5-Bis-O-diphenylmethyl-D-mannitol (19).
M.p. 100-101°C (from ethyl acetate-hexanes).- $[\alpha]_D^{20}$ = 4.2 (c 1.0, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.47-2.95 (OH), 3.49-4.15 (8H), 5.55 (s, benzyl. H's), 7.27-7.48 (Ar-H).- MS: m/z (%)= 347 (2, $(M-CHPh_2)^+$), 167 (100, Ph_2CH^+).- (Found: C, 74.73; H, 6.70. $C_{32}H_{34}O_6$ (514.6) requires C, 74.69; H, 6.66).

1-O-Acetyl-2,5-bis-O-diphenylmethyl-D-mannitol (34).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.90 (s, $COCH_3$), 2.40-2.55 (OH), 3.48-4.18 (7H), 4.20-4.33 (m, CH_2-1), 5.52 and 5.58 (2 s, benzyl. H), 7.25-7.40 (Ar-H).- IR ($CHCl_3$): 1725 cm^{-1} (C=O).- MS: m/z (%)= 389 (4, $(M-CHPh_2)^+$), 167 (100).- (Found: C, 73.40; H, 6.58. $C_{34}H_{36}O_7$ (556.7) requires C, 73.36; H, 6.52).

1,3(S)-O-Benzylidene-2,5-bis-O-diphenylmethyl-D-mannitol (35).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.35-4.05 (6H), 4.33-4.62 (m, 2H), 5.62 and 5.66 (2 s, benzyl. H), 5.80 (s, acetal. H), 7.25-7.35 (Ar-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ= 61.26, 61.49 (CH_2), 103.72 (acetal. C).- IR ($CHCl_3$): 3560, 3600-3300 cm^{-1} (OH).- MS: m/z (%)= 602 (1, M^+), 435 (4, $(M-CHPh_2)^+$), 167 (100).- (Found: C, 77.76; H, 6.39. $C_{39}H_{38}O_6$ (602.7) requires C, 77.72; H, 6.36).

1,3(R)-O-Benzylidene-2,5-bis-O-diphenylmethyl-D-mannitol (36).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.33-4.26 (8H), 5.10 (s, 1H, acetal. H), 5.52 and 5.56 (2 s, benzyl. H), 7.26-7.44 (Ar-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 61.93, 69.66 (CH_2), 100.24 (acetal. C).- IR ($CHCl_3$): 3600-3200 cm^{-1} (OH).- MS: m/z (%)= 602 (0.2, M^+), 435 (6), 167 (100).- (Found: C, 77.70; H, 6.32. $C_{39}H_{38}O_6$ (602.7) requires C, 77.72; H, 6.36).

Alkylation of 12.
a.) To a solution of **12** (101.6 mg, 0.281 mmol) in benzene (2 ml) was added NaH (55-60% suspension in oil, 53.0 mg, 1.215 mmol), and after 1 h at 80°C 1-hexadecyl methanesulfonate (89.7 mg, 0.281 mmol), dissolved in benzene (2 ml). The reaction mixture was stirred for 4 h at 90°C and for 4 h at 20°C. Usual work-up (CH_2Cl_2), MPLC (hexanes-ethyl acetate 15:1) and SC (hexanes-ethyl acetate 5:1) furnished **20** (31.0 mg, 14%) along with other alkylation products.[35] 47.3 mg (47%) of **12** were recovered.
b.) A mixture of **12** (95.3 mg, 0.263 mmol), tetra-n-butylammonium hydrogensulfate (68.7 mg, 0.202 mmol) and 1-bromo-hexadecane (210.5 µl, 0.689 mmol) in a two-phase system of toluene (2 ml) and 12.5 N NaOH (2 ml) was intensively stirred at 60°C for 5 h. Usual work-up (CH_2Cl_2), MPLC (hexanes-ethyl acetate 8:1) and SC (hexanes-ethyl acetate 30:1) gave **20** (32.4 mg, 15%) along with other alkylation products.[35]

2,5-Di-O-benzyl-1,6-di-O-hexadecyl-D-mannitol (20).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.80-1.40 (62H), 3.04-3.98 (14H), 4.61 and 4.70 (J_{AB}= 12.0 Hz, benzyl. H's), 7.30 (Ar-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 14.10 (CH_3), 22.68, 26.12, 29.35, 29.49, 29.64, 29.69, 31.92 (CH_2), 70.24 (C-3, C-4), 71.04, 71.84, 73.01 (OCH_2), 78.94 (C-2, C-5), 127.68, 127.93, 128.35 (Ar-CH), 138.33 (Ar-C).- (Found: C, 76.88; H, 11.20. $C_{52}H_{90}O_6$ (811.3) requires C, 76.99; H, 11.18).

Alkylation of 19.
21 was prepared from **19** as described for the phase-transfer alkylation of **12**. After MPLC (hexanes-ethyl acetate 8:1) and SC (hexanes-ethyl acetate 30:1) **21** was obtained in 26% yield, along with other alkylation products.[35]

2,5-Bis-O-diphenylmethyl-1,6-di-O-hexadecyl-D-mannitol (21).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.70-1.70 (62H), 2.94 (broad d, OH), 3.33 (t, ^3J= 6 Hz; $OCH_2C_{15}H_{31}$), 3.44-3.83 (6H), 3.97 (dd, 3-H, 4-H), 5.68 (s, benzyl. H's), 7.13-7.49 (Ar-H); $J_{2,3}=J_{4,5}=J_{3,OH}=J_{4,OH}$= 5 Hz.- (Found: C, 79.84; H, 10.18. $C_{64}H_{98}O_6$ (963.5) requires C, 79.78; H, 10.25).

(S)-2-Benzyloxy-3-(2,2-dimethyl-propionyloxy)-propan-1-ol (24).
To a solution of **13** (230.6 mg, 0.435 mmol) in methanol (8.5 ml) and THF (8.5 ml) was added $NaIO_4$ (219.9 mg, 1.025 mmol), dissolved in H_2O (14.5 ml). The reaction mixture was stirred for 23 h at 20°C. Then $NaBH_4$ (84.8 mg, 2.243 mmol) was added. After 0.5 h at 20°C neutralization (2 N HCl), usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 3:1) furnished **24** (213.0 mg, 92%).- $[\alpha]_D^{20}$ = -16.7 (c 1.1, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.23 (s, $C(CH_3)_3$), 2.15-2.35 (OH), 3.50-4.03 (2-H, CH_2-1), 4.13-4.36 (m, CH_2-3), 4.62 and 4.74 (J_{AB}= 12.0 Hz, benzyl. H's), 7.35 (Ar-H).- IR (CCl_4): 1730 cm^{-1} (C=O).- MS: m/z (%)= 266 (0.1, M^+), 235 (1, $(M-H_2COH)^+$), 181 (3, $(M-COC(CH_3)_3)^+$), 91 (100), 85 (8), 57 (34).- (Found: C, 67.57, H, 8.25. $C_{15}H_{22}O_4$ (266.3) requires C, 67.65; H, 8.33).

Determination of the optical purity of 24.
For the determination of the optical purity of **24** the $NaIO_4$ cleavage of **13** was performed as described above (3 h at 20°C). The resulting solution was then devided into two equal parts (A and B), $NaBH_4$ was added to both of them. Reaction mixture A was neutralized after 45 min at 20°C, solution B after 1.5 h. From both reaction mixtures **24** was isolated as described above. The Mosher esters were prepared[32] from **24** (A and B) and from a racemic mixture of **24**/ent-**24** (prepared from 2-benzyloxy-propan-1,3-diol).

a.) Mosher ester of **24**/ent-**24**.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18, 1.19 ($C(CH_3)_3$), 3.51, 3.52 (OCH_3), 3.84-3.91 (m, 2-H), 4.06-4.23, 4.31-4.36, and 4.52-4.62 (CH_2-1, CH_2-3, benzyl. H's), 7.24-7.55 (Ar-H).
b.) **24** from reaction A.
$[\alpha]_D^{20}$ = -15.1 ± 0.2 (c 1.1, $CHCl_3$), % e.e.: 78±3 (determined by cutting and weighing the peak areas under the tert-butyl signals in the 400 MHz ^{1}H NMR spectrum of the Mosher esters)
c.) **24** from reaction B.
$[\alpha]_D^{20}$ = -11.7 (c 1.1, $CHCl_3$), % e.e.: 57±2 (determined as described above).
Calculated $[\alpha]_D^{20}$ of optically pure **24**: -19.3 ± 0.8 (from experiment A), -20.7 ± 0.8 (from experiment B).

[1-D_1]-**24** and [3-D_1]-ent-**24** from **13**.
The $NaIO_4$ cleavage of **13** was performed as described above. $NaBD_4$ was added after 3 h. After 45 min at 20°C, neutralization, work-up and SC (hexanes-ethyl acetate 3:1) gave a mixture of [1-D_1]-**24** and [3-D_1]-ent-**24** (71%).- $[\alpha]_D^{20}$ = -15.3 ± 0.2.- ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 3.48, 4.07 (ratio: 90:10, relative error: 4%). From these values an $[\alpha]_D^{20}$ = -19.3 ± 0.8 for optically pure **24** can be estimated.

(S)-3-Benzoyloxy-2-benzyloxy-propan-1-ol (**25**).
The reaction was performed as described for **24** using methanol-THF-H_2O 1:1:1. $NaBH_4$ was added after 3.5 h at 20°C (reduction: 20 min at 20°C). SC (hexanes-ethyl acetate 5:1) gave **25** (72%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 2.05-2.25 (OH), 3.65 (3H), 4.37-4.53 (CH_2-3), 4.62 and 4.76 (J_{AB}= 12.0 Hz, benzyl. H's), 7.20-8.05 (Ar-H).- IR (CCl_4): 3600-3300 (OH), 1725 (C=O)cm^{-1}.- MS: m/z (%)= 286 (0.3, M^+), 255 (2, $(M-H_2COH)^+$), 105 (72), 91 (100), 77 (34).- (Found: C, 71.17; H, 6.40. $C_{17}H_{18}O_4$ (286.3) requires C, 71.31; H, 6.34).

Determination of the optical purity of **25**.
$[\alpha]_D^{20}$ of **25** (prepared from **14**): -6.1 ± 0.2 (c 2.0, $CHCl_3$).
For the determination of the optical purity the Mosher esters were prepared[32] from **25** and from a racemic mixture of **25**/ent-**25** (derived from 2-benzyloxy-propan-1,3-diol as described for **14**).- ^{1}H NMR (400 MHz, C_6D_6): δ = 3.39 and 3.42 (2 m, OCH_3), 3.54 (2-H), 4.03-4.42 (CH_2-1, CH_2-3, benzyl. H), 6.97-8.06 (Ar-H).
% e.e. of **25**: 43 ± 2 (determined by cutting and weighing the areas under the methoxy signals of the Mosher esters).
From these data an $[\alpha]_D^{20}$ = -14.3 ± 0.7 of optically pure **25** can be calculated (lit.[19] $[\alpha]_D^{25}$ = -11.9, c 2, $CHCl_3$).

[1-D_1]-**25** and [3-D_1]-ent-**25** from **14**.
The oxidative cleavage of **14** followed by reduction were performed as described for **25**. $NaBD_4$ was added after 7.25 h (reduction: 30 min at 20°C). SC (hexanes-ethyl acetate 5:1) gave a mixture of [1-D_1]-**25** and [3-D_1]-ent-**25** (86%).- $[\alpha]_D^{20}$ = -4.5 ± 0.2 (c 2.0, $CHCl_3$).- ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 3.74 and 4.50 (ratio: 66:34, relative error: 2.5%). From these data an $[\alpha]_D^{20}$ = -13.9 ± 0.7 of optically pure **25** can be estimated.

(S)-2-Benzyloxy-3-tert-butyldiphenylsilanyloxy-propan-1-ol (**26**).
To a solution of **15** (3.06 g, 3.65 mmol) in methanol (60 ml) and THF (80 ml) was added $NaIO_4$ (2.46 g, 11.50 mmol), in H_2O (60 ml). The reaction mixture was stirred for 23 h at 20°C. After filtration of the reaction mixture, $NaBH_4$ (3.55 g, 93.92 mmol) was added at 0°C. After 1 h at 0°C, neutralization, usual work-up, and SC (hexanes-ethyl acetate 3:1) provided **26** (2.89 g, 94%).- $[\alpha]_D^{20}$ = -24.5 (c 1.1, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.05 (s, $SiC(CH_3)_3$), 3.55-3.90 (5H), 4.51 and 4.63 (J_{AB}= 12.0 Hz, benzyl. H's), 7.20-7.75 (Ar-H).- (Found: C, 74.31; H, 7.59. $C_{26}H_{32}O_3Si$ (420.6) requires C, 74.24; H, 7.67).

Determination of the optical purity of **26**.
For the determination of the optical purity the Mosher esters were prepared[32] from **26** (prepared from **15**) and from a racemic mixture of **26**/ent-**26** (prepared from 2-benzyloxy-propan-1,3-diol as described for **15**).

Mosher esters of **26**/ent-**26**.
^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.05, 1.06 (2 s, $SiC(CH_3)_3$), 3.50 (m, OCH_3), 3.67-3.77 (m, 2-H, CH_2-1), 4.38-4.45 (3-H), 4.65-4.73 (3-H'), 4.46, 4.48 (s, benzyl. H's), 7.15-7.66 (Ar-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 19.16 ($SiC(CH_3)_3$), 26.75, 26.77 ($SiC(CH_3)_3$), 55.41, 55.47 (OCH_3), 62.62, 62.70 (CH_2-1), 65.06, 65.60 (CH_2-3), 71.98, 72.11 (benzyl.

CH_2), 77.20, 77.00 (C-2), 127.37, 127.43, 127.57, 127.74, 128.30, 128.37, 129.54, 129.56, 129.78 (Ar-CH), 132.21, 132.27, 132.99, 133.13, 133.16, 137.94, 137.97 (Ar-C), 135.51, 135.56 (CF_3), 166.52 (COO).

Mosher ester of **26**.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, $SiC(CH_3)_3$), 3.50 (m, OCH_3), 3.67-3.79 (CH_2-1, 2-H), 4.42 (3-H), 4.68 (3-H'), 4.48 (s, benzyl. H's), 7.15-7.67 (Ar-H); $J_{2,3}$ = 5.5 Hz, $J_{2,3'}$ = 3.0 Hz, $J_{3,3'}$ = 11.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 19.18 ($SiC(CH_3)_3$), 26.77 ($SiC(CH_3)_3$), 55.41 (OCH_3), 62.70 (CH_2-1), 65.58 (CH_2-3), 72.10 (benzyl. CH_2), 77.20 (C-2), 127.43, 127.57, 127.60, 127.76, 128.30, 128.38, 129.57, 129.80 (Ar-CH), 132.22, 132.99, 133.13, 137.97 (Ar-C), 135.55 (CF_3), 166.53 (COO).
No trace of the second isomer could be detected.

(S)-2-Benzyloxy-3-trityloxy-propan-1-ol (**27**).
To a solution of **16** (19.2 mg, 0.023 mmol) in pyridine (100 µl) lead tetraacetate (10.4 mg, 0.023 mmol) was added, and the reaction mixture was stirred for 3.75 h at 20°C. Solid $NaBH_4$ (7.9 mg, 0.209 mmol) was added, and the mixture was left for 3 h at 20°C. Usual work-up (CH_2Cl_2) and MPLC (hexanes-ethyl acetate 6:1) gave **27** (14.2 mg, 73%).- $[\alpha]_D^{20}$ = -23.5 (c 0.8, $CHCl_3$).- MS: m/z (%)= 333 (2, $(M-91)^+$), 243 (100), 181 (43), 91 (92).[42]

(S)-2-Benzyloxy-3-(toluene-4-sulfonyloxy)-propan-1-ol (**28**).
28 was prepared from **17** as described for **24** (in methanol-THF-H_2O 1:1:1 solution). $NaBH_4$ was added after 3 h. Neutralization after 30 min, usual work-up and SC (hexanes-ethyl acetate 2:1) furnished **28** (93%).- $[\alpha]_D^{20}$ = -30.7 (c 1.8, $CHCl_3$), lit.,[19] $[\alpha]_D^{25}$ = -30.5 (c 2.0, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.66-1.95 (OH), 2.43 ($Ar-CH_3$), 3.40-3.90 (CH_2-1, 2-H), 4.04-4.20 (m, CH_2-3), 4.53 and 4.62 (J_{AB}= 11.2 Hz, benzyl. H's), 7.20-7.88 (Ar-H).- IR ($CHCl_3$): 1360, 1170 cm^{-1} (SO_2).- MS: m/z (%)= 336 (0.5, M^+), 279 (1), 181 (1), 173 (3), 155 (7), 107 (30), 91 (100).- (Found: 336.1028 (MS). Calc for $C_{17}H_{20}O_5S$: 336.1031).

(S)-2-Benzyloxy-1-tert-butyldiphenylsilanyloxy-3-trityloxy-propane (**23**).
23 was prepared from **26** as described for **16** (22.5 h at 35°C). Usual work-up (CH_2Cl_2) and SC (hexanes-ethylacetate 25:1) gave **23** (96%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.95 ($SiC(CH_3)_3$), 3.20-3.35 (2H), 3.57-3.86 (3H), 4.63 (s, benzyl. H's), 7.10-7.70 (Ar-H).- CD (CH_3CN, c 0.241 mmol/l): λ_{max} (Δε) = 272 (0.09), 265 (0.09), 260 (0.07), 212 nm (6.17).- (Found: C, 81.60; H, 6.90. $C_{45}H_{46}O_3Si$ (662.9) requires C, 81.53; H, 6.99).

(R)-2-Benzyloxy-3-trityloxy-propan-1-ol (**22**).
23 (69.0 mg, 0.104 mmol) was stirred in THF (410 µl) with tetra-n-butylammonium fluoride trihydrate (65.1 mg, 0.206 mmol) for 6 h at 20°C. After usual work-up (CH_2Cl_2), SC (hexanes-ethyl acetate 15:1) provided **22** (40.0 mg, 91%).- $[\alpha]_D^{20}$ = 23.6 (c 0.9, $CHCl_3$).[42]

(S)-2-Benzyloxy-1-hexadecyloxy-3-trityloxy-propane (**30**).
30 was prepared from **27** as described by Ohno[11] for ent-**30** (=**29**) using NaH instead of KH. Usual work-up (CH_2Cl_2) and MPLC (hexanes-ethyl acetate 30:1) gave **30** in 86% yield.- CD (CH_3CN, c 0.272 mmol/l): λ_{max} (Δε) = 272 (-0.05), 264 nm (-0.05).[42]

Alkylation of **26**.
a.) To a suspension of NaH (55-60% suspension in oil, 11.1 mg, 0.254 mmol) in DMF (4 ml) was added at 0°C a solution of **26** (101.3 mg, 0.241 mmol) and tetra-n-butylammonium iodide (10.5 mg, 0.028 mmol) in DMF (2 ml). After 1.5 h, 1-bromo-hexadecane (75 µl. 0.244 mmol) was added. The reaction mixture was stirred for 1 h at 0°C and for 21.5 h at 20°. Usual work-up (CH_2Cl_2), MPLC (hexanes-ethyl acetate 75:1) and SC (hexanes-ethyl acetate 10:1) gave **31** (23.9 mg, 15%), **32** (25.7 mg, 16%), **5a**/ent-**5a** (12.9 mg, 13%), **33** (8.2 mg, 5%) and **26** (8.1 mg, 8%).
b.) A solution of **26** (107.1 mg, 0.255 mmol) and 1-hexadecyl 4-toluenesulfonate (99.7 mg, 0.252 mmol) in DMF (4 ml) was added to a suspension of NaH (55-60% suspension in oil, 18.2 mg, 0.417 mmol) in DMF (4 ml). After 18 h at 20°C, usual work-up (CH_2Cl_2) and MPLC (hexanes-ethyl acetate 75:1) furnished **31** (56.3 mg, 34%), **33** (21.8 mg, 14%), **32** (1.2 mg, 1%) and 31.2 mg of a mixture of **5a**/ent-**5a** and **26**.

(R,S)-2-Benzyloxy-1-tert-butyldiphenylsilanyloxy-3-hexadecyloxy-propane (**31**).
The sample of **31** prepared from **26** was optically inactive.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.50 (31H), 1.05 ($SiC(CH_3)_3$), 3.30-3.80 (7H), 4.63 (s, benzyl. H's), 7.20-7.80 (Ar-H).- MS: m/z (%)= 587 (2, $(M-57)^+$), 419 (14), 195 (56), 91 (100).- (Found: C, 78.08; H,

9.93. $C_{42}H_{64}O_3Si$ (645.1) requires C, 78.20; H, 10.00).

(R,S)-2-Benzyloxy-3-hexadecyloxy-propan-1-ol (5a/ent-5a).
The samples of **5a**/ent-**5a** prepared from **26** (vide supra) and by desilylation of **31** using the method described for **22** (yield: 93% after SC (hexanes-ethyl acetate 15:1)) proved to be optically inactive. The ^{1}H NMR and the mass spectrum were identical to those reported by Ohno[11] for **5a**.

2-Benzyloxy-1,3-bis-tert-butyldiphenylsilanyloxy-propane (32).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.05 ($SiC(CH_3)_3$), 3.55-4.00 (5H), 4.63 (s, benzyl. H's), 7.20-7.80 (Ar-H).- MS: m/z (%)= 601 (0.2, $(M-57)^+$), 433.1656 (7.5, $(M-57-PhCH_2Ph)^+$, Calc for $C_{25}H_{29}O_3Si_2^+$: 433.1655), 91 (100).

2-Benzyloxy-1,3-di-O-hexadecyloxy-propane (33).
^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.80-1.60 (62H), 3.30-3.80 (9H), 4.68 (s, benzyl. H's), 7.25-7.45 (Ar-H).- MS: m/z (%)= 630 (0.7, M^+), 91 (100).- (Found: C, 79.89; H, 12.45. $C_{42}H_{78}O_3$ (631.1) requires C, 79.94; H, 12.46).

(S)-2-Benzyloxy-3-hexadecyloxy-propan-1-ol (5a).
5a was prepared from **20** as described for **27**, using benzene as solvent instead of pyridine. $NaBH_4$ was added after 2.75 h at 20°C, and the mixture was allowed to react for 3.5 h at 20°C. Methanol (0.1 ml) was added, and after 0.5 h usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 6:1) **5a** was obtained in 72% yield.- $[\alpha]_D^{20}$ = -12.9 (c 1.0, $CHCl_3$) (lit.,[41] for ent-**5a**: 7.98 (c 5, $CHCl_3$)).- The ^{1}H NMR and the mass spectrum were identical to those reported by Ohno.[11]

1,3(R):4,6(R)-Bis-O-(4-methoxy-benzylidene)-D-mannitol (37).
To a solution of D-mannitol (50.0 mg, 0.27 mmol) in DMF (0.3 ml) were added 4-methoxy-benzaldehyde (62 µl, 0.54 mmol), conc. sulfuric acid (10 µl), and trimethyl orthoformate (74 µl, 0.81 mmol). The reaction mixture was stirred for 1.5 h at 60°C, then at $2x10^3$ Pa for 2 h at 20°C. The reaction mixture was poured into ice-cold aqueous K_2CO_3 solution (2.5 ml, 75 mg K_2CO_3). Usual work-up ($CHCl_3$) and MPLC (hexanes-ethyl acetate 2:3) provided **37** (40.7 mg, 35%).- M.p. 224-225°C (from methanol).- ^{1}H NMR (80 MHz, acetone-d_6): δ= 3.45-4.60 (8H), 3.77 (OCH_3), 5.48 (s, acetal. H's), 6.75-7.50 (Ar-H).- MS: m/z (%)= 418 (5, M^+),239 (16), 209 (16), 179 (23), 137 (91), 135 (100). (Found: C, 63.20; H, 6.30. $C_{22}H_{26}O_8$ (418.5) requires C, 63.15; H, 6.26).

2,5-Di-O-benzyl-1,3(R):4,6(R)-bis-O-(4-methoxy-benzylidene)-D-mannitol (38).
38 was prepared from **37** as described for **9** with inverse addition sequence of NaH and **37**. Usual work-up ($CHCl_3$) and SC (hexanes-ethyl acetate 5:1) gave **38** (91%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.58-4.40 (8H), 3.78 (OCH_3), 4.55 (s, benzyl. H's), 5.34 (s, acetal. H's), 6.80-7.45 (Ar-H).- MS: m/z (%)= 598 (8, M^+), 299 (6), 135 (52), 91 (100).- (Found: C, 71.98; H, 6.38. $C_{36}H_{38}O_8$ (598.7) requires C, 72.22; H, 6.40).

2,5-Di-O-allyl-1,3(R):4,6(R)-bis-O-(4-methoxy-benzylidene)-D-mannitol (39).
39 was prepared from **37** as described for **38**, using allyl bromide instead of benzyl bromide. SC (hexanes-ethyl acetate 5:1) gave **39** (83%).- M.p. 94-96°C (from ether).- $[\alpha]_D^{20}$ = -13.9 (c 2.1, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.40-4.50 (12H), 3.78 (OCH_3), 5.00-5.34 (m, $H_2C=CHCH_2$), 5.44 (s, acetal. H's), 5.60-6.15 (m, $H_2C=CHCH_2$), 6.75-7.53 (Ar-H).- MS: m/z (%)= 498 (15, M^+), 457 (2), 249 (85), 135 (100), 121 (60), 41 (60).- (Found: C, 67.50; H, 6.90. $C_{28}H_{34}O_8$ (498.6) requires C, 67.45; H, 6.87).

1,3(R):4,6(R)-Bis-O-(4-methoxy-benzylidene)-2,5-bis-O-methoxyethoxymethyl-D-mannitol (40).
40 was prepared from **37** as described for **38**, using methoxyethoxymethyl chloride instead of benzyl bromide. SC (hexanes-ethyl acetate 5:1) gave **40** (70%).- $[\alpha]_D^{20}$ = 38.5 (c 0.4, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.30-4.15 (16H), 3.33 (OCH_3), 3.78 (Ar-OCH_3), 4.74 (s, -OCH_2O-), 5.43 (s, acetal. H's), 6.75-7.53 (Ar-H).- MS: m/z (%)= 594 (6, M^+), 505 (3), 297 (2), 135 (45), 89 (100).- (Found: C, 60.60; H, 7.14. $C_{30}H_{42}O_{12}$ (594.7) requires C, 60.59; H, 7.12).

2,5-Di-O-benzyl-1,6-bis-O-(4-methoxy-benzyl)-D-mannitol (41).
To a suspension of $NaBH_3CN$ (1.39 g, 21 mmol), 3 Å molecular sieves (powder), and **38** (1.26 g, 2.1 mmol) in DMF (20 ml) was added a solution of TFA (2.4 ml, 21 mmol) in DMF (5 ml). The reaction mixture was stirred for 6 h at 80°C. Usual work-up ($CHCl_3$) and SC (hexanes-

ethyl acetate 1:1) furnished **41** (0.99 g, 78%).- ^{1}H NMR (80 MHz, acetone-d_6): δ= 3.55-4.10 (8H), 3.78 (OCH_3), 4.50 (s, 4H, benzyl. H's), 4.62 and 4.77 (J_{AB}= 11.2 Hz, 4H, benzyl. H's), 6.75-7.40 (Ar-H).- ^{13}C NMR (100.6 MHz, acetone-d_6, DEPT): δ = 55.43 (OCH_3), 70.10 (C-3, C-4), 71.47, 73.16, 73.44 (C-1, C-6, and benzyl. C's), 80.05 (C-2, C-5), 114.38, 127.98, 128.33, 128.91, 129.88 (Ar-CH), 131.68, 140.19, 160.06 (Ar-C).- FIB-MS (triethyl citrate): m/z = 603 ($(M+H)^+$), 481.- (Found: C, 71.62; H, 7.00. $C_{36}H_{42}O_8$ (602.7) requires C, 71.74; H, 7.02).

2,5-Di-O-allyl-1,6-bis-O-(4-methoxy-benzyl)-D-mannitol (42).
42 was prepared from **39** as described for **41**, using 20 equivalents of TFA. After 7 h at 60°C usual work-up ($CHCl_3$) and SC (hexanes-ethyl acetate 3:1) provided **42** (76%).- $[\alpha]_D^{20}$ = -0.4 (c 0.1, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.47-4.00 (8H), 3.78 (OCH_3), 4.01-4.21 (m, $CH_2CH=CH_2$), 4.46 (s, benzyl. H's), 5.00-5.40 (m, $CH_2CH=CH_2$), 5.63-6.17 (m, $CH_2CH=CH_2$), 6.85-7.35 (Ar-H).- MS: m/z (%)= 381 (25), 121 (100), 41 (10).- (Found: C, 66.87; H, 7.63. $C_{28}H_{38}O_8$ (502.6) requires C, 66.91; H, 7.62).

(R)-2-Benzyloxy-3-(4-methoxy-benzyloxy)-1-(2,2-dimethyl-propionyloxy)-propane (43).
43 was prepared from **45** as described for **13**. Usual work-up ($CHCl_3$) and SC (hexanes-ethyl acetate 2:1) gave **43** (80%).- $[\alpha]_D^{20}$ = -7.0 (c 1.2, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.17 ($C(CH_3)_3$), 3.45-3.70 (3H), 3.78 (OCH_3), 4.12-4.30 (CH_2-1), 4.45 and 4.63 (2 s, benzyl. H's), 6.78-7.36 (Ar-H).- MS: m/z (%)= 386 (0.6, M^+), 295 (6), 159 (100), 121 (85), 91 (82), 57 (32).- (Found: C, 71.50; H, 7.83. $C_{23}H_{30}O_5$ (386.5) requires C, 71.48; H, 7.82).

(R)-2-Benzyloxy-1-tert-butyldiphenylsilanyloxy-3-(4-methoxy-benzyloxy)-propane (44).
44 was prepared from **45** as described for **15**, leaving the reaction mixture for 17 h at 40°C. Usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 3:1 and hexanes-acetone-methanol 15:1:0.1) furnished **44** (82%).- $[\alpha]_D^{20}$ = 4.9 (c 0.9, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.05 ($SiC(CH_3)_3$), 3.60-3.85 (5H), 3.80 (OCH_3), 4.44 and 4.60 (2 s, benzyl. H's), 6.76-7.72 (Ar-H).- MS: m/z (%)= 449 (0.1), 419 (0.2), 121 (100), 91 (42).- (Found: C, 75.39; H, 7.53. $C_{34}H_{40}O_4Si$ (540.8) requires C, 75.52; H, 7.46).

(S)-2-Benzyloxy-3-(4-methoxy-benzyloxy)-propan-1-ol (45).
45 was prepared from **41** as described for **24** (in methanol-THF-H_2O 1:1:1 solution). $NaBH_4$ was added after 6 h (reduction: 1.5 h at 20°C). Usual work-up ($CHCl_3$) and SC (hexanes-ethyl acetate 2:1) gave **45** (86%).- $[\alpha]_D^{20}$ = -15.9 (c 1.1, $CHCl_3$).- ^{1}H NMR (80 MHz, acetone-d_6): δ= 3.50-3.74 (6H), 3.78 (OCH_3), 4.46 and 4.67 (2 s, benzyl. H's), 6.76-7.60 (Ar-H).- MS: m/z (%)= 302 (0.8, M^+), 211 (26), 181 (25), 137 (44), 121 (100), 91 (80).- (Found: C, 71.47; H, 7.29. $C_{18}H_{22}O_4$ (302.4) requires C, 71.50; H, 7.33).

(S)-2-Allyloxy-3-(4-methoxy-benzyloxy)-propan-1-ol (46).
46 was prepared from **42** as described for **24** (in methanol-THF-H_2O 1:1:1 solution). $NaBH_4$ was added after 6.5 h (reduction: 30 min at 20°C). Usual work-up ($CHCl_3$) and SC gave **46** (67%).- $[\alpha]_D^{20}$ = -16.6 (c 0.5, $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 3.40-3.90 (5H), 3.79 (OCH_3), 4.02-4.17 (m, $CH_2CH=CH_2$), 4.45 (s, benzyl. H's), 5.06-5.41 (m, $CH_2CH=CH_2$), 5.65-6.22 (m, $CH_2CH=CH_2$), 6.78-7.37 (Ar-H).- MS: m/z (%)= 252 (20, M^+), 211 (25), 137 (90), 121 (90), 41 (100).- (Found: C, 66.73; H, 8.00. $C_{14}H_{20}O_4$ (252.3) requires C, 66.65; H, 7.99).

(R)-2-Benzyloxy-3-(2,2-dimethyl-propionyloxy)-propan-1-ol (47).
At 0°C to a solution of **43** (92 mg, 0.24 mmol) in acetonitrile (1.6 ml) and H_2O (0.2 ml) cerium(IV) ammonium nitrate (329 mg, 0.6 mmol) was added. The reaction mixture was stirred for 2.5 h at 20°C. Usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 7:2) gave **47** (52.2 mg, 82%).- The spectroscopic data were the same as reported for **24**.-$[\alpha]_D^{20}$ = 12.3 (c 1.1, $CHCl_3$).[43]

(R)-2-Benzyloxy-3-tert-butyldiphenylsilanyloxy-propan-1-ol (48).
48 was prepared from **44** as described for **47** (in acetonitrile-H_2O 22:1 solution). After 17 h usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 15:1) gave **48** (65%).- The spectroscopic data were the same as reported for **26**.- $[\alpha]_D^{20}$ = 24.3 (c 1.1, $CHCl_3$).

(S)-2-Benzyloxy-3-hexadecyloxy-1-(4-methoxy-benzyloxy)-propane (49).
49 was prepared from **45** as described for **38**, using 1-bromo-hexadecane instead of benzyl bromide. The reaction mixture was stirred for 4 h at 40°C. Usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 15:1) furnished **49** (90%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.86 (CH_3), 1.28 (28H), 3.30-3.70 (7H), 3.80 (OCH_3), 4.47 and 4.69 (2 s, benzyl. H's), 6.76-7.40 (Ar-

H).- MS: m/z (%)= 435 (30, $(M-91)^+$), 405 (20), 137 (50), 121 (100), 91 (92).- CD (CH_3CN, c 0.585 mmol/l): λ_{max} ($\Delta\varepsilon$)= 274 (-0.02), 269 (-0.02), 261 nm (-0.02).- (Found: C, 77.50; H, 10.29. $C_{34}H_{54}O_4$ (526.8) requires C, 77.52; H, 10.33).

ent-5a.

ent-5a was prepared from **49** as described for **47**. After 8 h at 20°C usual work-up (CH_2Cl_2) and SC (hexanes-ethyl acetate 15:1 to 10:1) provided ent-5a (82%).- The ^1H NMR and the mass spectrum were identical to those reported by Ohno.[11] $[\alpha]_D^{20}$ = 13.4 (c 1.0, $CHCl_3$), (lit.,[41] 7.98 (c 5, $CHCl_3$)).

Acknowledgements - We wish to thank Dr.W.Dietrich, H.Kühne, and M.Gartmann for the NMR spectra, Dr.D.Müller and D.Grzelak for the mass spectra, and Prof.Dr.G.Snatzke for the CD spectra. Financial support by the Deutsche Forschungsgemeinschaft, the Fond der Chemischen Industrie, and the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen (Heinrich-Hertz grant to W.B.) is gratefully acknowledged.

References and notes

1) Dedicated to Professor Ulrich Schöllkopf on the occasion of his 60th birthday.
2) Review: J.Jurczak, St.Pikul, and T.Bauer, Tetrahedron **42**, 447 (1986).
3) Review: J.Mulzer, Nachr.Chem.Tech.Lab. **32**, 146 (1984).
4) Review: S.Takano, Pure Appl.Chem. **59**, 353 (1987).
5) C.Morpain and M.Tisserand, J.Chem.Soc.Perkin Trans. I **1979**, 1379.
6) Review: H.Eibl, Angew.Chem. **96**, 247 (1984).
7) Th.Schubert, F.Kunisch, and P.Welzel, Tetrahedron **39**, 2211 (1983).
8) Ch.Hubschwerlen, Synthesis **1986**, 962, and references therein.
9) C.M.Lok, J.P.Ward, and D.A.van Dorp, Chem.Phys.Lipids **16**, 115 (1976).
10) T.Tsuri and S.Kamata, Tetrahedron Lett. **26**, 5195 (1985).
11) M.Ohno, K.Fujita, H.Nakai, S.Kobayashi, K.Inoue, and Sh.Nojima, Chem.Pharm.Bull. **33**, 572 (1985).
12) T.Mukaiyama, T.Tanabe, and M.Shimizu, Chem.Lett. **1984**, 401; J.Ishikawa, M.Asami, and T.Mukaiyama, Chem.Lett. **1984**, 949.
13) T.Fujisawa, T.Itoh, M.Nakai, and T.Sato, Tetrahedron Lett. **26**, 771 (1985).
14) G.Guanti, L.Banfi, and E.Narisano, Tetrahedron Lett. **27**, 3547 (1986).
15) T.Mukaiyama, S.Tanaka, and M.Asami, Chem.Lett. **1982**, 433, and references therein.
16) S.Y.Ko and K.B.Sharpless, J.Org.Chem. **51**, 5413 (1986); review: A.Pfenninger, Synthesis **1986**, 89.
17) G.Solladie and J.Hutt, Tetrahedron Lett. **28**, 797 (1987).
18) D.Breitgoff, K.Laumen, and M.P.Schneider, J.Chem.Soc.,Chem.Commun. **1986**, 1523.
19) V.Kerscher and W.Kreiser, Tetrahedron Lett. **28**, 531 (1987).
20) see also: H.Suemune, Y.Mizuhara, H.Akita, K.Sakai, Chem.Pharm.Bull. **34**, 3440 (1986); G.M.Ramos Tombo, H.-P.Schär, X.Fernandez i Busquets, O.Ghisalba, Tetrahedron Lett. **27**, 5707 (1986).
21) For (S)-glyceric acid as starting material, see S.K.Bhatia and J.Hajdu, Tetrahedron Lett. **28**, 271 (1987).
22) see, for example: C.A.A.van Boeckel and J.H.van Boom, Tetrahedron **41**, 4545 (1985), and references therein.
23) Reviews: B.B.Vargaftig and J.Benveniste, Trends Pharmacol.Sci. **4**, 341 (1983); N.Weber, Pharmazie in unserer Zeit **15**, 107 (1986).
24) Review: M.C.Venuti, Ann.Rep.Med.Chem. **20**, 193 (1985).
25) C.A.A.van Boeckel, G.A.van der Marel, P.Westerduin, and J.H.van Boom, Synthesis **1982**, 399.
26) F.Heymans, E.Michel, M.-C.Borrel, B.Wichrowski, and J.-J.Godfroid, C.R.Acad.Sci., Ser.2 **293**, 49 (1981), and references therein.
27) G.Hirth and R.Barner, Helv.Chim.Acta **65**, 1059 (1982).
28) G.Hirth, H.Saroka, W.Bannwarth, and R.Barner, Helv.Chim.Acta **66**, 1210 (1983).
29) B.Cimetiere, L.Jacob, and M.Julia, Tetrahedron Lett. **27**, 6329 (1986).
30) Th.Schubert, K.Hobert, and P.Welzel, Tetrahedron **39**, 2219 (1983).
31) c.f. M.T.Reetz and K.Kessler, J.Org.Chem. **50**, 5434 (1985).
32) J.A.Dale, D.L.Dull, and H.S.Mosher, J.Org.Chem. **34**, 2543 (1969).
33) Kerscher and Kreiser reported an $[\alpha]_D^{25}$ = -11.9 for 25.[19]
34) Simular observations have been reported by Prof. Kreiser, Chemiedozententagung, Göttingen, 22.-25.3.1987.
35) U.Peters, Dissertation, Ruhr-Universität Bochum, in preparation.
36) R.Johansson, B.Samuelsson, J.Chem.Soc.,Chem.Commun. **1984**, 201.
For a review on this subject, see P.J.Garegg, Pure Appl.Chem. **56**, 845 (1984).
37) R.Allerton, H.G.Fletcher, Jr., J.Am.Chem.Soc. **76**, 1757 (1954).
38) W.Stoffel, G.D.Wolf, Hoppe-Seyler's Z.Physiol.Chem. **347**, 94 (1966).
39) S.K.Chaudhary, O.Hernandez, Tetrahedron Lett. **1979**, 99.
40) V.W.Goodlett, Anal.Chem. **37**, 431 (1965); I.R.Trehan, C.Monder, A.K.Bose, Tetrahedron Lett. **1968**, 67.
41) H.Prinz, L.Six, K.-P.Rueß, M.Liefländer, Liebigs Ann.Chem. **1985**, 217.
42) The ^1H NMR spectrum was identical to that reported by Ohno.[11]
43) The optical purity was not determined.