Diastereo- and Enantioselective Synthesis of 1,2:5,6-Diepoxy-4-hydroxyalkyl Carbamates. – Regioselective Ring Opening and Their Transformation into Doubly *C*-Branched Deoxy Sugar Analogues[1]

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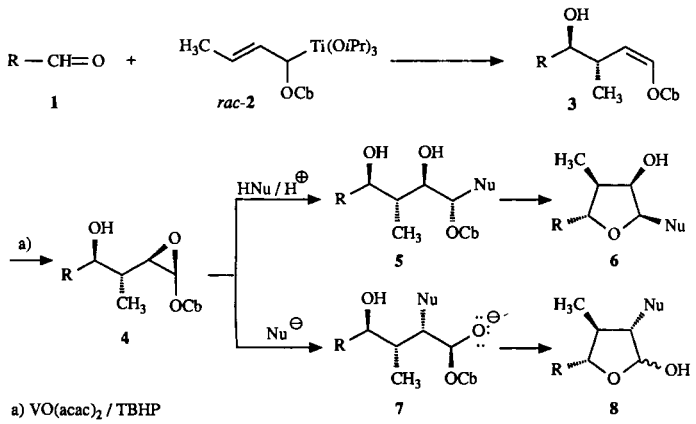
Enantiomerically enriched (*Z*)-*anti*-3,5-dialkyl-4-hydroxy-1,5-alkadienyl *N,N*-diisopropylcarbamates **12**, readily obtained by the homoaldol approach, were oxidized with essentially complete diastereoselectivity to afford 1,2:5,6-diepoxides **14** of D-*allo* configuration. Conditions were worked out for the transformation of **14** into furanosides of types **19**, **21**, and **22** and for the selective nucleophilic introduction of carbon residues into the 6-position to give chain-elongated analogues **25**. Altogether, a "brick-box system" for the enantioselective construction of polystereogenic building blocks with a few synthetic steps from simple achiral starting materials [(*E*)-2-alkenyl carbamates of type **9** and 2-alkyl-2-alkenals (**11**)] and nucleophiles, like Grignard reagents, is demonstrated.

The homoaldol reaction[2,3] of α-titanated 2-alkenyl carbamates like *rac*-**2** with aldehydes leads with nearly complete diastereoselectivity to (*Z*)-*anti*-4-hydroxy-1-alkenyl *N,N*-diisopropylcarbamates *rac*-**3** (Scheme 1). Enantiomerically enriched derivatives are readily accessible by the use of optically active aldehydes[4] and subsequent separation of the diastereomers or by application of non-racemic titanium reagents of type **2** obtained by lithiation of the precursor in the presence of the chiral diamine (–)-sparteine (**10**)[5,6], followed by lithium-titanium exchange[7].

Scheme 1. Cb = C(=O)N(*i*Pr)$_2$



The epoxidation of the homoallylic double bond in **3** by the Sharpless-Mihelich method[8], which is directed by the hydroxy group, to furnish 2-(carbamoyloxy)oxiranes **4** proceeds with essentially complete diastereoselectivity. Nucleophiles under acidic conditions attack position 1 (numbering as in **14**) in **4** with inversion of the configuration[9,4c,10] to yield diols **5**, which can cyclize to tetrahydrofurans **6**. Strong nucleophiles, under basic conditions, attack position 2 with inversion of configuration to afford γ-lactols **8** via open-chain intermediates **7** (Scheme 1). On the basis of these reactions, an easy protocol for the synthesis of 3,6-dideoxy-3-*C*-methylaldofuranosides was developed[4c].

We expected that the extension of this method to 1,5-dienyl carbamates of type **12** (Scheme 2) could give rise to chiral building blocks in four steps, bearing up to five consecutive stereogenic centres.

Homoaldol Reactions

The reaction of the 2-butenyl carbamate **9**, after lithiation with *n*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA)[10] and addition of tetraisopropoxytitanium[11], with 2-methylpropenal (**11a**) or 2-isopropylpropenal (**11b**) affords the homoaldol adducts *rac*-**12a** in 81% or *rac*-**12b** in 82% yield, respectively. Application of the sparteine method[5] in each case leads to a single diastereomer (–)-**12** (86% *ee*) and to (–)-**12b** (90% *ee*) in 78 and 81% yield, respectively.

The assumed relative (*Z*)-*anti*-configuration of **12** is based on several findings[3,11–13] and has been confirmed for **12a** at the stage of **19a** by an X-ray crystal structure analysis. Since the addition of the titanium compound **4** proceeds in a pericyclic process accompanied by chirality transfer[5,14,15] the absolute configuration of **12** is induced by the configuration of **2**. The enantiomeric excess is easily determined with the aid of the chiral NMR-shift reagent Eu(hfc)$_3$.

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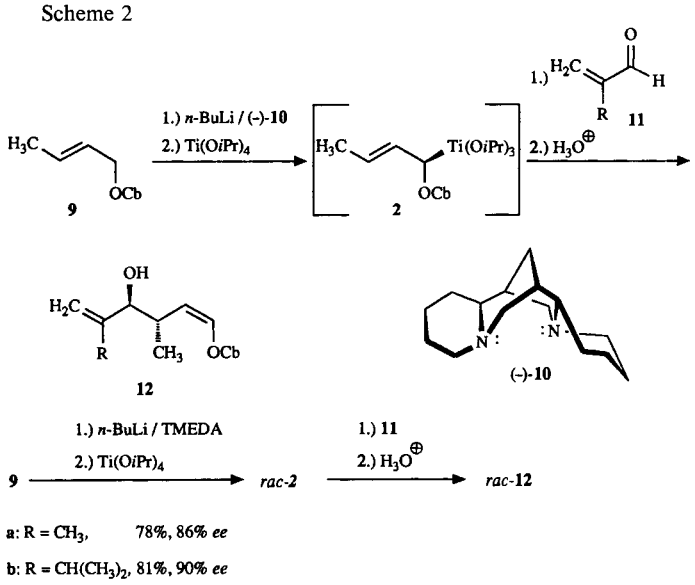
Scheme 2



a: R = CH_3, 78%, 86% *ee*

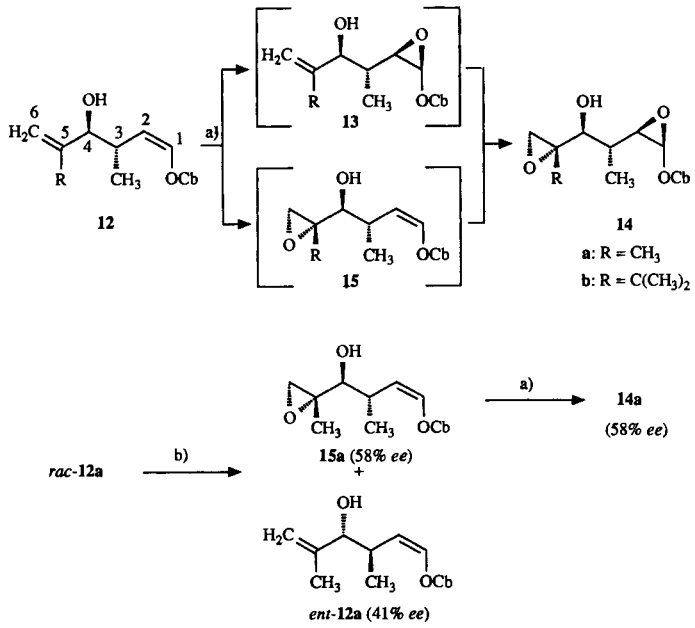
b: R = $CH(CH_3)_2$, 81%, 90% *ee*

Epoxidation

Oxidation of either (−)- or *rac*-**12a,b** with two equivalents of *tert*-butyl hydroperoxide/vanadyl bis(acetylacetonate)[9,4c,8] affords diastereomerically pure bisepoxides[16] (−)- or *rac*-**14a,b** in high yields (Scheme 3).

Whereas the configuration at C-1 and C-2 of **14** is deduced from the preceding results with high reliability, the configuration at C-5 is less predictable. On the other hand, much experience about the stereochemical course of kinetic racemate resolution by asymmetric Sharpless epoxidation[17] of allylic alcohols is available. Therefore, *rac*-**12a** in subjected to the titanium-catalyzed epoxidation in the presence of (+)-(*R,R*)-diisopropyl tartrate, which gives 5,6-monoepoxide (+)-**15a** (26%, 58% *ee*) besides recovered (+)-*ent*-**12a** (59%, 41% *ee*), according to expectation. Vanadium-catalyzed epoxidation of (+)-**15a** yields (−)-**14a**. The NMR data of the new epoxides are collected in Tables 3 and 4.

Scheme 3



[a] *t*BuOOH/VO(acac)$_2$. — [b] 1.00 equiv. of TIPT/1.20 equiv. of (+)-DIPT/0.55 equiv. of *t*BuOOH.

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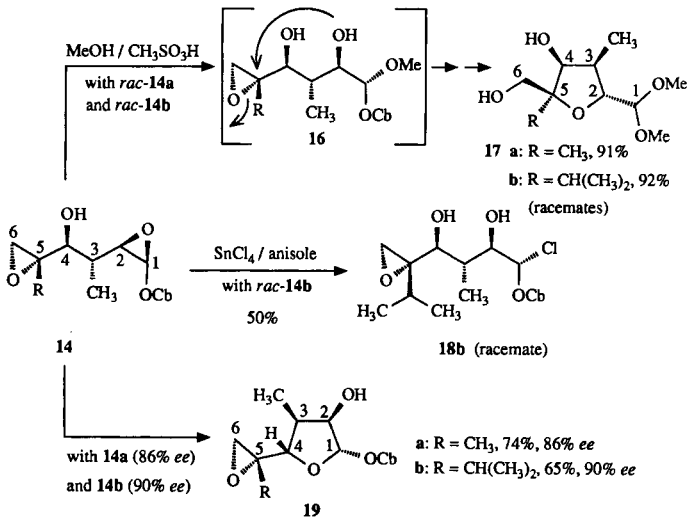
The preparative utilization of the diastereomerically pure bisepoxides requires a differentiation between both oxirane moieties.

Treatment of *rac*-**14** with excess methanol in the presence of methanesulfonic acid results in the formation of a single tetrahydrofuran *rac*-**17** (yields 91 and 92%, respectively). The first intermediate *rac*-**16** results from the methanolysis of the oxirane moiety at C-1 and C-2. It cyclizes by nucleophilic attack of the 2-OH group at C-5 to give a tetrahydrofuran. Substitution of the carbamoyloxy group by a methoxy group leads to *rac*-**17** (Scheme 4).

Scheme 4



17 a: R = CH_3, 91%
b: R = $CH(CH_3)_2$, 92%
(racemates)

18b (racemate)

a: R = CH_3, 74%, 86% *ee*
b: R = $CH(CH_3)_2$, 65%, 90% *ee*

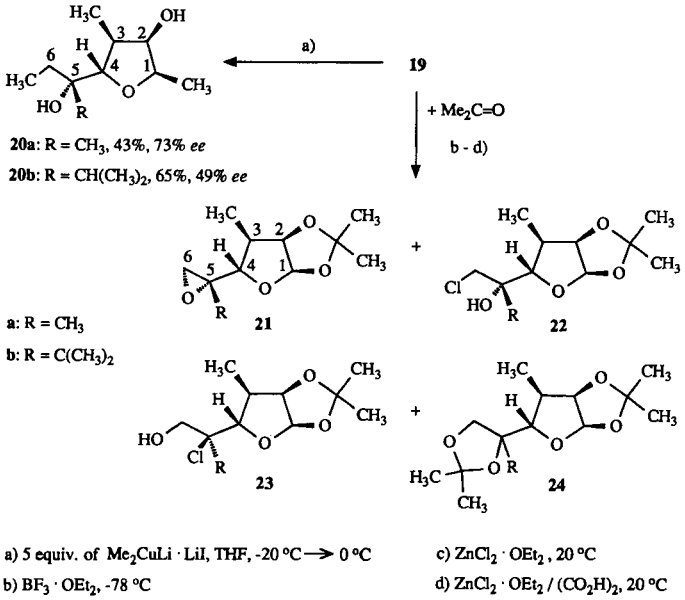
The reaction of *rac*-**14b** with tin tetrachloride in anisole furnishes diastereomerically pure 1-chloroalkyl carbamate *rac*-**18b**. The relative configuration at C-1 is concluded from the ^{1}H-NMR coupling constant $J_{1,2}$ = 4.4 Hz, which is rather close to that of similar azides[1b] and acetylenes[1b] (Scheme 4).

In the presence of zinc chloride–ether in THF, the 4-hydroxy group in **14a,b** acts as internal nucleophile, followed by Lewis acid-catalyzed anomerization to furnish the oxirane-substituted furanosyl carbamates **19a,b** (Scheme 4). A racemic sample of **19a** affords suitable crystals for an X-ray crystal structure analysis[18], which confirms its constitution and relative configuration (Figure 1). The NMR data of **19a**, together with those of several tetrahydrofurans, are given in Tables 5 and 6.

The furanosyl carbamates **19** have turned out to be unsuitable for the selective substitution by carbon nucleophiles. For example, the reaction of **19a,b** with excess lithium

dimethylcuprate[19,20,21] results in a 1,6-dimethylation with formation of the diols **20a,b** (Scheme 5).

Scheme 5



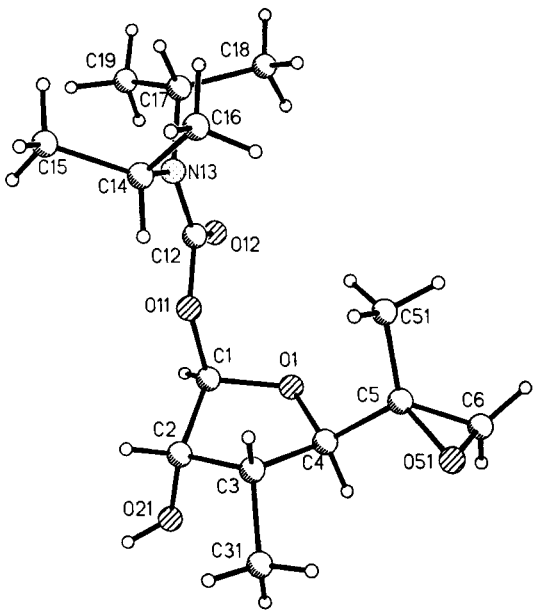


Figure 1. X-ray analysis of *rac*-**19a** in the crystal. Depicted is (+)-**19a**. Hatched circles symbolize oxygen atoms, dotted circles symbolize nitrogen atoms. Large white circles represent carbon atoms. The locations of the hydrogen atoms are shown by small white circles

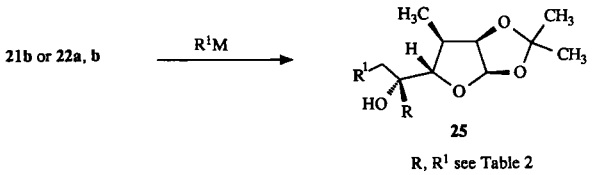
In order to deactivate position C-1[22] by the formation of the 1,2-acetonides, the carbamates **19** are treated with acetone in the presence of different Lewis acids. The oxirane ring of the isopropyl derivative **19b** can be retained under several conditions in the product **21b** (Table 1), whereas treatment of the less shielded **19a** with zinc chloride furnishes chlorohydrin **22a**. Occasionally, the isomer **23a** or the bisacetonide **24a**[23] is formed (Scheme 5).

Tab. 1. Formation of 1,2-acetonides from carbamates **19**

	Lewis acid	Temperature [°C]	Time	**21** (%)	**22** (%)	**23** (%)	**24** (%)
19a	$BF_3 \cdot OEt_2$	−78	30 min	—	—	—	45
19b	$BF_3 \cdot OEt_2$	−78	30 min	47	—	—	—
19a	$ZnCl_2 \cdot OEt_2$	20	4 d	—	51	—	—
19b	$ZnCl_2 \cdot OEt_2$	20	4 d	44	12	—	—
19a	$ZnCl_2 \cdot OEt_2$/ $(CO_2H)_2$	20	1 h	—	48	12	—
19b	$ZnCl_2 \cdot OEt_2$/ $(CO_2H)_2$	20	1 h		59	—	—

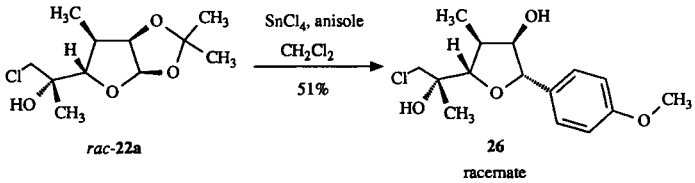
However, epoxides **21** and chlorohydrins **22** have proved to be synthetically equivalent in a number of carbanioic substitution reactions investigated, in particular cuprate-mediated[19,20,21,24,25] methylation, vinylation, phenylation as well as phenylethynylation with the appropriate dimethylalane[26,27,28] affording the 6-substituted furanosides **25** proceed without any problems (Scheme 6, Table 2).

Scheme 6



On the other hand, in chlorohydrins of type **22** the 1-position can be further elaborated in Lewis acid-catalyzed nucleophilic substitution reactions by utilizing the high stabilization of the intermediate tetrahydrofuranyl cation. Thus, *rac*-**22a** is converted into the *p*-methoxyphenyl derivative *rac*-**26** in 51% yield by the action of anisole in the presence of tin tetrachloride[29,30] (Scheme 7).

Scheme 7



Structure Elucidation of Tetrahydrofurans and Furanosides

The structure assignments in the tetrahydrofuran derivatives are based on the known configuration of **19a**, a comparison of the proton coupling constants with those observed in compounds of similar substitution patterns[1b,31] (see Tables 3 and 4), and on the well established fact[32] that in nucleophilic ring opening of epoxides the remaining C−O bond remains unaffected.

Table 2. Chain elongation by the reaction of **21b** and **22a,b** with carbon nucleophiles

Starting material	R^1M	Equiv.	Product	R	R^1	Yield (%)	% *ee*
rac-**21b**	$Me_2CuLi \cdot LiI$	5	*rac*-**25a**	$(CH_3)_2CH$	CH_3	80	0
21b (90% *ee*)	MeMgCl, CuI	3	**25a**	$(CH_3)_2CH$	CH_3	79	90
rac-**21b**	$CH_2=CH-MgBr$, CuI	3	*rac*-**25b**	$(CH_3)_2CH$	$CH_2=CH$	54	0
rac-**21b**	$Ph_2CuLi \cdot LiCN$	5	*rac*-**25c**	$(CH_3)_2CH$	C_6H_5	52	0
rac-**21b**	$PhC\equiv C-AlMe_2$	2	*rac*-**25d**	$(CH_3)_2CH$	$PhC\equiv C$	53[a]	0
rac-**22a**	$Me_2CuLi \cdot LiI$	5	*rac*-**25e**	CH_3	CH_3	57	0
22b (90% *ee*)	$Me_2CuLi \cdot LiI$	5	**25a**	$(CH_3)_2CH$	CH_3	57	90

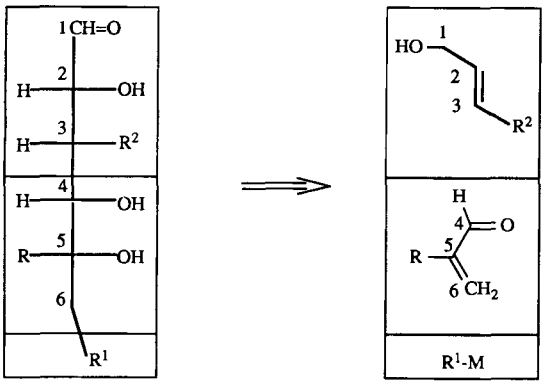
[a] In addition 21% of *rac*-**22b**.

Conclusions

Compounds **14a**, **19a**, or **22a** can be regarded as selectively protected and activated derivatives of 3,5-di-*C*-methyl-3-deoxy-D-allose (**27a**), which is obtained with five steps by the asymmetric homoaldol coupling of two nonstereogenic subunits C-1–C-3 and C-4–C-6. In addition, further substitution at C-6 by various nucleophiles is particularly facile.

The methodology outlined above offers a versatile system for the construction of polystereogenic units from simple constituents by three synthetic steps: enantioselective homoaldol addition of an (*E*)-2-alkenyl carbamate, hydroxy-directed bisepoxidation, and nucleophilic substitution (Scheme 8).

Scheme 8



27a: $R = R^2 = CH_3$

$R^1 = OH$

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Experimental

Melting points: Melting point apparatus according to Dr. Tottoli (W. Büchi), uncorrected. – ^1H and ^{13}C NMR: Bruker AM 300 and Bruker AC 200 P, TMS as internal standard. – MS: Finnigan MAT 8320. – IR: Perkin Elmer 283 B. – Optical rotation: Perkin Elmer Polarimeter 241. – Elemental analyses: Mikroanalytisches Laboratorium Beller, Göttingen, or Institut für Anorganische Chemie der Universität Kiel. – R_f data: ether/pentane (1:1). – All reactions were performed in oven-dried glassware under dry argon. – Analytical TLC: Macherey & Nagel Sil G/UV_{254}. – Flash chromatography: 33–63 mm silica gel, ICN Biochemicals.

Homoaldol Reactions

(1Z,3R,4R*)-4-Hydroxy-3,5-dimethylhexa-1,5-dienyl N,N-Diisopropylcarbamate* (*rac*-**12a**): A solution of 7.96 g (40 mmol) of **9**[10] and 6.7 ml (45 mmol) of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in 120 ml of ether was cooled to −78°C. 25 ml of a 1.6 N solution of *n*-butyllithium was added dropwise to the mixture. After 30 min 12.8 ml (45 mmol) of tetraisopropoxytitanium was added. The mixture was stirred for 5 min. Then 4.2 g (60 mmol) of 2-methylpropenal was added. The mixture was stirred at −78°C for 16 h and then warmed up to room temp. The solution was poured into 200 ml of 2 N HCl and 200 ml of ether. After separation, the aqueous layer was extracted with ether (2 × 50 ml). The combined organic solutions were neutralized with satd. sodium hy-

Table 3. ^1H-NMR data of compounds **12**, **14**, **15**, **17**, and **18**; chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$

	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H ($J_{3,4}$)	3-CH_3 ($J_{3,3'}$)	4-H	4-OH ($J_{4,OH}$)	5-R	6-H_2 ($J_{6,6}$)
12a[a]	7.17 dd (*6.8*)	4.66 dd (*10.0*)	2.89 qddd (*8.5*)	0.94 d (*7.0*)	3.76 ddd	1.93 m	1.74 dd	4.93, 4.95 both ddq (*2.1*)
12b[b]	7.15 dd (*6.4*)	4.68 dd (*9.9*)	2.93 qddd (*7.8*)	0.98 d (*6.9*)	3.82 ddd	1.82 d (*2.5*)	2.34 qqd	4.99, 5.04 both dd (*1.0*)
14a[c]	5.61 d (*2.8*)	3.06 dd (*9.2*)	1.97 qdd (*2.9*)	1.19 d (*7.1*)	3.79 ddd	2.38 m	1.37 d	2.74, 3.04 dd, qdd (*4.4*)
14b[d]	5.61 d (*2.8*)	3.06 dd (*9.4*)	1.99 qdd (*2.2*)	1.19 d (*7.2*)	3.97 dd	2.31 m (m)	2.02 qq	2.88, 2.98 both dd (*4.0*)
15a[e]	7.06 dd (*6.5*)	4.79 dd (*10.1*)	3.00 qdddd (*4.0*)	1.21 d (*7.0*)	3.51 m	2.11 dd (*1.2*)	1.36 d	2.62, 2.93 d, dd (*4.7*)
17a[f]	4.28 d (*5.3*)	3.88 dd (*10.2*)	2.34 qdd (*5.0*)	1.12 d (*6.9*)	3.95 d	2.92 m	1.13 s	3.78 s
17b[g]	4.26 d (*5.5*)	3.81 dd (*10.2*)	2.18 qdd (*5.7*)	1.10 d (*6.9*)	4.09 dd	3.67 d (*8.0*)	1.71 qq	3.75, 3.96 dd, dd (*11.5*)
18b[h]	6.75 d (*4.4*)	4.46 dd (*8.7*)	2.18 qqd (*6.2*)	1.17 d (*7.2*)	4.14 d	1.7 - 2.5 m	2.24 qq	2.55, 2.69 both d (*4.3*)

[a] $J_{1,3} = 0.9$, $J_{4,6} = 1.0$, $J_{4,6} = 0.6$, $J_{6,5\text{-}R} = 0.8$, $J_{6,5\text{-}R} = 1.5$ Hz. – [b] $J_{1,3} = 0.9$, $J_{4,6} = 1.1$, $J_{6,5\text{-}CH} = 0.9$ Hz. – [c] $J_{4,6} = 0.5$, $J_{4,6} = 0.6$, $J_{6,5\text{-}CH_3} = 0.6$ Hz. – [d] $J_{4,6} = 0.5$, $J_{4,6} = 0.5$ Hz. – [e] $J_{1,3} = 0.9$, $J_{3,OH} = 1.2$, $J_{6,5\text{-}CH_3} = 0.7$ Hz. – [f] Numbering of the open-chain compound is retained; further signals at δ = 3.45 and 3.46 (both s, OCH_3); 3.78 (s, 6-OH). – [g] Numbering of the open-chain compound is retained; further signals at δ = 3.45 and 3.47 (both s, OCH_3); 2.69 (dd, 6-OH); $J_{6,OH} = 9.6$, $J_{6,OH} = 3.2$ Hz. – [h] δ = 1.7–2.5: two hydroxy protons can be detected.

drogen carbonate solution, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on 500 g of silica gel (ether/pentane, 1:2). 8.72 g (81%) of colourless crystals of *rac*-**12a** were obtained, m.p. 61°C (without solvent). R_f = 0.35. – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1690 (C=O). – ^{1}H- and ^{13}C-NMR data see Tables 3 and 4.

Table 4. ^{13}C-NMR data of compounds **12**, **14**, **15**, **17**, **18**; chemical shifts (δ)

	C-1	C-2	C-3	3-CH_3	C-4	C-5	5-R	C-6
12a	136.45	112.85	34.34	17.58	79.72	145.42	17.14	112.85
12b	136.55	112.70	35.42	17.90	78.90	156.78	30.04	109.23
14a	75.19	55.61	34.61	14.04	74.29	58.26	18.39	50.44
14b	75.36	55.25	34.52	14.48	71.45	63.28	27.60	48.31
15a	135.51	111.49	32.75	17.82	75.34	58.15	18.35	50.73
17a[a]	106.87	83.25	40.01	10.62	81.34	84.53	23.72	66.80
17b[b]	107.08	83.33	40.74	10.66	78.78	88.95	33.96	63.53
18b	98.59	86.41	34.53	13.36	73.04	61.43	27.72	47.27

[a] Numbering of open-chain compounds is retained; further signals at δ = 54.58 and 55.80 (OCH_3). – [b] Numbering of open-chain compounds is retained; further signals at δ = 54.98 and 55.55 (OCH_3).

(1Z,3R,4R*)-4-Hydroxy-5-isopropyl-3-methylhexa-1,5-dienyl N,N-Diisopropylcarbamate* (*rac*-**12b**): According to an analogous procedure 9.74 g (82%) of *rac*-**12b** was obtained from 7.96 g (40 mmol) of **9** and 5.9 g (60 mmol) of 2-isopropylpropenal as a colourless oil, R_f = 0.42. – IR (film): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1700 (C=O), 1680 (C=C).

Homoaldol Reactions by Means of the Sparteine Method

(1Z,3S,4S)-(–)-4-Hydroxy-3,5-dimethylhexa-1,5-dienyl N,N-Diisopropylcarbamate [(–)-**12a**]: 1.4 g (4.9 mmol) of (–)-sparteine was dissolved in 10 ml of pentane and 2 ml of cyclohexane. The resulting mixture was cooled to –78°C. 4.7 mmol of *n*-butyllithium (as a 1.6 N solution in hexane) and after 15 min a solution of 796 mg (4.0 mmol) of carbamate **9** in 2 ml of pentane were added. The mixture was stirred for 15 min. The crystals which had precipitated at the glass-wall were warmed to –20°C for 1 min and stirred at –78°C for additional 15 min. 8 ml (28 mmol) of tetraisopropoxytitanium was quickly added. After 5 min 769 mg (10.0 mmol) of 2-methylpropenal was added. The solution was stirred at –78°C for 3 h and then warmed up to room temp. The workup was the same as in the TMEDA method. 840 mg (78%) of (–)-**12a** was obtained as a colourless oil. The enantiomeric excess (86% *ee*) was determined by a ^{1}H-NMR shift experiment in tetrachloromethane with 11 mol % of Eu(hfc)$_3$ by using the signals of 1-H at δ = 8.45 [(–)-**12a**] and 7.60 [(+)-**12a**]. $[\alpha]_D^{20}$ = –16.4 (*c* = 3.5, CH_2Cl_2) for 86% *ee*.

(1Z,3S,4S)-(–)-4-Hydroxy-5-isopropyl-3-methylhexa-1,5-dienyl N,N-Diisopropylcarbamate [(–)-**12b**]: According to an analogous procedure 962 mg (81%) of (–)-**12b** was obtained from 796 mg (4.0 mmol) of **9** and 980 mg (10 mmol) of 2-isopropylpropenal as a colourless oil. The enantiomeric excess (90% *ee*) was determined by an ^{1}H-NMR shift experiment in tetrachloromethane with 8 mol % of Eu(hfc)$_3$ by using the signals of 1-H at δ = 8.2 [(–)-**12b**] and 7.6 [(+)-**12b**]. $[\alpha]_D^{20}$ = –0.8 (*c* = 4.4, CH_2Cl_2) for 90% *ee*.

Epoxidations

Vanadyl-Catalyzed Epoxidation

(1R,2S*,3S*,4R*,5S*)- and (1S,2R,3R,4S,5R)-(–)-1,2:5,6-Diepoxy-4-hydroxy-3,5-dimethylhexyl N,N-Diisopropylcarbamate* [*rac*-**14a** and (–)-**14a**]: 8.07 g (30 mmol) of *rac*-**12a** and 240 mg (3 mol %) of vanadyl acetylacetonate were dissolved in 75 ml of dichloromethane. Then 11.2 ml (90 mmol) of *tert*-butyl hydroperoxide (80% in di-*tert*-butyl peroxide) was added to the solution while cooling with an ice bath. The mixture was stirred at room temp. for 16 h. Then 6.6 ml (90 mmol) of dimethyl sulfide was added. The resulting mixture was poured into a mixture of 150 ml of ether and 90 ml of satd. sodium hydrogen carbonate solution. The aqueous phase was extracted with ether (2 × 30 ml). The combined organic phases were dried with magnesium sulfate, and the ether was evaporated. The residue was crystallyzed from ether/hexane (1:3) to afford 7.13 g (79%) of colourless crystals of *rac*-**14a** of m.p. 89°C (ether/hexane, 1:3). R_f = 0.25. – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 1700 (C=O). – ^{1}H- and ^{13}C-NMR data see Tables 3 and 4. – By using an analogous procedure for the reaction of 660 mg (2.5 mmol) of (–)-**12a** (86% *ee*) and workup followed by purification of the crude product by chromatography on 40 g of silica gel, 562 mg (76%) of (–)-**14a** (86% *ee*) was obtained as a colourless oil, $[\alpha]_D^{20}$ = –13.8 (*c* = 4.1, CH_2Cl_2) for 86% *ee*.

(1R,2S*,3S*,4R*,5S*)- and (1S,2R,3R,4S,5R)-1,2:5,6-Diepoxy-4-hydroxy-5-isopropyl-3-methylhexyl N,N-Diisopropylcarbamate* [*rac*-**14b** and (–)-**14b**]: By the application of an analogous procedure to the reaction of *rac*-**12b** (8.91 g, 30 mmol) and workup and subsequent purification of the crude product by chromatography on 600 g of silica gel (ether/pentane, 1:1) 7.99 g (81%) of *rac*-**14b** was obtained as a colourless oil. R_f = 0.35. – IR (film): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1700 (C=O). – According to an analogous procedure and workup followed by purification by chromatography on 17 g of silica gel (ether/pentane, 1:1) 297 mg (1.0 mmol) of (–)-**12b** (90% *ee*) afforded 210 mg (64%) of (–)-**14b** (90% *ee*) as a colourless oil, $[\alpha]_D^{20}$ = –11.3 (*c* = 1.1, CH_2Cl_2) for 90% *ee*.

Kinetic Resolution by the Sharpless-Epoxidation

*Epoxidation of rac-***12a**; (+)-**12a** *and (1Z,3S,4S,5R)-(+)-5,6-Epoxy-4-hydroxy-3,5-dimethylhex-1-enyl N,N-Diisopropylcarbamate* [(+)-**15a**]: A solution of 538 mg (2.0 mmol) of *rac*-**12a**, 0.6 ml (2.0 mmol) of tetraisopropoxytitanium, and 0.5 ml (2.4 mmol) of (+)-diisopropyl tartrate in 15 ml of dichloromethane was stirred at room temp. for 15 min and then cooled to –20°C. Then 0.21 ml (1.1 mmol) of *tert*-butyl hydroperoxide (5.3 M in 1,2-dichloroethane) was added. The mixture was kept in the refrigerator (–16°C) for 24 h. 0.21 ml (2.8 mmol) of dimethyl sulfide was added at –20°C. The solution was stirred for 30 min. Then 447 mg (3.0 mmol) of triethanolamine, dissolved in 2 ml of dichloromethane, was added. The mixture was warmed up to 0°C and filtered through a plug of 100 g of silica gel. The silica gel was washed with 300 ml of ether. Then the solution was evaporated and the residue chromatographed on 30 g of silica gel (ether/pentane, 1:2) to give 316 mg (59%) of (+)-**12a** as a colourless oil [41% *ee*, $[\alpha]_D^{20}$ = +8.6 (*c* = 4.2, CH_2Cl_2)] and 135 mg (26%) of (+)-**15a** [57% *ee*, $[\alpha]_D^{20}$ = +14.6 (*c* = 3.0, CH_2Cl_2)]. The enantiomeric excess of (+)-**12a** was determined by a ^{1}H-NMR shift experiment in tetrachloromethane with 11 mol % Eu(hfc)$_3$ by using the absorptions of 1-H at δ = 8.45 [(–)-**12a**] and 8.15 [(+)-**12a**].

(+)-**15a**: R_f = 0.27. – IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 1690 (C=O). – $[\alpha]_D^{20}$ = +14.6 (*c* = 3.0, CH_2Cl_2) for 57% *ee*. – ^{1}H- and ^{13}C-NMR data see Tables 3 and 4.

Epoxidation of (+)-**12a**; *(1R,2S,3S,4R,5S)-(+)-1,2:5,6-Diepoxy-4-hydroxy-3,5-dimethylhexyl N,N-Diisopropylcarbamate* [(+)-**14a**]: By epoxidation with 3.5 g (1.5 mol%) of vanadyl acetylacetonate and 0.16 ml (1.29 mmol) of *tert*-butyl hydroperoxide, by analogy with the procedure described for *rac*-**12a**, 232 mg (0.86

mmol) of (+)-**12a** (41% *ee*) was converted into 179 mg (63%) of (+)-**14a** with $[\alpha]_D^{20} = +7.7$ ($c = CH_2Cl_2$).

Epoxidation of (+)-**15a**; *(1S,2R,3R,4S,5R)-1,2:5,6-Diepoxy-4-hydroxy-3,5-dimethylhexyl N,N-Diisopropylcarbamate* [(−)-**14a**]: 125 mg (0.44 mmol) of (+)-**15a** (57% *ee*) and 2 mg (1.7 mol-%) of vanadyl acetylacetonate were dissolved in 1.5 ml of dichloromethane. Then 0.08 ml (0.66 mmol) of *tert*-butyl hydroperoxide (80% in di-*tert*-butyl peroxide) was added to the solution while cooling with a water bath. The mixture was stirred at room temp. for 16 h. Then 0.05 ml (0.66 mmol) of dimethyl sulfide was added. The mixture was stirred for additional 30 min and subsequently poured into 30 ml of ether and 20 ml of satd. sodium hydrogen carbonate solution. The aqueous phase was extracted with ether (2 × 10 ml). The combined organic phases were dried with magnesium sulfate, and the solvent was evaporated. The residue was chromatographed on 9 g of silica gel to afford 74 mg (56%) of (−)-**14a** (57% *ee*) with $[\alpha]_D^{20} = -11.0$ ($c = 3.5$, CH_2Cl_2).

Nucleophilic Substitution Reactions of Diepoxides

(2R,3R*,4S*,5S*)-5-(Dimethoxymethyl)-tetrahydro-2-(hydroxymethyl)-2,4-dimethylfuran-3-ol* (*rac*-**17a**): To a solution of 301 mg (1.0 mmol) of *rac*-**14a** in 3 ml of methanol and 1 ml of dichloromethane was added 0.065 ml (1.0 mmol) of methanesulfonic acid at room temp. The mixture was stirred for 30 min and then poured into 20 ml of ether and 20 ml 2 N HCl. The aqueous phase was extracted with pentane (2 × 20 ml). The combined organic phases were neutralized with satd. sodium hydrogen carbonate solution, dried with sodium sulfate, and concentrated. The crude product was purified by chromatograhy on 17 g of silica gel (ether/pentane, 2:1) to give 199 mg (91%) of *rac*-**17a** as a colourless oil, $R_f = 0.07$. – IR (film): $\tilde{\nu} = 3500\ cm^{-1}$ (OH). – ^{1}H- and ^{13}C-NMR data see Tables 3 and 4.

(2R,3R*,4S*,5S*)-5-(Dimethoxymethyl)-tetrahydro-2-(hydroxymethyl)-2-isopropyl-4-methylfuran-3-ol* (*rac*-**17b**): According to an analogous procedure 329 mg (10 mmol) of *rac*-**14b** afforded 230 mg (92%) of *rac*-**17b** as a colourless oil, $R_f = 0.10$. – IR (film): $\tilde{\nu} = 3500\ cm^{-1}$ (OH).

(1R,2S*,3S*,4R*,5S*)-1-Chloro-5,6-epoxy-2,4-dihydroxy-5-isopropyl-3-methylhexyl N,N-Diisopropylcarbamate* (*rac*-**18b**): 329 mg (1.0 mmol) of *rac*-**14b** was dissolved in 2 ml of anisole. This mixture was added dropwise to a solution of 42 mg (0.16 mmol) of tin(IV) chloride, 0.1 ml of dichloromethane, and 1 ml of anisole at 0°C. The mixture was stirred at 0°C for 6 h. It was then poured into 25 ml of ether and 25 ml of 2 N HCl. The aqueous phase was extracted with ether (2 × 10 ml). The combined organic phases were neutralized with 15 ml of satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The crude product was chromatographed on 17 g of silica gel (ether/pentane, 2:1) to give 181 mg (50%) of *rac*-**18b** as a colourless oil, which could not be obtained analytically pure. $R_f = 0.15$. – IR (film): $\tilde{\nu} = 3440\ cm^{-1}$ (OH), 1690 (C=O). – MS (CI, isobutane): *m/z* (%) = 368 (12) [$M^+ + 3$], 366 (34) [$M^+ + 1$].

[2R,3S*,4R*,5R*,5(2S*)]- and [2S,3R,4S,5S,5(2R)]-(−)-Tetrahydro-3-hydroxy-4-methyl-5-(2-methyloxiran-2-yl)furan-2-yl N,N-Diisopropylcarbamate* [*rac*-**19a** and (−)-**19a**]: 3.0 g (10.0 mmol) of *rac*-**14a** was dissolved in 10 ml of THF. This mixture was added dropwise to a solution of 5.5 ml of zinc chloride–ether (12.0 mmol, as a 2.2 M solution in dichloromethane) in 30 ml of THF, during cooling with a water bath. The mixture was stirred at room temp. for 16 h and subsequently poured into 100 ml of ether and 100 ml of 2 N HCl. The aqueous phase was extracted with ether (2 × 50 ml). The combined etheral extracts were neutralized with satd. sodium hydrogen carbonate solution (50 ml), dried with magnesium sulfate, and the solvent was evaporated. The residue was chromatographed on 170 g of silica gel (ether/pentane, 1:1) to give 2.2 g (74%) of colourless crystals of *rac*-**19a**, m.p. 88°C (without solvent), $R_f = 0.10$. – IR (KBr): $\tilde{\nu} = 3445\ cm^{-1}$ (OH), 1675 (C=O). – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6, for the X-ray crystal structure analysis Tables 7 and 8[18].

According to an analogous procedure 903 mg (3 mmol) of (−)-**14a** (86% *ee*) was converted into 671 mg (74%) of colourless crystals of (−)-**19a** (86% *ee*), m.p. 114°C (without solvent). $[\alpha]_D^{20} = -10.4$ ($c = 4.2$, CH_2Cl_2) for 86% *ee*.

Table 5. ^{1}H-NMR data of compounds **19**, **20**–**26**[a]; chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$

	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H ($J_{3,4}$)	3-CH_3 ($J_{3,3'}$)	4-H	5-R	6-H_2 ($J_{6,6}$)	OH ($J_{2,OH}$)	acetonide ($^5J_{A,B}$)
19a[b]	6.01 s	4.15 m (4.4)	2.36 qdd (10.0)	1.18 d (6.9)	3.61 d	1.35 d	2.62, 2.70 d, dd (4.8)	2.80 m	
19b	6.00 s	4.12 m (4.0)	2.26 qdd (9.1)	1.13 d (7.0)	4.09 d	2.25 qq	2.56, 2.65 both d (4.5)	2.80 m	
20a[c]	3.82 qd (5.0)	3.74 ddd (7.1)	2.29 qdd (7.3)	1.07 d (7.1)	3.53 d	1.18 s	1.44, 1.58 both qd (13.8)	1.70, 1.92 m, m (5.3)	
20b[d]	3.78 qd (5.2)	3.73 dd (7.1)	2.39 qdd (7.1)	1.11 d (7.0)	3.77 d	2.00 qq	1.56, 1.57 both m	1.68, 2.08 both m	
21b	5.79 d (3.6)	4.53 dd (4.9)	1.92 qdd (10.0)	1.10 d (6.8)	3.85 d	2.18 qq	2.60, 2.70 both d (4.5)		1.13, 1.51 both s
22a	5.73 d (3.6)	4.56 dd (4.9)	2.13 qdd (10.0)	1.20 d (6.9)	3.86 d	1.27 s	3.57, 3.72 both d (11.1)	2.26 s	1.34, 1.52 both q (0.7)
22b	5.74 d (3.6)	4.56 dd (4.6)	2.37 qdd (10.3)	1.22 d (6.9)	4.08 d	2.19 dd	3.65, 3.70 both d (11.3)	2.39 s	1.33, 1.53 m
23a	5.79 d (3.6)	4.57 dd (5.0)	2.44 qdd (9.1)	1.23 d (6.9)	3.95 d	1.56 s	3.77, 3.79 both d (11.7)	2.45 m	1.34, 1.52 both q (0.7)
24a[e]	5.74 d (3.6)	4.52 dd (5.1)	2.13 qdd (9.5)	1.12 d (6.9)	3.74 d	1.30 s	3.65, 4.03 both d (8.6)		
25a[f]	5.72 d (3.6)	4.52 dd (4.8)	2.21 qdd (9.8)	0.98 d (6.9)	3.96 d	1.97 qq	1.50, 1.58 both qd (14.5)	2.01 s	1.34, 1.51 both s
25b[g]	5.72 d (3.6)	4.53 dd (4.9)	2.24 qdd (9.8)	1.18 d (6.9)	3.92 d	1.98 qq	2.23, 2.38 both dddd (14.4)	2.07 m	1.34, 1.51 both q (0.7)
25c[h]	5.74 d (3.6)	4.53 dd (4.7)	2.15 qdd (10.1)	1.00 d (6.8)	3.57 d	1.94 qq	2.65, 3.06 both d (13.3)	1.53 s	1.29, 1.38 both s
25d[i]	5.76 d (3.5)	4.58 dd (4.9)	2.45 qdd (10.0)	1.28 d (6.8)	4.26 d	2.19 qq	2.67, 2.73 both d (17.3)	2.20 s	1.35, 1.54 both s
25e[j]	5.76 d (3.7)	4.55 dd (5.0)	2.26 qdd (9.8)	1.20 d (6.8)	3.74 d	1.23 s	1.48, 1.60 both qd (13.9)	1.87 m	1.36, 1.54 both m
26[k]	4.53 d (6.6)	3.98 ddd (7.9)	2.43 qdd (6.2)	1.14 d (7.1)	3.79 d	1.32 s	3.67, 3.71 both d (11.1)	4.18 d (5.4)	

[a] Numbering of the open-chain compounds is retained. – [b] Further absorptions and coupling constants: $J_{6,5\text{-}CH_3} = 0.6$ Hz. – [c] δ = 0.95 (dd, $J_{6,6\text{-}CH_3} = 7.6$, $J_{6,6\text{-}CH_3} = 7.5$ Hz, 6-CH_3); 1.25 (d, $J_{1,1'} = 6.1$ Hz). – [d] δ = 0.97 (dd, $J_{6,6\text{-}CH_3} = 7.6$, $J_{6,6\text{-}CH_3} = 7.6$ Hz, 6-CH_3); 1.24 (d, $J_{1,1'} = 6.1$ Hz, 1-CH_3). – [e] δ = 1.30, 1.37, 1.42, and 1.47 (all s, acetonides). – [f] δ = 0.94 (dd, $J_{6,6\text{-}CH_3} = 7.6$, $J_{6,6\text{-}CH_3} = 7.6$ Hz, 6-CH_3). – [g] δ = 5.11 (dddd, $^{cis}J = 9.5$, $J_{A,B} = 2.2$, $J_{6,6\text{-}CH=CHA} = 1.1$, $J_{6,6\text{-}CH=CHA} = 1.1$ Hz, 6-CH=CH_A); 5.11 (dddd, $^{trans}J = 17.8$, $J_{6,6\text{-}CH=CHB} = 1.4$, $J_{6,6\text{-}CH=CHB} = 1.4$ Hz, 6-CH=CH_B); 5.92 (dddd, $J_{6,6\text{-}CH} = 7.7$, $J_{6,6\text{-}CH} = 6.8$ Hz, 6-CH). – [h] δ = 7.10–7.50 (m, phenyl H). – [i] δ = 7.20–7.40 (m, phenyl H). – [j] δ = 0.96 (dd, $J_{6,6\text{-}CH_3} = 7.4$, $J_{6,6\text{-}CH_3} = 7.7$ Hz, 6-CH_3). – [k] δ = 3.77 (s, OCH_3); 3.93 (s, 6-OH); 6.88 and 7.34 (both m, aromatic H); solvent was [D_6]acetone.

Table 6. ^{13}C-NMR data of compounds **19**, **20**–**26**[a]; chemical shifts (δ)

	C-1	C-2	C-3	3-CH_3	C-4	C-5	5-R	C-6	acetonide
19a	102.80	78.04	36.78	9.92	87.96	55.88	16.55	52.72	
19b	102.77	77.94	35.24	11.07	86.23	61.28	28.10	47.56	
20a	79.59	79.17	36.44	13.11	90.50	73.30	23.04	29.88	26.46, 26.90, 111.31
20b	79.41	78.64	36.53	13.26	87.39	75.88	34.19	25.50	26.46, 26.90, 111.61
21b	104.73	83.02	38.23	10.52	83.88	60.45	28.42	48.10	26.46, 26.90, 111.31
22a	104.25	83.88	38.77	11.04	84.54	72.56	20.48	52.68	26.49, 26.82, 111.61
22b	103.69	84.06	38.43	11.06	84.29	75.03	32.33	46.37	26.61, 26.91, 111.72
23a	104.50	83.85	39.57	12.14	86.36	73.90	24.28	69.53	26.50, 27.04, 111.81
24a[b]	104.76	83.99	39.01	11.72	86.33	81.60	24.35	71.53	
25a[c]	103.92	84.37	34.55	11.94	85.14	75.51	37.94	25.61	26.68, 27.07, 111.31
25b[d]	103.94	84.45	38.01	11.86	84.30	75.29	34.68	37.81	26.68, 27.07, 111.94
25c[e]	103.69	83.30	38.70	11.41	84.80	75.16	33.38	38.14	26.62, 26.73, 111.32
25d[f]	104.02	84.67	38.38	11.48	85.21	75.61	34.34	24.35	26.70, 27.04, 111.64
25e[g]	104.14	84.49	37.91	11.68	88.24	73.04	23.64	30.52	26.55, 26.97, 111.36
26[h]	85.37	80.15	38.23	13.87	88.42	73.63	20.71	53.60	

[a] Numbering of the open-chain compounds is retained. – [b] Further signals at δ = 26.31, 26.58, 27.01, 27.38, 109.68, and 111.50 (acetonides). – [c] δ = 8.26 (6-CH_3). – [d] δ = 117.71 (6-CH=CH_2), 134.20 (6-CH=CH_2). – [e] δ = 126.44, 128.11, 131.12, and 136.75 (phenyl C). – [f] δ = 83.43 and 84.67 (C≡C), 123.80, 127.83, 128.29, and 131.43 (phenyl C). – [g] δ = 7.63 (6-CH_3). – [h] δ = 55.47 (OCH_3), 114.31, 128.23, 134.13, and 160.08 (phenyl C); solvent was [D_6]acetone.

Table 7. Details of the X-ray structure analysis of *rac*-**19a**

$C_{15}H_{27}NO_5$, mol.mass 301.38, orthorhombic, space group $P2_12_12_1$, a = 767.7 (1), b = 1060.7 (1), c = 2172.2 (2) pm, V = 1.7692 (3) nm^3, Z = 4, d_{calc} = 1.13 g/cm^{-3}, μ = 0.66 mm^{-1}, Enraf Nonius CAD4 diffractometer, (Cu-K_α radiation), highly oriented graphite crystal monochromator, crystal size 0.25 x 0.25 x 0.45 mm^3, ω scans, 2627 reflections measured ($2\Theta_{max}$ = 120°), $-8 \le h \le 6$, $0 \le k \le 11$, $0 \le l \le 24$, 2383 unique reflections, 2300 with $|F| > 3\sigma(F)$ treated as observed, structure solved with direct methods and refined by full-matrix least-squares technique to R = 0.092 (wR = 0.148), H atoms located by difference electron-density synthesis and refined with fixed individual temperature factors using a "riding" model, all other atoms refined anisotropically, data-to-parameter ratio 11.9, program used: Siemens SHELXTL PLUS. The intermolecular packing is stabilized by a hydrogen bond from O21 to O12 [O21···O12 278.6 pm, O12···H—O21 147.0°]

[2R,3S*,4R*,5R*,5(2S*)]- and [2S,3R,4S,5S,5(2R)]-(–)-Tetrahydro-3-hydroxy-5-(2-isopropyloxiran-2-yl)-4-methylfuran-2-yl N,N-Diisopropylcarbamate* [*rac*-**19b** and (–)-**19b**]: According to an analogous procedure 4.7 g (14.3 mmol) of *rac*-**14b** was converted into 3.1 g (64%) of *rac*-**19b** as a slowly crystallizing, colourless oil, m.p. 59°C (without solvent). – IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 1675 (C=O). – MS (70 eV): *m/z* (%) = 329 (2) [M$^+$].

According to an analogous procedure the reaction of 2.2 g (6.7 mmol) of (–)-**14b** (90% *ee*) afforded 1.5 g (65%) of (–)-**19b** (90% *ee*) as a colourless oil, $[\alpha]_D^{20}$ = –19.2 (*c* = 1.6, CH_2Cl_2) for 90% *ee*.

[2R,3R,4S,5S,5(1R)]-(+)-Tetrahydro-5-(1-hydroxy-1-methylpropyl)-2,4-dimethylfuran-3-ol [(+)-**20a**]: 6.25 ml (10.0 mmol, as a 1.6 N solution in ether) of methyllithium was added dropwise to a mixture of 957 mg (5.0 mmol) of copper(I) iodide and 8 ml of ether at –78°C. The mixture was stirred at –78°C for 5 min and at –20°C for additional 15 min. Then 301 mg (1.0 mmol) of (–)-**19a** (73% *ee*), dissolved in 4 ml of THF, was added at –78°C. The mixture was warmed to –20°C and stirred for 16 h, then warmed slowly to room temp. The solution was poured into 30 ml of ether, 20 ml of satd. ammonium chloride solution, and 2 ml of concd. ammonia. The resulting mixture was stirred in air for 1 h. The phases were then separated and the aqueous layer extracted with ether (2 × 10 ml). The combined organic phases were neutralized with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The crude product was chromatographed on 17 g of silica gel (ether/pentane, 1:1) to give 80 mg (43%) of (+)-**20a** (73% *ee*) as a colourless oil. R_f = 0.07. – IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (OH), 3260 (OH), 1455 (CH_3). – $[\alpha]_D^{20}$ = +9.2 (*c* = 2.1, CH_2Cl_2) for 73% *ee*. – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6.

Table 8. Atomic coordinates (× 10^4) and equivalent isotropic displacement coefficients [pm^2 × 10^{-1}] of **19a**. Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U(eq)
O(1)	-658(4)	6344(3)	5071(2)	70(1)
C(1)	1101(6)	6675(4)	4999(2)	65(1)
C(2)	2064(6)	6060(5)	5531(2)	70(2)
O(21)	1913(6)	6804(6)	6058(2)	102(2)
C(3)	1076(6)	4846(5)	5596(2)	70(1)
C(31)	1283(11)	4182(7)	6223(3)	109(3)
C(4)	-794(7)	5245(5)	5443(2)	74(2)
C(5)	-1897(8)	4254(6)	5119(3)	103(2)
C(6)	-3685(11)	4154(10)	5326(6)	164(5)
C(51)	-1321(13)	3923(8)	4462(4)	127(3)
O(51)	-2356(8)	3231(5)	5501(3)	146(3)
O(11)	1818(5)	6130(3)	4449(1)	69(1)
C(12)	1388(6)	6690(4)	3909(2)	66(1)
O(12)	445(5)	7608(3)	3883(2)	82(1)
N(13)	2142(6)	6128(4)	3430(2)	73(1)
C(14)	3353(9)	5051(6)	3489(2)	91(2)
C(15)	5188(10)	5432(11)	3265(5)	156(5)
C(16)	2737(12)	3898(6)	3170(4)	114(3)
C(17)	1777(9)	6602(6)	2798(3)	92(2)
C(18)	-84(12)	6392(8)	2621(3)	118(3)
C(19)	2406(15)	7899(7)	2702(4)	139(4)

[2R,3R,4S,5S,5(1S)]-(+)-5-(1-Ethyl-1-hydroxy-2-methylpropyl)-tetrahydro-2,4-dimethylfuran-3-ol [(+)-**20b**]: According to an analogous procedure 658 mg (2.0 mmol) of (–)-**19b** (49% *ee*) was converted into 279 mg (65%) of (+)-**20b** (49% *ee*) as a colourless oil. R_f = 0.14. – IR (film): $\tilde{\nu}$ = 3420 cm^{-1} (OH), 1460 (CH_3). – $[\alpha]_D^{20}$ = +1.6 (*c* = 2.8, CH_2Cl_2) for 49% *ee*.

[4R,6S*,6(1R*),7R*,8R*]-6-(2-Isopropyloxiran-2-yl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**21b**): A solution of 525 mg (1.6 mmol) of *rac*-**19b** in 4.8 ml of acetone was cooled to –78°C, and 0.20 ml (1.6 mmol) of boron trifluoride–ether was added. The solution was stirred at –78°C for 30 min and at –20°C for additional 30 min and subsequently poured into 50 ml of ether and 40 ml of satd. sodium hydrogen carbonate solution. The aqueous phase was extracted with ether (2 × 10 ml). The combined etheral extracts were dried with magnesium sulfate, and the ether was evaporated. The residue was chromatographed on 30 g of silica gel (ether/pentane, 1:4) to give 183 mg (47%) of *rac*-**21b** as a colourless oil. R_f = 0.54. – IR (film): $\tilde{\nu}$ = 1025 cm^{-1} (C–O–C).

[4R,6S*,6(1S*),7R*,8R*]- and [4R,6S,6(1S),7R,8R]-(+)-6-(2-Chloro-1-hydroxy-1-methylethyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* [*rac*-**22a** and (+)-**22a**]: A solution of 903 mg (3.0 mmol) of *rac*-**19a** and 1.5 ml (3.3 mmol) of zinc chloride–ether (as 2.2 M solution in dichloromethane) in 10 ml of acetone was stirred at room temp. for 4 d, then poured into 90 ml of ether and 30 ml of 2 N HCl. The etheral phase was extracted with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and concentrated. The crude product was chromatographed on 30 g of silica gel (ether/pentane, 1:3) to give 384 mg (51%) of colourless crystals of *rac*-**22a**, m.p. 48°C (without solvent), R_f = 0.38.

– IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 800 (C–Cl). – MS (CI, isobutane): *m/z* (%) = 253 (27) [M^+ + 3], 251 (83) [M^+ + 1], 233 [M^+ + 1 – H_2O]. – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6.

The application of an analogous procedure to the reaction of 364 mg (1.2 mmol) of (–)-**19a** (86% *ee*) afforded 141 mg (47%) of (+)-**22a** (86% *ee*) accompanied by 79 mg (22%) of starting material. (+)-**22a** is a colourless oil, $[\alpha]_D^{20}$ = +18.0 (*c* = 2.2, CH_2Cl_2) for 86% *ee*.

[4R,6S,6(1R),7R,8R]-(+)-6-(2-Isopropyloxiran-2-yl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane and [4R,6S,6(1S),7R,8R]-(+)-6-[1-(Chloromethyl)-1-hydroxy-2-methylpropyl]-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane [(+)-**21b** and (+)-**22b**]: The reaction of 656 mg (2.0 mmol) of (–)-**19b** (90% *ee*) and workup of the product according to an analogous procedure followed by purification by chromatography on 45 g of silica gel (ether/pentane, 1:4) afforded 213 mg (44%) of (+)-**21b** (90% *ee*) as a colourless oil, 67 mg (12%) of (+)-**22b** (90% *ee*) as a colourless oil, and 112 mg (17%) of starting material. – (+)-**21b**: $[\alpha]_D^{20}$ = +26.9 (*c* = 1.8, CH_2Cl_2) for 90% *ee*. – (+)-**22b**: R_f = 0.44. – IR (film): $\tilde{\nu}$ = 3490 cm^{-1} (OH), 740 (C–Cl). – MS (CI, isobutane): *m/z* (%) = 281 (8) [M^+ + 3], 279 (25) [M^+ + 1]. – $[\alpha]_D^{20}$ = +11.4 (*c* = 0.6, CH_2Cl_2) for 90% *ee*.

rac-**22a** and *[4R*,6S*,6(1S*),7R*,8R*]-(+)-6-(1-Chloro-2-hydroxy-1-methylethyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**23a**): To a solution of 2.10 g (7.0 mmol) of *rac*-**19a** and 693 mg (7.7 mmol) of anhydrous oxalic acid[33] in 20 ml of acetone was added 2.6 ml (8.4 mmol) of zinc chloride–ether (as 2.2 M solution in dichloromethane) at room temp. The resulting mixture was stirred at this temp. for 1 h and then poured into 100 ml of ether and 40 ml of 2 N HCl. The phases were separated. The aqueous phase was extracted with ether (2 × 30 ml). The combined etheral extracts were neutralized with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the ether was evaporated. The residue was chromatographed on 80 g of silica gel (ether/pentane, 1:2) to give 838 mg (48%) of *rac*-**22a** and 216 mg (12%) of *rac*-**23a** as a colourless oil. – *rac*-**23a**: R_f = 0.25. – IR (film): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 680 (C–Cl). – MS (CI, isobutane): *m/z* (%) = 253 (14) [M^+ + 3], 251 (43) [M^+ + 1], 215 (44) [M^+ – Cl]. – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6.

[4R,6S*,6(1S*),7R*,8R*]-6-[1-(Chloromethyl)-1-hydroxy-2-methylpropyl]-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**22b**): A solution of 99 mg (1.1 mmol) of anhydrous oxalic acid[33] and 329 mg (1.0 mmol) of *rac*-**19b** in 3 ml of acetone was stirred at room temp. for 5 h. Then 0.68 ml (1.5 mmol) of zinc chloride–ether (as a 2.2 M solution in dichloromethane) was added dropwise, and the resulting mixture was stirred for 30 min. It was then poured into 20 ml of ether and 15 ml of 2 N HCl. The etheral phase was extracted with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The crude product was chromatographed on 17 g of silica gel (ether/pentane, 1:2) to give 166 mg (59%) of *rac*-**22b** as a colourless oil.

(4R,6S*,7R*,8R*)-2,2,7-Trimethyl-6-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**24a**): A solution of 301 mg (1.0 mmol) of *rac*-**19a** in 3 ml of acetone was cooled to –78°C. Then 0.12 ml (1.0 mmol) of boron trifluoride–ether was added. The resulting mixture was stirred for 30 min and subsequently poured into 20 ml of ether and 20 ml of satd. sodium hydrogen carbonate solution. The aqueous phase was extracted with ether (2 × 10 ml). The combined etheral solutions were dried with magnesium sulfate, and the ether was evaporated. The residue was chromatographed on 17 g of silica gel (ether/pentane, 1:4) to give 124 mg (45%) of *rac*-**24a** as a colourless oil. R_f = 0.53. – IR (film): $\tilde{\nu}$ = 1445 cm^{-1}, 1380, 1212, 1100, 1030 and 875. – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6.

[4R,6S*,6(1S*),7R*,8R*]-6-(1-Ethyl-1-hydroxy-2-methylpropyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**25a**) *from rac*-**21b** *with Dimethylcuprate:* 6.25 ml (10.0 mmol) of methyllithium (as 1.6 N solution in ether) was added to a mixture of 950 mg (5.0 mmol) of copper(I) iodide and 3 ml of THF at –78°C. The mixture was stirred at –20°C for 20 min. Then a solution of 242 mg (1.0 mmol) of *rac*-**21b** in 2 ml of THF was added at –78°C. The resulting mixture was stirred for 19 h, warmed up slowly from –20°C to room temp., and subsequently poured into a mixture of 40 ml of ether, 20 ml of satd. ammonium chloride solution, and 2 ml of concd. ammonia. The obtained solution was stirred in the air for 1 h. The phases were separated. The aqueous layer was extracted with ether (2 × 10 ml). The combined *etheral solutions* were washed with 20 ml of satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The crude product was chromatographed on 20 g of silica gel (ether/pentane, 1:2) to give 207 mg (80%) of *rac*-**25a** as a colourless oil. R_f = 0.35. – IR (film): $\tilde{\nu}$ = 2505 cm^{-1} (OH). – ^{1}H- and ^{13}C-NMR data see Tables 5 and 6.

[4R,6S,6(1S),7R,8R]-(+)-6-(1-Ethyl-1-hydroxy-2-methylpropyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane [(+)-**25a**] *by Treatment of* (+)-**21b** *with Dimethylcuprate:* The reaction of 85 mg (0.3 mmol) of (+)-**22b** (90% *ee*) and workup of the product according to an analogous procedure followed by purification by chromatography on 9 g of silica gel (ether/pentane, 1:3) afforded 45 mg (57%) of (+)-**25a** (90% *ee*) as a colourless oil. – $[\alpha]_D^{20}$ = +20.1 (*c* = 1.1, CH_2Cl_2) for 90% *ee*.

(+)-**25a** *from* (+)-**21b** *with Methylmagnesium Chloride:* 0.75 ml (2.25 mmol) of methylmagnesium chloride (as a 3 M solution in THF) were added dropwise to a mixture of 181 mg (0.75 mmol) of (+)-**21b** (90% *ee*), 8 mg (5 mol%) of copper(I) iodide, and 2.5 ml of THF at –78°C. The mixture was stirred at –78°C for 1 h and then warmed to –20°C. It was then stirred for an additional 16 h and warmed up slowly to room temp. The solution was poured into 30 ml of ether and 15 ml of satd. ammonium chloride solution. The aqueous phase was extracted with ether (2 × 10 ml). The combined organic phases were washed with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The crude product was chromatographed on 17 g of silica gel (ether/pentane, 1:1) to give 153 mg (79%) of (+)-**25a** (90% *ee*) as a colourless oil.

[4R,6S*,6(1S*),7R*,8R*]-6-(1-Hydroxy-1-isopropylbut-3-enyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**25b**): 3.0 ml (3.0 mmol) of vinylmagnesium bromide (as a 1 M solution in THF) was added dropwise to a mixture of 183 mg (0.76 mmol) of *rac*-**21b**, 8 mg (5 mol-%) of copper(I) iodide, and 2.5 ml of THF at –78°C. The resulting mixture was stirred at –78°C for 1 h and was then allowed to warm to –20°C. It was stirred for additional 16 h and warmed up slowly to room temp. The workup was the same as in the reaction of (+)-**21b** with methylmagnesium chloride. The chromatography of the crude product on 17 g of silica gel (ether/pentane, 1:2) afforded 111 mg (54%) of colourless crystals of *rac*-**25b**, m.p. 59°C (without solvent). R_f = 0.36. – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1820 (overtone to 910), 1635 (C=C), 910 (C=CH_2).

[4R,6S*,6(1S*),7R*,8R*]-6-(1-Benzyl-1-hydroxy-2-methylpropyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**25c**): 7.5

ml (15.0 mmol) of phenyllithium (as a 2 M solution in ether/benzene) was added dropwise to a suspension of 716 mg (7.5 mmol) of copper(I) cyanide and 6 ml of THF at −78°C. The resulting mixture was stirred at −20°C for 20 min. After cooling to −78°C 363 mg (1.5 mmol) of *rac*-**21b**, dissolved in 1 ml of THF, was added. After 10 min the mixture was warmed to −20°C, stirred for 16 h and then warmed up slowly to room temp. The workup was the same as in the reaction of *rac*-**21b** with dimethylcuprate. The crude product was chromatographed on silica gel (ether/pentane, 1:4) to give 248 mg (52%) of *rac*-**25c** as a colourless oil. R_f = 0.59. — IR (film): $\tilde{\nu}$ = 3505 cm^{-1} (OH), 875, 735, and 705 (phenyl group).

Table 9. Microanalyses of the new compounds

Compound	Molecular Formular	Molecular Weight	Calcd. C	Calcd. H	Found C	Found H
12a	$C_{15}H_{27}NO_3$	269.38	66.88	10.10	66.97	9.98
12b	$C_{17}H_{31}NO_3$	297.44	68.65	10.51	68.67	10.52
14a	$C_{15}H_{27}NO_5$	301.38	59.78	9.03	59.63	9.13
14b	$C_{17}H_{31}NO_5$	329.44	61.98	9.48	62.00	9.48
15a	$C_{15}H_{27}NO_4$	285.38	63.13	9.54	63.13	9.64
17a	$C_{10}H_{20}O_5$	220.27	54.53	9.15	54.50	9.20
17b[a]	$C_{13}H_{22}O_6$	274.31	56.92	8.08	56.78	8.08
19a	$C_{15}H_{27}NO_5$	301.38	59.78	9.03	59.76	9.02
19b	$C_{17}H_{31}NO_5$	329.44	61.98	9.48	61.96	9.58
20a	$C_{10}H_{20}O_3$	188.27	63.80	10.71	63.91	10.62
20b	$C_{12}H_{24}O_3$	216.32	66.63	11.18	66.47	11.25
21b	$C_{13}H_{22}O_4$	242.32	64.44	9.15	64.29	9.18
22a	$C_{11}H_{19}ClO_4$	250.72	52.70	7.64	52.52	7.56
22b	$C_{13}H_{23}ClO_4$	278.78	56.01	8.32	56.05	8.33
23a	$C_{11}H_{19}ClO_4$	250.72	53.70	7.64	52.75	7.71
24a	$C_{14}H_{24}O_5$	272.34	61.74	8.88	61.91	8.80
25a	$C_{14}H_{26}O_4$	258.36	65.09	10.14	65.22	10.04
25b	$C_{15}H_{26}O_4$	270.37	66.64	9.69	66.48	9.71
25c	$C_{19}H_{28}O_4$	320.43	71.22	8.81	71.24	8.72
25d	$C_{21}H_{28}O_4$	344.45	73.23	8.19	73.27	8.13
25e	$C_{12}H_{22}O_4$	230.30	62.58	9.63	62.42	9.57
26	$C_{15}H_{21}ClO_4$	300.78	59.90	7.04	59.85	6.93

[a] 4,6-*O*-Carbonate of **17b**.

[4R,6S*,6(1S*),7R*,8R*]-6-(1-Hydroxy-1-isopropyl-4-phenylbut-3-ynyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**25d**): A solution of 0.24 ml (2.2 mmol) of phenylethyne in 1.5 ml of pentane was cooled to 0°C. Then 1.30 ml (2.2 mmol) of *n*-butyllithium (as a 1.6 N solution in hexane) was added. The resulting mixture was stirred at 0°C for 10 min and at room temp. for additional 15 min. 2.2 ml (2.2 mmol) of dimethylaluminium chloride (as a 1 N solution in hexane) was added at 0°C. The mixture was stirred at 0°C for 10 min and at room temp. for additional 20 min. Then 268 mg (1.1 mmol) of *rac*-**21b**, dissolved in 2 ml of pentane, was added at 0°C. The mixture was stirred at 0°C for 1 h and at room temp. for 16 h and then poured into 30 ml of ether and 20 ml of 2 N HCl. The aqueous phase was extracted with ether (2 × 15 ml). The combined etheral extracts were neutralized with 15 ml of satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the ether was evaporated. The residue was chromatographed on 25 g of silica gel (ether/pentane, 1:2) to give 65 mg (21%) of *rac*-**22b** and 203 mg (53%) of *rac*-**25d** as a colourless oil. — *rac*-**25d**: R_f = 0.30. — IR (film): $\tilde{\nu}$ = 3480 cm^{-1} (OH), 2210 (C≡C).

[4R,6S*,6(1R*),7R*,8R*]-6-(1-Hydroxy-1-methylpropyl)-2,2,7-trimethyl-1,3,5-trioxabicyclo[3.3.0]octane* (*rac*-**25e**): The reaction of 121 mg (0.48 mmol) of *rac*-**22a** and workup of the product according to a procedure applied in the reaction of *rac*-**21b** with dimethylcuprate followed by purification by chromatography on 9 g of silica gel (ether/pentane, 1:2) afforded 64 mg (57%) of colourless crystals of *rac*-**25e**, m.p. 45°C (neat). R_f = 0.20. — IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1} (OH).

[2R,3S*,4R*,5R*,5(1R*)]-5-(2-Chloro-1-hydroxy-1-methylethyl)-tetrahydro-2-(4-methoxyphenyl)-4-methylfuran-3-ol* (*rac*-**26**): 0.13 ml (1.1 mmol) of tin(IV) chloride and 1.1 ml (10.0 mmol) of anisole were dissolved in 2 ml of dichloromethane. Then 250 mg (1.0 mmol) of *rac*-**22a**, dissolved in 1 ml of dichloromethane, was added at 0°C to the solution. The mixture was stirred at room temp. for 40 min, then poured into 25 ml of ether and 20 ml of 2 N HCl. The aqueous phase was extracted with ether (2 × 15 ml). The combined organic phases were neutralized with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and the solvent was evaporated. The residue containing excess anisole was chromatographed on 17 g of silica gel (ether/pentane, 1:1). The crude product was crystallized from acetone/hexane (1:1) to give 154 mg (51%) of colourless crystals of *rac*-**26**, m.p. 111°C (acetone/hexane, 1:1). R_f = 0.08. — IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (OH), 825, 785 (*para*-substituted aromatic compound), 740 (C—Cl).

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CAS Registry Numbers

9: 79792-71-5 / *rac*-**12a**: 140835-62-7 / (−)-**12a**: 140923-56-4 / (+)-**12a**: 140923-59-7 / *rac*-**12b**: 140835-63-8 / (−)-**12b**: 140923-57-5 / *rac*-**14a**: 140835-64-9 / (+)-**14a**: 140923-60-0 / (−)-**14a**: 140923-61-1 / *rac*-**14b**: 140835-65-0 / (−)-**14b**: 140923-58-6 / (+)-**15a**: 140835-66-1 / *rac*-**17a**: 140835-67-2 / *rac*-**17b**: 140835-68-3 / *rac*-**18b**: 140835-69-4 / *rac*-**19a**: 140835-70-7 / (−)-**19a**: 140835-71-8 / *rac*-**19b**: 140835-72-9 / (−)-**19b**: 140835-73-0 / (+)-**20a**: 140835-74-1 / (+)-**20b**: 140835-75-2 / *rac*-**21b**: 140835-76-3 / (+)-**21b**: 140835-79-6 / *rac*-**22a**: 140835-77-4 / (+)-**22a**: 140835-78-5 / *rac*-**22b**: 140835-82-1 / (+)-**22b**: 140835-80-9 / *rac*-**23b**: 140835-81-0 / *rac*-**24a**: 140835-89-8 / *rac*-**25a**: 140835-83-2 / (+)-**25a**: 140835-84-3 / *rac*-**25b**: 140835-85-4 / *rac*-**25c**: 140835-86-5 / *rac*-**25d**: 140835-87-6 / *rac*-**25e**: 140835-88-7 / *rac*-**26**: 140853-11-8 / 2-Isopropylpropenal: 4417-80-5 / 2-Methylpropenal: 78-85-3 / (−)-Sparteine: 90-39-1