Intramolecular 1,3-Dipolar Cycloaddition of Transient Enantiomerically Pure Oxaalkenyl Nitrones

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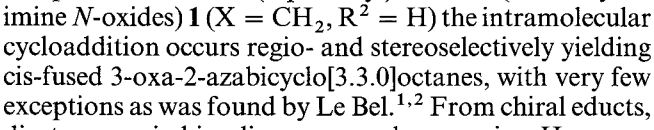
Dedicated to Professor Dr. Karl Dimroth on the occasion of his 85th birthday

A variety of enantiomerically pure α-hydroxy esters were converted into enantiomerically pure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **7** by the following reaction sequence. Allylation of the hydroxy group was followed by reduction of the ester group. The resulting aldehyde was treated with an *N*-alkylhydroxylamine to give an oxaalkenyl nitrone **6** which underwent spontaneously an intramolecular 1,3-dipolar cycloaddition affording **7**. Opening of the isoxazolidine ring of **7** by various reductive methods yielded the highly substituted tetrahydrofuran derivatives **11**.

Alkenyl nitrones in which the nitrone and alkene moieties are fixed at a suitable distance undergo intramolecular 1,3-dipolar cycloaddition affording bicyclic isoxazolidine compounds.[1] With *C*-(4-pentenyl) nitrones (5-hexenyl-1-imine *N*-oxides) **1** (X = CH_2, R^2 = H) the intramolecular cycloaddition occurs regio- and stereoselectively yielding cis-fused 3-oxa-2-azabicyclo[3.3.0]octanes, with very few exceptions as was found by Le Bel.[1,2] From chiral educts, diastereomeric bicyclic compounds can arise. However, usually the stereogenic center controls the process favoring the formation of one of the diastereomers.[3] In particular, a stereogenic center at position 2 affects the diastereoselectivity decisively.[4]



1 **2** **3**

Since the reaction creates several contiguous stereogenic centers in a well-defined manner it has been frequently used as an important stereogenic step in the synthesis of natural products and other stereochemically complicated molecules.[3,5]

Introduction of a heteroatom in the tether between the nitrone and alkene groups extends the synthetic potential of the reaction considerably. In particular, the intramolecular cycloaddition of several differently substituted 5-hexenyl-1-imine *N*-oxides with nitrogen,[6] sulfur[7,8] and oxygen[8-14] at the 3-position of the tether has been studied. In most of the nitrones of type **1** (X = O), the oxygen is part of an ester group, the carbonyl group being adjacent to the oxygen atom either at position 2[9] or position 4.[10-12] Even 3-oxa-5-hexenaldoximes which are thought to react via their tautomeric nitrone form **1** (X = O, R^1 = H, R^2 = H or $R^2 \neq$ H) undergo intramolecular cycloaddition under more vigorous conditions.[15]

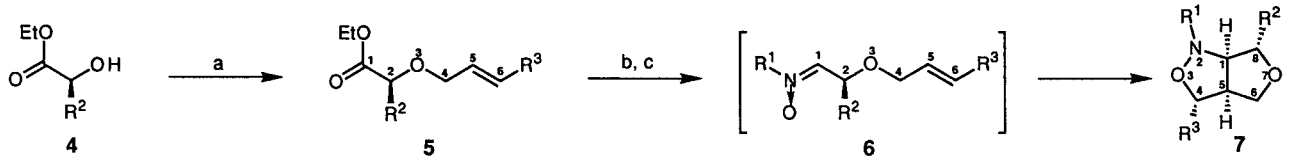
Among the chiral 3-oxa-5-hexenyl-1-imine N-oxides, again those with the stereogenic center at carbon atom 2 exhibited the highest diastereoselectivity favoring formation of bicyclic compounds of type **2** (X = O, $R^2 \neq$ H).[11-14]

Starting from enantiomerically pure ethyl (*S*)-(+)-lactate we generated enantiomerically pure nitrones **1** (X = O, R^2 = Me). The intramolecular cycloaddition proceeded spontaneously with complete diastereoselectivity yielding enantiomerically pure compounds **2** (X = O, R^2 = Me) which possess three contiguous stereogenic centers.[14]

Now we report on the conversion of a variety of other enantiomerically pure α-hydroxy esters to enantiomerically pure bicyclic compounds **7** via the corresponding nitrones **6**. Thus, 3,7-dioxa-2-azabicyclo[3.3.0]octanes **7** possessing additional stereogenic centers were synthesized (Scheme 1). Furthermore, introduction of a functional group was realized. Reductive opening of the isoxazolidine ring of **7** affords highly functionalized tetrahydrofuran derivatives.

The enantiomerically pure α-hydroxy esters **4a–c** were treated with allyl bromide or cinnamyl chloride in diethyl ether in the presence of silver(I) oxide[16] to give the allylated esters **5a–d**, respectively. In the same way compounds **5e–g** were synthesized from methyl (2*R*,3*S*)-(+)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyrate, diethyl (*R*,*R*)-(+)-tartrate and (*R*)-(−)-pantolactone, respectively. Compounds **5** were obtained in 55–97% yield in optically active form. No racemization was observed under the reaction conditions. They were characterized, in particular, by their ^{1}H and ^{13}C NMR spectra (Table 1). Compounds **5b, c** and **g** were also prepared as racemic mixtures from racemic educts by adding sodium hydride instead of silver(I) oxide, followed by tetrabutyl ammonium iodide and the allyl halide. Esters **5a–g** were reduced by diisobutylaluminium hydride (DIBAL-H) at −72 °C to the corresponding aldehydes[17] which were treated with *N*-alkylhydroxylamines without isolation in order to minimize racemization (Scheme 2). The only exception was the lactol **8** which was isolated as a mixture of two diastereomers in equilibrium with a small amount of the corresponding aldehyde.

Nitrones **6** could not be isolated. They underwent spontaneously an intramolecular 1,3-dipolar cycloaddition to give the 3,7-dioxa-2-azabicyclo[3.3.0]octanes **7** (Table 2) at 0 °C. Since lactol **8** reacts via its aldehyde tautomer, the original lactone ring is opened giving the 2-hydroxy-1,1-dimethylethyl substituent at position 8 in **7Ag**. In **7Af** and **Df**, two of the bicyclic units were combined. It is obvious that for the conversion of the diethyl tartrate with doubled functional groups to **7Af** and **Df** the yield should be the least of all, since in the three-step reaction every step must take place twice. The yields of **7** are not optimized. They cover a wide range from 9% for **7Af** to 83% for **7Cc**.



a: Br-CH_2-CH=CH_2 or Cl-CH_2-CH=CH-Ph (trans), Ag_2O, rf, Et_2O b: DIBAL-H, -72°C, Et_2O c: R^1-NHOH, 0-5°C to rt, Et_2O or CH_2Cl_2

A : R^1= Bzl **B** : R^1= t-Bu **C** : R^1= Me

4	R^2
a	Ph
b	Bzl
c	Me

5	R^2	R^3
a	Ph	H
b	Bzl	H
c	Me	Ph
d	Ph	Ph

6, 7	R^1	R^2	R^3
Aa	Bzl	Ph	H
Ba	t-Bu	Ph	H
Ca	Me	Ph	H
Ab	Bzl	Bzl	H

6, 7	R^1	R^2	R^3
Ac	Bzl	Me	Ph
Bc	t-Bu	Me	Ph
Cc	Me	Me	Ph
Ad	Bzl	Ph	Ph

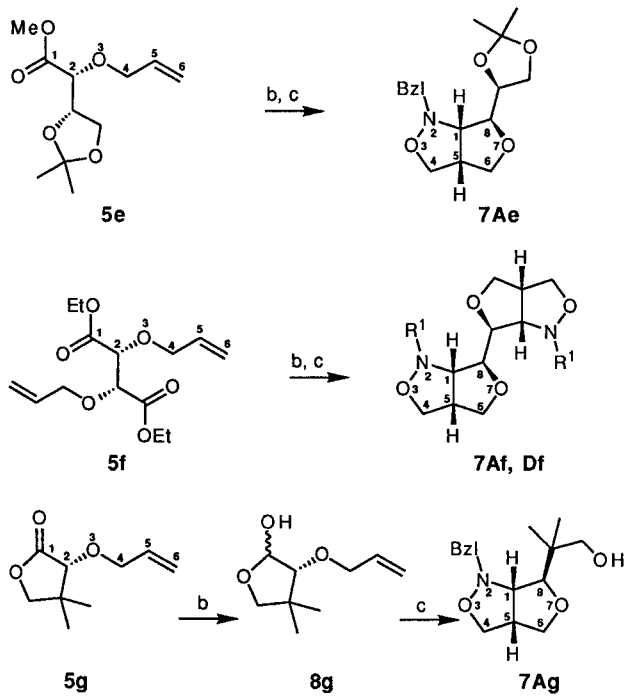
Bzl = C_6H_5-CH_2-

Scheme 1

Table 1. α-Allyloxy Esters **5a–g** Prepared[a,b]

Compound (% yield)	$[\alpha]_D$[c] (T, °C)	^{1}H NMR (300 MHz, $CDCl_3$) δ, J (Hz)	^{13}C NMR (75 MHz, $CDCl_3$) δ	MS (M^+) m/z (%)
5a (91)	+80.5 (23)	1.21 (t, 3H, $CO_2CH_2C\underline{H}_3$), 4.06 (d, 2H, 4-H), 4.18 (m, 2H, $CO_2C\underline{H}_2$), 4.92 (s, 1H, 2-H), 5.22 (m, 1H, 6-H), 5.29 (m, 1H, 6-H'), 5.95 (m, 1H, 5-H), 7.34 (m, 3H, ArH), 7.46 (m, 2H, ArH); ^3J 4/5 = 5.8, 5/6 = 10.3, 5/6′ = 17.3, CH_2/CH_3 = 7.1; ^2J 6/6′ = 1.6	13.9 ($CO_2CH_2\underline{C}H_3$), 61.0 ($CO_2\underline{C}H_2$), 70.3 (C-4), 79.7 (C-2), 118.0 (C-6), 127.1, 128.4, 128.5 (Ar), 133.7 (C-5), 136.3 (Ar), 170.7 (C=O)	EI: 220 (2)
5b (94)	−33.2 (26)	1.22 (t, 3H, $CO_2CH_2C\underline{H}_3$), 3.02 (dd, 1H, Ph—CH_2), 3.07 (dd, 1H, $PhCH_2'$), 3.87 (dd, 1H, 4-H), 4.09 (dd, 1H, 2-H), 4.11 (dd, 1H, 4-H′), 4.17 (q, 2H, CO_2CH_2), 5.13 (dd, 1H, 6-H), 5.18 (dd, 1H, 6-H′), 5.79 (m, 1H, 5-H), 7.20–7.32 (m, 5H, ArH); ^3J 2/CH_2 = 7.6, 2/CH_2' = 5.8, 4/5 = 5.9, 4′/5 = 5.0, 5/6 = 10.9, 5/6′ = 16.8, CH_2/CH_3 = 7.1; ^2J CH_2Ph = 13.7, 4/4′ = 13.0, 6/6′ = 1.5	14.0 ($CO_2CH_2\underline{C}H_3$), 39.2 ($\underline{C}H_2Ph$), 60.7 ($CO_2\underline{C}H_2$), 71.4 (C-4), 79.2 (C-2), 117.4 (C-6), 126.5, 128.1, 129.3 (Ar), 133.9 (C-5), 137.0 (Ar), 172.1 (C=O)	FD: 234 (6)
5c (79)	−38.8 (20)	1.28 (t, 3H, $CO_2CH_2C\underline{H}_3$), 1.44 (d, 3H, CH_3), 4.07 (q, 1H, 2-H), 4.12 (ddd, 1H, 4-H), 4.21 (q, 1H, CO_2CH_2), 4.22 (q, 1H, CO_2CH_2'), 4.30 (ddd, 1H, 4-H′), 6.30 (ddd, 1H, 5-H), 6.61 (d, 1H, 6-H), 7.21–7.40 (m, 5H, ArH); ^3J 2/CH_3 = 6.9, 4/5 = 6.5, 4′/5 = 6.0, 5/6 = 15.9, CH_2/CH_3 = 7.1, CH_2'/CH_3 = 7.1; ^2J 4/4′ = 13.7; ^4J 4/6 = 1.2, 4′/6 = 1.4	14.1 ($CO_2CH_2\underline{C}H_3$), 18.6 (CH_3), 60.7 ($CO_2\underline{C}H_2$), 70.6 (C-4), 74.0 (C-2), 125.3 (C-6), 126.5, 127.7, 128.4 (Ar), 133.0 (C-5), 136.5 (Ar), 173.2 (C=O)	EI: 234 (1)
5d (55)	+54.7 (26)	1.20 (t, 3H, $CO_2CH_2C\underline{H}_3$), 4.13 (dq, 1H, CO_2CH_2), 4.20 (dq, 1H, CO_2CH_2'), 4.24 (d, 2H, 4-H), 4.99 (s, 1H, 2-H), 6.32 (ddd, 1H, 5-H), 6.60 (d, 1H, 6-H), 7.22–7.52 (m, 10H, ArH); ^3J 4/5 = 6.3, 5/6 = 15.9, CH_2/CH_3 = 7.2, CH_2'/CH_3 = 7.2, ^2J CH_2/CH_2' = 10.9	14.0 ($CO_2CH_2\underline{C}H_3$), 61.0 ($CO_2\underline{C}H_2$), 70.1 (C-4), 79.8 (C-2), 125.1 (C-6), 126.5, 127.3, 127.8, 128.5, 128.5, 128.6, 128.6 (Ar), 133.4 (C-5), 136.5 (Ar), 170.8 (C=O)	
5e (90)	+41.5 (20)	1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.75 (s, 3H, CO_2CH_3), 3.95 (dd, 1H, $CHC\underline{H}_2$), 3.97 (d, 1H, 2-H), 3.98 (ddt, 1H, 4-H), 4.02 (dd, 1H, $CHC\underline{H}_2'$), 4.21 (ddt, 1H, 4-H′), 4.37 (ddd, 1H, $C\underline{H}CH_2$), 5.20 (ddd, 1H, 6-H), 5.28 (ddd, 1H, 6-H′), 5.88 (m, 1H, 5-H); ^3J 2/CH = 5.7, 4/5 = 6.4, 4′/5 = 5.5, 5/6 = 10.4, 5/6′ = 17.1, CH/CH_2 = 6.4, CH/CH_2' = 6.6; ^2J $C\underline{H}_2CH$ = 8.6, 4/4′ = 12.6, 6/6′ = 1.5; ^4J 4/6 = 1.2, 4′/6 = 1.4	25.1 (CH_3), 26.1 (CH_3), 51.9 ($CO_2\underline{C}H_3$), 65.4 (CH_2), 71.9 (C-4), 75.7 (CH), 78.4 (C-2), 109.8 ($\underline{C}Me_2$), 118.2 (C-6), 133.6 (C-5), 170.5 (C=O)	EI: 215 (19, $M^+ - CH_3$)
5f (97)	+70.0 (22)	1.28 (t, 3H, $CO_2CH_2C\underline{H}_3$), 3.93 (ddt, 1H, 4-H), 4.22 (q, 1H, CO_2CH_2), 4.23 (q, 1H, CO_2CH_2'), 4.28 (ddt, 1H, 4-H′), 4.37 (s, 1H, 2-H), 5.15 (ddd, 1H, 6-H), 5.21 (ddd, 1H, 6-H′), 5.82 (m, 1H, 5-H); ^3J 4/5 = 6.6, 4′/5 = 5.3, 5/6 = 10.3, 5/6′ = 17.1, CH_2/CH_3 = 7.1, CH_2'/CH_3 = 7.1; ^2J 4/4′ = 12.7, 6/6′ = 1.6; ^4J 4/6 = 1.2, 4′/6′ = 1.4	14.0 ($CO_2CH_2\underline{C}H_3$), 61.0 ($CO_2\underline{C}H_2$), 72.3 (C-4), 78.4 (C-2), 117.8 (C-6), 133.6 (C-5), 169.1 (C=O)	EI: 213 (3, $M^+ - CO_2Et$)
5g (77)	+60.0 (22)	1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3'), 3.72 (s, 1H, 2-H), 3.86 (d, 1H, CH_2), 3.96 (d, 1H, CH_2'), 4.18 (ddt, 1H, 4-H), 4.43 (ddt, 1H, 4-H′), 5.21 (ddd, 1H, 6-H), 5.30 (ddd, 1H, 6-H′), 5.87 (m, 1H, 5-H); ^3J 4/5 = 6.2 4′/5 = 5.1, 5/6 = 10.4, 5/6′ = 17.2; ^2J 4/4′ = 13.0, 6/6′ = 1.4, CH_2CH_2' = 8.8; ^4J 4/6 = 1.3, 4′/6′ = 1.5	19.1 (CH_3), 23.2 (CH_3), 40.2 ($\underline{C}Me_2$), 71.6 (C-4), 76.2 (CH_2), 80.6 (C-2), 117.9 (C-6), 133.7 (C-5), 175.2 (C=O)	EI: 170 (1)

[a] All compounds are oils.
[b] Satisfactory microanalyses were obtained (C ± 0.23, H ± 0.23) except for **5e** (C − 0.69, H + 0.23).
[c] c (g/mL, EtOH): **5a, f, g**, 0.01; **5d, e**, 0.008; **5b**, 0.005; **5e**, 0.0025.



Scheme 2

The structures of compounds **7** were confirmed particularly by their ^1H and ^{13}C NMR spectra. In no case could a diastereomer of **7** be detected in the reaction mixture, indicating that the intramolecular cycloaddition of nitrones of type **6** proceeds with complete diastereoselectivity. The configuration of compounds **7**, in particular the cis arrangement of 1-H and 5-H and the trans arrangement of 1-H and 8-H, was further confirmed by X-ray analyses of **7Ad**, **Af**, **Df** and rac-**7Ag**.[18]

The primary alcohol group of substituent R^2 in **7Ag** enables reactions at this position. Thus, treatment with (1*S*)-(−)-camphanoyl chloride yielded ester **10** (Scheme 3).[19] Starting from racemic pantolactone, compound rac-**7Ag** was synthesized. Its reaction with (1*S*)-(−)-camphanoyl chloride **9** furnished a diastereomeric mixture of **10** and dia-**10**. Comparison of the ^1H and ^{13}C NMR spectra of this diastereomeric mixture and of the ester **10** obtained from **7Ag** revealed that in the latter dia-**10** was not detectable. This indicates that **7Ag** was enantiomerically pure, confirming that the reaction sequence from (*R*)-(−)-pantolactone to **7Ag** proceeded without racemization.

Reductive opening of the isoxazolidine ring of compounds **7** can occur under various conditions.[20] Thus **7Aa**, **Ac** and **Ag** were converted into the highly functionalized tetrahydrofurans **11Aa**, **Ac** and **Ag** by reduction

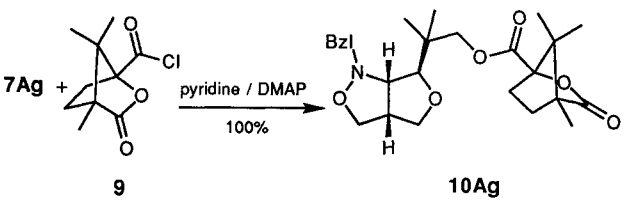
Table 2. 3,7-Dioxa-2-azabicyclo[3.3.0]octanes **7** Prepared[a]

Compound (% yield)	mp (°C)	$[\alpha]_D$[b] (T, °C)	^1H NMR ($CDCl_3$) δ, J (Hz)[c]	^{13}C NMR (75 MHz, $CDCl_3$)	MS (M^+) *m/z* (%)
7Aa (72)	oil	−51.9 (24)	3.43 (m, 1H, 5-H), 3.69 (dd, 1H, 1-H), 3.74 (dd, 1H, 6-H), 3.76 (d, 1H, CH_2), 3.82 (dd, 1H, 4-H), 4.09 (d, 1H, CH'_2), 4.20 (dd, 1H, 4-H'), 4.37 (dd, 1H, 6-H'), 4.65 (d, 1H, 8-H), 7.20–7.34 (m, 10H, ArH); ^3J 1/5 = 8.7, 1/8 = 6.0, 4/5 = 2.4, 4'/5 = 2.3, 5/6 = 6.7, 5/6' = 7.9; ^2J 4/4' = 9.0, 6/6' = 9.1, CH_2/CH'_2 = 12.9	48.8 (C-5), 60.1 (CH_2), 69.9 (C-4), 73.1 (C-6), 78.8 (C-1), 84.6 (C-8), 125.4, 127.2, 127.3, 128.1, 128.2, 129.0, 136.5, 140.3 (Ar)	EI: 281 (13)
7Ba (28)	oil	+3.6 (24)	0.97 (s, 9H, CMe_3), 3.31 (m, 1H, 5-H), 3.70 (dd, 1H, 4-H), 3.72 (dd, 1H, 6-H), 3.76 (dd, 1H, 1-H), 4.05 (dd, 1H, 4-H'), 4.26 (dd, 1H, 6-H'), 4.65 (d, 1H, 8-H), 7.19–7.36 (m, 5H, ArH); ^3J 1/5 = 8.9, 1/8 = 5.2, 4/5 = 3.9, 4'/5 = 7.2, 5/6 = 6.2, 5/6' = 7.6, ^2J 4/4' = 8.2, 6/6' = 9.0	26.6 [$C(\underline{C}H_3)_3$], 50.9 (C-5), 59.1 ($\underline{C}Me_3$), 72.6 (C-4), 73.0 (C-1), 73.1 (C-6), 86.8 (C-8), 126.2, 127.6, 128.3, 140.1 (Ar)	FD: 247 (100)
7Ca (54)	oil	−42.0 (24)	2.58 (s, 3H, CH_3), 3.35 (m, 1H, 5-H), 3.44 (dd, 1H, 1-H), 3.65 (dd, 1H, 6-H), 3.71 (dd, 1H, 4-H), 4.09 (dd, 1H, 4-H'), 4.30 (dd, 1H, 6-H'), 4.54 (d, 1H, 8-H), 7.19–7.35 (m, 5H, ArH); ^3J 1/5 = 8.7, 1/8 = 5.9, 4/5 = 2.3, 4'/5 = 6.7, 5/6 = 6.6, 5/6' = 7.8, ^2J = 4.4' = 9.0, 6/6' = 9.1	43.8 (CH_3), 48.8 (C-5), 69.3 (C-4), 73.1 (C-6), 81.4 (C-1), 84.4 (C-8), 125.6, 127.4, 128.3, 140.5 (Ar)	EI: 205 (39)
7Ab (42)	48	−21.0 (24)	2.67 (dd, 1H, CH_2), 2.76 (dd, 1H, CH'_2), 3.26 (m, 1H, 5-H), 3.40 (dd, 1H, 1-H), 3.53 (dd, 1H, 6-H), 3.59 (d, 1H, CH_2), 3.72 (dd, 1H, 4-H), 3.84 (ddd, 1H, 8-H), 4.01 (d, 1H, CH'_2), 4.12 (dd, 1H, 4-H'), 4.17 (dd, 1H, 6-H'), 7.01 + 7.16–7.33 (2m, 10H, ArH); ^3J 1/5 = 8.8, 1/8 = 6.1, 4/5 = 2.4, 4'/5 = 6.8, 5/6 = 6.9, 5/6' = 8.3; 8/CH_2 = 7.2, 8/CH'_2 = 5.0; ^2J 4/4' = 9.0, 6/6' = 8.9, CH_2Ph/CH'_2Ph = 14.1, CH_2N/CH'_2N = 12.5	38.6 (CH_2), 48.6 (C-5), 60.1 (CH_2), 69.9 (C-4), 72.6 (C-6), 75.1 (C-1), 83.8 (C-8), 126.2, 127.6, 128.2, 128.4, 129.3, 129.4, 136.7, 137.8 (Ar)	EI: 295 (43)
7Ac (55)	59–60	+15.9 (23)	0.87 (d, 3H, CH_3), 3.21 (m, 1H, 5-H), 3.36 (dd, 1H, 1-H), 3.82 (qd, 1H, 8-H), 3.88 (d, 1H, CH_2), 3.90 (dd, 1H, 6-H), 3.92 (dd, 1H, 6-H'), 4.36 (d, 1H, CH'_2), 4.79 (d, 1H, 4-H), 7.24–7.40 (m, 10H, ArH); ^3J 1/5 = 9.0, 1/8 = 1.8, 4/5 = 7.5, 5/6 = 6.8, 5/6' = 3.5, 8/CH_3 = 6.6, ^2J 6/6' = 9.5, CH_2Ph/CH'_2Ph = 12.5	17.3 (CH_3), 57.7 (C-5), 62.7 (CH_2), 68.8 (C-6), 79.1 (C-8), 79.5 (C-1), 84.9 (C-4), 126.6, 127.7, 128.1, 128.3, 128.5, 129.6, 136.1, 138.8 (Ar)	FD: 295 (100)

Table 2. (continued)

Compound (% yield)	mp (°C)	$[\alpha]_D^b$ (T, °C)	^{1}H NMR ($CDCl_3$) δ, J (Hz)[c]	^{13}C NMR (75 MHz, $CDCl_3$)	MS (M^+) m/z (%)
7Bc (80)	50	+19.1 (23)	1.15 (d, 3H, CH_3), 1.19 (s, 9H, CMe_3), 2.96 (m, 1H, 5-H), 3.54 (dd, 1H, 1-H), 3.82 (dd, 1H, 6-H), 3.90 (dd, 1H, 6-H′), 4.20 (qd, 1H, 8-H), 4.64 (d, 1H, 4-H), 7.28–7.37 (m, 5H, ArH); ^3J 4/5 = 9.2, 1/8 = 1.8, 4/5 = 8.7, 5/6 = 5.7, 5/6′ = 1.4, 8/CH_3 = 6.7; ^2J 6/6′ = 9.6	17.0 (CH_3), 25.7 [C($\underline{C}H_3)_3$], 58.0 ($\underline{C}Me_3$), 58.3 (C-5), 67.5 (C-6), 72.5 (C-1), 81.3 (C-8), 83.6 (C-4), 126.7, 128.1, 128.5, 138.9 (Ar)	EI: 261 (66)
7Cc (83)	oil	+16.7 (24)	1.17 (d, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.17 (dd, 1H, 1-H), 3.22 (m, 1H, 5-H), 3.95 (dd, 1H, 6-H), 3.97 (dd, 1H, 6-H′), 4.16 (qd, 1H, 8-H), 4.76 (d, 1H, 4-H), 7.27–7.36 (m, 5H, ArH); ^3J 1/5 = 8.8, 1/8 = 1.6, 4/5 = 6.8, 5/6 = 3.8, 5/6′ = 6.1, 8/CH_3 = 6.6; ^2J 6/6′ = 9.4	17.9 (CH_3), 44.7 (CH_3), 57.8 (C-5), 69.3 (C-6), 78.1 (C-8), 81.9 (C-1), 85.4 (C-4), 126.5, 128.1, 128.4, 138.7 (Ar)	EI: 219 (85)
7Ad (59)	98	−5.5 (23)	3.30 (m, 1H, 5-H), 3.87 (dd, 1H, 1-H), 4.05 (d, 1H, CH_2), 4.07 (dd, 1H, 6-H), 4.11 (dd, 1H, 6-H′), 4.36 (d, 1H, CH'_2), 4.92 (d, 1H, 4-H), 4.95 (d, 1H, 8-H), 7.05–7.44 (m, 15H, ArH); ^3J 1/5 = 8.8, 1/8 = 2.2, 4/5 = 7.2, 5/6 = 6.5, 5/6′ = 3.4, ^2J 6/6′ = 9.3, CH_2N/CH'_2N = 13.1	57.9 (C-5), 62.6 (CH_2Ph), 70.4 (C-6), 80.2 (C-1), 84.3 (C-8), 85.1 (C-4), 125.7, 126.6, 127.4, 127.6, 128.1, 128.3, 128.4, 128.5, 129.4, 136.3, 138.9, 139.7 (Ar)	FD: 357 (85)
7Ae (25)	64	+18.1 (24)	1.28 (d, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.36 (dd, 1H, $OC\underline{H}_2CHO$), 3.37 (m, 1H, 5-H), 3.54 (dd, 1H, 1-H), 3.55 (dd, 1H, 8-H), 3.59 (dd, 1H, $OC\underline{H}'_2CHO$), 3.62 (dd, 1H, 6-H), 3.69 (d, 1H, CH_2), 3.76 (dd, 1H, 4-H), 3.88 (ddd, 1H, $OC\underline{H}CH_2O$), 4.05 (d, 1H, CH'_2), 4.17 (dd, 1H, 4-H′), 4.26 (dd, 1H, 6-H′), 7.27–7.36 (m, 5H, ArH); ^3J 1/5 = 6.7, 1/8 = 5.3, 4/5 = 2.5, 4′/5 = 6.8, 5/6 = 6.4, 5/6′ = 7.8, 8/CH = 6.1, OCH/CH_2O = 6.4, OCH/CH'_2O = 8.0; ^2J 4/4′ = 9.0, 6/6′ = 9.0, CH_2N/CH'_2N = 12.1, $OC\underline{H}_2CHO/OC\underline{H}'_2CHO$ = 8.3	25.5 (CH_3), 26.3 (CH'_3), 48.4 (C-5), 60.4 (CH_2), 65.2 (OCH_2CHO), 70.1 (C-4), 72.9 (C-1), 73.6 (C-6), 76.9 ($OCHCH_2O$), 83.7 (C-8), 109.3 (C_{quart}) 127.9, 128.5, 129.5, 136.0 (Ar)	EI: 305 (6)
7Af (9)	114–115	+15.7 (26)	3.27 (m, 1H, 5-H), 3.53 (dd, 1H, 6-H), 3.59 (d, 1H, CH_2), 3.61 (d, 1H, 8-H), 3.62 (dd, 1H, 4-H), 3.74 (dd, 1H, 1-H), 3.89 (d, 1H, CH'_2), 4.07 (dd, 1H, 6-H′), 4.10 (dd, 1H, 4-H′), 7.16–7.27 (m, 5H, ArH); ^3J 1/5 = 8.0, 1/8 = 4.3, 4/5 = 3.0, 4′/5 = 7.6, 5/6 = 5.7, 5/6′ = 7.1, ^2J 4/4 = 8.7, 6/6′ = 8.9, CH_2/CH'_2 = 13.4	48.7 (C-5), 60.0 (CH_2), 70.0 (C-4), 73.4 (C-1), 73.5 (C-6), 83.8 (C-8), 127.5, 128.4, 128.8, 136.9 (Ar)	FD: 408 (100)
7Df (28)	98–100	+17.4 (26)	3.31 (m, 1H, 5-H), 3.57 (d, 1H, CH_2), 3.59 (dd, 1H, 6-H), 3.64 (d, 1H, 8-H), 3.67 (dd, 1H, 4-H), 3.74 (s, 3H, CH_3), 3.77 (dd, 1H, 1-H), 3.87 (d, 1H, CH'_2), 4.11 (dd, 1H, 6-H′), 4.14 (dd, 1H, 4-H′), 6.83 and 7.23 (2m, 4H, ArH); ^3J 1/5 = 8.5, 1/8 = 5.0, 4/5 = 3.0, 4′/5 = 7.5, 5/6 = 5.6, 5/6′ = 7.2, ^2J 4/4′ = 8.9, 6/6 = 8.9, CH_2/CH'_2 = 13.2	48.6 (C-5), 55.2 (CH_3), 59.4 (CH_2), 70.1 (C-4), 73.2 (C-1), 73.4 (C-6), 83.7 (C-8), 113.8, 128.9, 130.0, 159.0 (Ar)	FD: 468 (100)
7Ag (62)	20–30[d]	−6.3 (23)	0.70 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.61 (s, 1H, OH), 3.18 (s, 2H, $HOC\underline{H}_2$), 3.31 (m, 1H, 5-H), 3.42 (d, 1H, 8-H), 3.49 (dd, 1H, 6-H), 3.69 (dd, 1H, 1-H), 3.71 (d, 1H, CH_2), 3.74 (dd, 1H, 4-H), 3.99 (d, 1H, CH'_2), 4.15 (dd, 1H, 4-H′), 4.27 (dd, 1H, 6-H′), 7.25–7.35 (m, 5H, ArH); ^3J 1/5 = 8.8, 1/8 = 7.8, 4/5 = 1.4, 4′/5 = 6.6, 5/6 = 7.5, 5/6′ = 8.3; ^2J = 4/4′ = 9.2, 6/6′ = 8.9, CH_2N/CH'_2N = 12.5	19.7 (CH_3), 21.4 (CH_3), 37.2 (s, C_{quart}), 47.9 (C-5), 59.7 (CH_2), 69.7 (C-4), 71.4 (CH_2OH), 71.8 (C-1), 73.5 (C-6), 88.9 (C-8), 127.8, 128.5, 129.5, 136.1 (Ar)	FD: 277 (100)

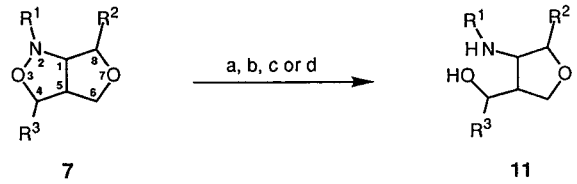
[a] Satisfactory microanalyses were obtained (C ± 0.30, H ± 0.22, N ± 0.19); **7Df** contains 1 mol H_2O.
[b] c = 0.01 g/mL in EtOH; except **7Ba** c = 0.006 (EtOH).
[c] Spectrometer used: 500 MHz, **7Aa**, **Ca**, **Ab**, **Ac**, **Ad**, **Ag**, 400 MHz, **7Bc**, **Cc**, **Ae**, **Af**, **Df**, 300 MHz, **7Ba**.
[d] Melting point of *rac*-**7Ag**, 82 °C.



9 10Ag

Scheme 3

with zinc and acetic acid, reduction with activated nickel and catalytic hydrogenation in the presence of palladium hydroxide, respectively (Scheme 4). Whereas **11Ag** was formed from **7Ag** by catalytic hydrogenation in ethanol under pressure (90 bar) at 60 °C over 24 h, **11Eg** arose at prolonged reaction time and slightly increased pressure in ethanol containing a small amount of acetone. Under these conditions, the benzylic group R^1 was removed from **11Ag** forming a primary amino group at first. Condensation of the amino moiety with acetone afforded an isopropylidene imino group which was subsequently reduced to give the *N*-isopropylamino substituent R^1.



7 11

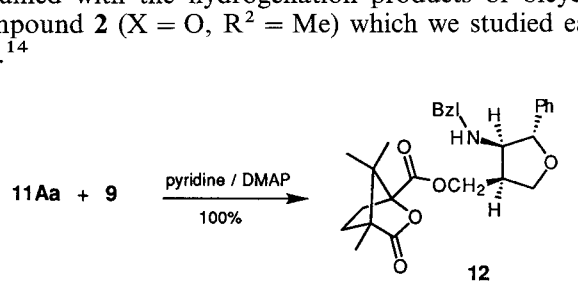
11	R^1	R^2	R^3
Aa	Bzl	Ph	H
Ac	Bzl	Me	Ph
Ag	Bzl	$(CH_3)_2CCH_2OH$	H
Eg	i-Pr	$(CH_3)_2CCH_2OH$	H

11Aa : method a Zn/HOAc, 80% **11Ac** : method b Raney-Ni, EtOH, 77%
11Ag : method c H_2, $Pd(OH)_2/C$, 60°C, 90 bar, EtOH, 1d, 21%
11Eg from **7Ag** : method d H_2, $Pd(OH)_2/C$, 60°C, 100 bar, $EtOH/Me_2CO$, 4d, 97%

The configuration of compounds **11** corresponds to the configuration of the starting compounds **7** (see Schemes 1 and 2).

Scheme 4

Treatment of **11Aa** with (1*S*)-(−)-camphanoyl chloride gave the ester **12** (Scheme 5). As in the case of ester **10**, the ^1H and ^{13}C NMR spectra of **12** revealed that the compound is diastereomerically pure, indicating that the educt **11Aa** and consequently its precursor **7Aa** must be enantiomerically pure. The same result had also been obtained with the hydrogenation products of bicyclic compound **2** (X = O, R^2 = Me) which we studied earlier.[14]



12

Scheme 5

Since the risk of racemization during the reaction sequence **4** → **5** → **6** → **7** seems to be highest for compounds with the substituent R^2 = Ph (**a** and **d**) because of the electron-withdrawing properties of the phenyl group, it can be assumed that the reaction starting with the other hydroxy esters proceeded also without racemization thus giving enantiomerically pure products **7**. This assumption is also confirmed by the formation of diastereomerically pure compounds **7Ae, Af,** and **Df**. Due to the existence of more than one stereogenic center in their starting compounds, diastereomers would have been formed in these cases if racemization had occurred.

In summary, starting from enantiomerically pure α-hydroxy esters enantiomerically pure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **7** were prepared. They were formed from transient nitrones **6** by an intramolecular cycloaddition which proceeded with complete diastereoselectivity. Thus the stereogenic center originating from the α-hydroxy esters gave high asymmetric induction, resulting in the formation of three or four contiguous stereogenic centers in **7**.

Commercially available compounds were used without further purification if their purity was > 97%. Otherwise they were purified by standard procedures. Methyl (2*R*,3*S*)-(+)-3,4-*O*-isopropylidine-2,3,4-trihydroxybutyrate and (1*S*)-(−)-camphanoyl chloride (99.5% purity) were purchased from Fluka, DIBAL-H in hexane from Aldrich. The *N*-alkylhydroxylamines were prepared by known procedures. Silver(I) oxide was precipitated from dilute aq silver nitrate which was free of carbon dioxide by addition of aq NaOH free of carbonate. It was dried carefully at 60°C under reduced pressure (0.1 mbar) in the dark. Et_2O was first dried over calcium chloride and subsequently refluxed over sodium and benzophenone; finally it was distilled under argon atmosphere. CH_2Cl_2 was refluxed over phosphorous pentoxide and subsequently distilled. Pyridine was distilled and dried over molecular sieves (4 Å). All reactions with the exception of the reductive ring opening were performed under nitrogen or argon. For column chromatography Merck aluminum oxide 90 (particle size distribution 0.063–0.200 mm) and Merck silica gel 60 (particle size distribution 0.063–0.200 mm) were used. Flash chromatography was performed at 1.5–2.3 bar using silica gel for flash chromatography (J.T. Baker, particle size distribution 0.030–0.060 mm, average pore diameter 40 Å). Mps are uncorrected, they were measured with an apparatus from Büchi. Microanalyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: Bruker AMX 500, AM 400 and AC 300, using the residues of ^1H (δ = 7.24) or of ^{13}C (δ = 77.0) of the solvent $CDCl_3$ as internal standard. MS: Varian MAT CH-7 (70 eV, EI) and Varian MAT 711 (FD). Optical rotations were obtained using the polarimeter Perkin-Elmer 241 at 589 mm.

Compounds **8**, **10Ag**, **11Aa**, **Ac**, **Ag**, **Eg** and **12** gave C, H (N where appropriate) analyses ± 0.26%; except **11Ag**, C − 0.39%.

Enantiomerically Pure α-Allyloxy Esters 5; General Procedure:
A solution of the α-hydroxy ester (25 mmol) and allyl bromide (40 mmol) or cinnamyl chloride (15 mmol for **5c**, 25 mmol for **5d**) in Et_2O (100 mL) was gently refluxed in the dark. Within 10 min, well-dried silver(I) oxide (15 g, 65 mmol) was added in three portions. After refluxing for 2 h the reaction mixture was stirred for 1–3 d. The solid residue was separated and washed repeatedly with Et_2O. The combined etheral solutions were dried ($MgSO_4$) (the etheral solutions of **5c** and **5g** were washed beforehand with water about 15 times). After removal of the solvent, the volatile parts were removed at 0°C under reduced pressure (ca. 0.1 mbar). Compounds **5a**, **5b**, **e** and **f** were isolated without further purification, **5c** and **d** were purified by column chromatography [SiO_2; EtOAc/petroleum ether (bp 40–60°C)]. Compound **5g** was prepared in an analogous manner from (*R*)-(−)-pantolactone (50 mmol) and allyl iodide (40 mmol).

Racemic α-Allyloxy Esters *rac*-5b, c and g; General Procedure:
NaH (5.4 g, 180 mmol, 80% in paraffin) was added in small portions at 0°C within 2 h to a solution of the α-hydroxy ester (150 mmol) in Et_2O (300 mL). After stirring at r.t. for 18 h, firstly Bu_4NI (5.54 g, 15 mmol) and then 10 min later allyl bromide (27.22 g, 225 mmol) or cinnamyl chloride (19.26 g, 100 mmol) were added. The reaction mixture was stirred for 1–4 d. Then aq NH_4Cl (100 mL) was added. The aqueous layer and the paraffin were separated and the organic layer was washed with water 15 times. Further purification as described above gave colourless or slightly yellow oils of *rac*-**5b** (81), *rac*-**5c** (90) and *rac*-**5g** (70%).

Reduction of α-Allyloxy Esters 5a–f and Treatment of the Resulting Aldehydes with *N*-Alkylhydroxylamines; General Procedure:
A 1 M solution of DIBAL-H in hexane (2.13 g, 15.0 mL) was added

dropwise to a solution of **5** (10 mmol; **5f**, 5 mmol) in Et_2O (30 mL) over 30 min at −72 °C. The reaction mixture was stirred for 80 min. Subsequently MeOH (0.2 mL, 5 mmol) was added and the mixture was warmed to 0 °C. Then water (1.5 mL, 83 mmol) was added dropwise to the mixture which was then stirred for 10 min at 0–5 °C.

A solution of *N*-alyklhydroxylamine (10 mmol) in Et_2O or CH_2Cl_2 was added dropwise to the reaction mixture within 5 min at 0–5 °C. After 15 min molecular sieves (5 g, 4 Å) were added. Subsequently the mixture was stirred for 2 h at 0–5 °C and then for 1–3 d at room temperature. The solid residue was separated and washed several times with Et_2O or $CHCl_3$. The combined organic solution was concentrated and the remaining solvent was removed under reduced pressure (ca. 0.1 mbar). The products were purified as follows: **7Aa**, **Ab**, **Ac**, **Ba**, **Bc**, **Ca**, **Cc**, **Ad**, column chromatography [Al_2O_3, neutral; EtOAc/petroleum ether (bp 40–60 °C)]; **7Ae**, **Af**, **Df**, flash chromatography [SiO_2; 1.5–2.3 bar; EtOAc/petroleum ether (bp 40–60 °C)]. **7Df** was isolated as a monohydrate. It could be obtained particularly pure by freezing out from the reaction mixture after separation of the solid residue.

Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-3-Allyloxy-4,4-dimethyloxolan-2-ol (8g):

1 M DIBAL-H in hexane (4.26 g, 30 mL) was added to a solution of **5g** (3.40 g, 20 mmol) in Et_2O or CH_2Cl_2 (80 mL) within 1 h at −72 °C. After a further 80 min with stirring, the reaction mixture was poured onto 60 g ice containing 4.2 mL of conc H_2SO_4. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The remaining solvent was cautiously removed at 0 °C and 0.1 mbar to give a light yellow oil in 95% yield (3.28 g).

IR (neat): $\nu = 3416\ cm^{-1}$ (OH).

MS (EI): $m/z = 131$ (M^+ – allyl, 27%).

First Diastereomer:

^1H NMR ($CDCl_3$): $\delta = 0.99$ (s, 3H, Me), 1.05 (s, 3H, Me), 3.39 (d, $^3J = 3.0$ Hz, 1H, Me_2CCHO), 3.54 (d, $^2J = 8.3$ Hz, 1H, CH_2CMe_2), 3.74 (d, $^2J = 8.3$ Hz, 1H, CH_2CMe_2), 3.97 (ddt, $^2J = 13.1$, $^3J = 5.6$, $^4J = 1.5$ Hz, 1H, $CH_2CH=CH_2$), 4.09 (ddt, $^2J = 13.1$, $^3J = 5.1$, $^4J = 1.5$ Hz, 1H, $CH'_2CH=CH_2$), 4.40 (s, 1H, OH), 5.10 (m, $^2J = 1.6$, $^3J = 10.3$, $^4J = 1.5$ Hz, 1H, $CH=CH_2$), 5.20 (m, $^2J = 1.6$, $^3J = 17.3$, $^4J = 1.5$, 1H, $CH=CH'_2$), 5.30 (d, $^3J = 3.0$ Hz, 1H, $OCHOH$), 5.84 (m, $^3J = 17.3$, 10.3, 5.6, 5.1 Hz, 1H, $CH_2CH=CH_2$).

^{13}C NMR ($CDCl_3$): $\delta = 20.2$ (Me), 24.0 (Me), 41.8 (CMe_2), 71.3 ($CH_2CH=CH_2$), 78.5 (CH_2CMe_2), 91.3 (Me_2CCHO), 102.7 ($OCHOH$), 116.5 ($CH=CH_2$), 134.6 ($CH=CH_2$).

Second Diastereomer:

^1H NMR ($CDCl_3$): $\delta = 1.00$ (s, 3H, Me), 1.02 (s, 3H, Me), 3.30 (d, $^3J = 4.2$ Hz, 1H, Me_2CCHO), 3.35 (d, $^2J = 8.1$ Hz, 1H, CH_2CMe_2), 3.64 (d, $^2J = 8.1$ Hz, 1H, CH_2CMe_2), 4.02 (ddt, $^2J = 13.1$, $^3J = 5.6$, $^4J = 1.5$ Hz, 1H, $CH_2CH=CH_2$), 4.08 (ddt, $^2J = 13.1$, $^3J = 5.1$, $^4J = 1.5$ Hz, 1H, $CH'_2CH=CH_2$), 4.14 (d, $^3J = 9.6$ Hz, 1H, OH), 5.16 (m, $^2J = 1.6$, $^3J = 10.3$, $^4J = 1.5$ Hz, 1H, $CH=CH_2$), 5.20 (m, $^2J = 1.6$, $^3J = 17.3$, $^4J = 1.5$ Hz, 1H, $CH=CH'_2$), 5.37 (dd, $^3J = 9.6$, $^3J = 4.2$ Hz, 1H, $OCHOH$), 5.84 (m, $^3J = 17.3$, 10.3, 5.6, 5.1 Hz, 1H, $CH_2CH=CH_2$).

^{13}C NMR ($CDCl_3$): $\delta = 19.6$ (Me), 25.6 (Me), 41.8 (CMe_2), 73.1 ($CH_2CH=CH_2$), 76.7 (CH_2CMe_2), 85.0 (Me_2CCHO), 97.4 ($OCHOH$), 117.7 ($CH=CH_2$), 133.8 ($CH=CH_2$).

The ^1H NMR spectrum exhibits in addition the signal of the aldehyde form at $\delta = 9.65$ (d, $^3J = 2.8$ Hz) corresponding to an aldehyde content of approximately 2%.

(1*S*,5*R*,8*R*)-(−)-2-Benzyl-8-(1,1-dimethyl-2-hydroxyethyl)-3,7-dioxa-2-azabicyclo[3.3.0]octane (7Ag):

A solution of **8g** (1.72 g, 10 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0–5 °C to a stirred solution of *N*-benzylhydroxylamine (1.23 g, 10 mmol) in CH_2Cl_2 (40 mL) containing molecular sieves (5 g, 4 Å) within 15 min. Stirring was continued at 0–5 °C for 2 h and at r.t. for 5 d. After filtration the solid residue was washed with CH_2Cl_2 (ca. 5 × 40 mL). The combined solutions were concentrated and the remaining solvent as well as other residues were removed under reduced pressure (ca. 0.1 mbar). The product was purified by flash chromatography [EtOAc/petroleum ether (bp 40–60 °C) 1:1] ($R_f = 0.34$). **7Ag** was obtained as yellow oil in 62% yield (1.73 g). Spectroscopic data are presented in Table 2.

rac-**7Ag** was obtained as colourless needles, mp 82 °C [Et_2O/petroleum ether (bp 40–60 °C) 1:4].

7Ag and *rac*-7Ag with (1*S*)-(−)-Camphanoyl Chloride; (1*S*,5*R*,8*R*)-2-(2-Benzyl-3,7-dioxa-2-azabicyclo[3.3.0]oct-8-yl)-2-methylpropyl (1*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (10Ag):

A solution of camphanoyl chloride (0.16 g, 0.75 mmol) in pyridine (2 mL) was added dropwise at 0 °C to a solution of **7Ag** (0.14 g, 0.50 mmol) and *N*,*N*-dimethyl-4-aminopyridine (ca. 5 mg) in pyridine (2 mL) within 5 min. The reaction mixture was stirred for 2 h at 0–5 °C and subsequently for 18 h at r.t. Then aq $NaHCO_3$ (5 mL) followed by Et_2O (20 mL) were added. The organic layer was separated, washed twice with aq $NaHCO_3$ (5 mL) and once with water. The solvents were evaporated at r.t. under reduced pressure to give a viscous, colourless oil in 96% yield (0.22 g).

MS (FD): $m/z = 457$ (M^+, 100%).

IR (neat): $\nu = 1790$, 1749 cm^{-1}.

NMR Spectra: In brackets the deviation of the second signal produced by the diastereomeric component dia-**10Ag** is given.

^1H NMR ($CDCl_3$): $\delta = 0.76$ (s, 3H, Me), [+0.0036], 0.78 (s, 3H, Me), 0.89 (s, 3H, Me), [−0.0211], 0.98 (s, 3H, Me), [+0.0030], 1.04 (s, 3H, Me), 1.60 (ddd, $^2J = 13.2$, $^3J = 9.4$, $^3J = 4.7$ Hz, 1H, CH_2), [+0.0101], 1.84 (ddd, $^2J = 13.2$, $^3J = 10.8$, $^3J = 4.6$ Hz, 1H, CH_2), [+0161], 1.89 (ddd, $^2J = 13.6$, $^3J = 9.4$, $^3J = 4.6$ Hz, 1H, CH_2), [+0.0484], 2.33 (ddd, $^2J = 13.6$, $^3J = 10.8$, $^3J = 4.7$ Hz, 1H, CH_2), [+0.0192], 3.25 (m, $^3J = 8.6$, $^3J = 8.1$, $^3J = 7.3$, $^3J = 6.4$, $^3J = 1.4$ Hz, 1H, 5-H), 3.36 (d, $^3J = 7.0$ Hz, 1H, 8-H), [+0.0083], 3.42 (dd, $^2J = 8.9$, $^3J = 7.3$ Hz, 1H, 6-H), 3.64 (dd, $^2J = 9.1$, $^3J = 1.4$ Hz, 1H, 4-H), 3.70 (d, $^2J = 12.7$ Hz, 1H, $PhCH_2$) [−0.0204], 3.77 (dd, $^3J = 8.6$, $^3J = 7.0$ Hz, 1H, 1-H), [+0.0049], 3.89 (d, $^2J = 10.9$ Hz, 1H, CO_2CH_2) [+0.0173], 3.94 (d, $^2J = 10.9$ Hz, 1H, $CO_2CH'_2$) [−0.0174], 3.94 (d, $^2J = 12.7$ Hz, 1H, Ph–CH'_2) [+0.0131], 4.09 (dd, $^2J = 9.1$, $^3J = 6.4$ Hz, 1H, 4-H'), 4.13 (dd, $^2J = 8.9$, $^3J = 8.1$ Hz, 1H, 6-H'), 7.18–7.31 (m, 5H, ArH).

The spectrum of **10Ag** showed no signals at the positions where the signals of dia-**10Ag** appeared, indicating that **10Ag** was diastereomerically pure and hence **7Ag** was enantiomerically pure with respect to the NMR method.

^{13}C NMR ($CDCl_3$): $\delta = 9.7$ (Me), 16.7 (Me), 16.7 (Me), 20.3 (Me) [−0.1169], 21.6 (Me) [+0.3724], 29.0 (CH_2), 30.7 (CH_2), 36.6 (C_{quart}), 48.6 (C-5), 54.1 (C_{quart}), 54.8 (C_{quart}), 59.8 (Ph–CH_2), 69.3 (CO_2CH_2), 71.3 (C-4), 71.9 (C-1), 73.1 (C-6), 87.9 (C-8) [+0.1397], 91.3 (C_{quart}), 167.3 (CO_2CH_2), 179.2 (CO_2C_{quart}), 127.6, 128.4, 129.5, 136.8 (Ar).

Reductive Ring Opening of Compounds 7; (2*S*,3*R*,4*R*)-(3-Benzylamino-2-phenyltetrahydrofuran-4-yl)methanol (11Aa):

A solution of **7Aa** (0.84 g, 3.0 mmol) in AcOH (21 mL) was added dropwise with stirring to a suspension of zinc (0.78 g, 12 mmol) in aq AcOH (30%, 100 mL). The reaction mixture was stirred for 24 h at 65 °C. Then aq K_2CO_3 (30%, 400 mL) was added. After extraction with CH_2Cl_2 (3 ×) the organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Light yellow solid, 80% yield (0.68 g), mp 74 °C (from CH_2Cl_2). $[\alpha]_D^{17} = -46.45°$ ($c = 0.009$, EtOH).

MS (EI): $m/z = 283$ (M^+, 5%).

^1H NMR ($CDCl_3$): $\delta = 2.59$ (m, $^3J = 8.0$, $^3J = 6.9$, $^3J = 6.8$, $^3J = 5.7$ Hz, 1H, 4-H), 3.37 (dd, $^3J = 6.9$, $^3J = 5.8$ Hz, 1H, 3-H), 3.83 (d, $^2J = 13.1$ Hz, 1H, NCH_2), 3.88 (d, $^2J = 13.1$ Hz, 1H, NCH'_2),

3.90 (d, ^3J = 5.7 Hz, 2 H, CH_2OH), 3.96 (dd, ^2J = 8.8, ^3J = 6.8 Hz, 1 H, 5-H), 4.27 (dd, ^2J = 8.8, ^3J = 8.0 Hz, 1 H, 5-H'), 4.78 (d, ^3J = 5.8 Hz, 1 H, 2-H), 7.21–7.36 (2 m, 10 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 41.6 (C-4), 53.0 (CH_2N), 61.6 (CH_2OH), 68.0 (C-3), 69.5 (C-5), 84.8 (C-2), 125.8, 127.4, 127.8, 128.0, 128.5, 128.6, 138.9, 140.7 (Ar).

(*R*)-(+)-[(2*S*,3*R*,4*S*)-(3-Benzylamino-2-methyltetrahydrofuran-4-yl)](phenyl)methanol (11 Ac):

Small portions of activated Raney nickel (total amount 2–4 g) were added in intervals of 15 min to a solution of **7 Ac** (0.89 g, 3.0 mmol) in EtOH (30 mL). The progress of the reaction was controlled by TLC. After about 150 min the Raney nickel was separated and washed with EtOH. From the combined solutions the solvent was removed under reduced pressure to give 0.69 g (77%) of **11 Ac** as highly viscous oil. $[\alpha]_D^{24}$ = + 10.35° (*c* = 0.008, EtOH).

MS (EI): *m/z* = 297 (M^+, 5%).

^{1}H NMR ($CDCl_3$): δ = 1.22 (d, ^3J = 6.2 Hz, Me), 2.67 (m, ^3J = 9.1, ^3J = 7.5, ^3J = 7.3, ^3J = 7.2 Hz, 1 H, 4-H), 3.09 (dd, ^3J = 7.3, ^3J = 5.1 Hz, 1 H, 3-H), 3.56 (dd, ^2J = 9.2, ^3J = 7.2 Hz, 1 H, 5-H), 3.68 (dd, ^2J = 9.2, ^3J = 7.5 Hz, 1 H, 5-H'), 3.83 (d, ^2J = 12.7 Hz, 1 H, CH_2), 3.88 (d, ^2J = 12.7 Hz, 1 H, CH_2), 4.01 (qd, ^3J = 6.2, ^3J = 5.1 Hz, 1 H, 2-H), 4.79 (d, ^3J = 9.1 Hz, 1 H, C*H*OH), 7.19–7.36 (2 m, 10 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 19.9 (Me), 48.1 (C-4), 52.9 (CH_2), 66.0 (C-3), 68.6 (C-5), 73.5 (C-2), 79.7 (CHOH), 126.5, 127.4, 127.6, 128.2, 128.4, 128.6, 138.9, 142.8 (Ar).

(2*R*,3*S*,4*S*)-(+)-2-(3-Benzylamino-4-hydroxymethyltetrahydrofuran-2-yl)-2-methylpropan-1-ol (11 Ag):

A solution of **7 Ag** (1.39 g, 5 mmol) in EtOH (150 mL) and $Pd(OH)_2$ (20% on charcoal, 1 g) was hydrogenated at 60 °C and 90 bar hydrogen pressure for 1 d in a 250 mL autoclave. After filtration, the solvent was removed under reduced pressure. The product was purified by flash chromatography (SiO_2; EtOAc/EtOH, 10:1; R_f = 0.58) to give a yellow solid in 21% yield (0.30 g), mp 114 °C ($CHCl_3$). $[\alpha]_D^{24}$ = + 63.68° (*c* = 0.01, EtOH).

MS (FD): *m/z* = 560 (2 × M^+ + 2, 100%).

^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 3 H, Me), 0.93 (s, 3 H, Me), 2.49 (m, ^3J = 7.2, ^3J = 6.1, ^3J = 5.0, ^3J = 4.9 Hz, 1 H, 4-H), 3.31 (d, ^2J = 11.6 Hz, 1 H, CH_2OH), 3.36 (d, ^2J = 11.6 Hz, 1 H, CH_2OH), 3.37 (dd, ^3J = 7.7, ^3J = 7.2 Hz, 1 H, 3-H), 3.51 (d, ^3J = 7.7 Hz, 1 H, 2-H), 3.77 (d, ^2J = 12.1 Hz, 1 H, CH_2N), 3.87 (d, ^3J = 5.0 Hz, 2 H, CH_2OH), 3.88 (dd, ^2J = 9.0, ^3J = 4.9 Hz, 1 H, 5-H), 3.90 (d, ^2J = 12.1 Hz, 1 H, CH_2N), 3.93 (dd, ^2J = 9.0, ^3J = 6.1 Hz, 1 H, 5-H'), 7.27–7.33 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 18.7 (Me), 22.4 (Me), 38.8 (*C*Me_2), 42.4 (C-4), 53.4 (CH_2-N), 61.0 (C-3), 61.6 (CH_2OH), 70.2 (CH_2OH), 71.0 (C-5), 89.4 (C-2), 127.6, 128.5, 128.7, 138.6 (Ar).

(2*R*,3*S*,4*S*)-(+)-2-(4-Hydroxymethyl-3-isopropylaminotetrahydrofuran-2-yl)-2-methylpropan-1-ol (11 Eg):

7 Ag was hydrogenated as described above changing the following parameters: **7 Ag** (2.77 g, 10 mmol) in a mixture of EtOH (150 mL) and acetone (3 mL), hydrogen pressure 100 bar, reaction time 4 d. Slightly yellow solid in 97% yield (2.25 g), mp 115 °C (EtOH). $[\alpha]_D^{24}$ = + 81.16° (*c* = 0.007, EtOH).

MS (FD): *m/z* = 231 (M^+, 100%).

^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 3 H, Me), 0.92 (s, 3 H, Me), 1.07 (d, ^3J = 6.2 Hz, 3 H, Me), 1.09 (d, ^3J = 6.2 Hz, 3 H, Me), 2.39 (m, ^3J = 6.8, ^3J = 5.9, ^3J = 5.4, ^3J = 5.0, ^3J = 3.7 Hz, 1 H, 4-H), 2.93 (m, ^3J = 6.2 Hz, 1 H, C*H*Me_2), 3.28 (d, ^2J = 11.5 Hz, 1 H, CH_2OH), 3.34 (d, ^2J = 11.5 Hz, 1 H, CH_2OH), 3.36 (dd, ^3J = 8.4, ^3J = 6.8 Hz, 1 H, 3-H), 3.43 (d, ^3J = 8.4 Hz, 1 H, 2-H), 3.73 (dd, ^2J = 11.3, ^3J = 5.0 Hz, 1 H, 5-H), 3.79 (dd, ^2J = 11.3, ^3J = 5.4 Hz, 1 H, 5-H'), 3.84 (dd, ^2J = 9.1, ^3J = 3.7 Hz, CH_2OH), 3.88 (dd, ^2J = 9.1, ^3J = 5.9 Hz, 1 H, CH_2OH).

^{13}C NMR ($CDCl_3$): δ = 18.2 (Me), 21.6 (Me), 23.0 (CH*M*e_2), 23.6 (CH*M*e_2), 39.0 (C_{quart}), 42.2 (C-4), 47.6 (*C*HMe$_2$), 58.3 (C-3), 61.6 (CH_2OH), 70.2 (CH_2OH), 70.8 (C-5), 89.0 (C-2).

(2*S*,3*R*,4*S*)-(3-Benzylamino-2-phenyltetrahydrofuran-2-yl)-methyl (1*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (12):

Compound **12** was prepared from **11 Aa** and (1*S*)-(−)-camphanoyl chloride in the same way as described for **10 Ag**.

^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 3 H, Me), 1.07 (s, 3 H, Me), 1.14 (s, 3 H, Me), 1.71 (ddd, ^2J = 13.3, ^3J = 9.4, ^3J = 4.1 Hz, 1 H, CH_2), 1.93 (ddd, ^2J = 13.3, ^3J = 10.7, ^3J = 4.6 Hz, 1 H, CH_2), 2.02 (ddd, ^2J = 13.5, ^3J = 9.4, ^3J = 4.6 Hz, 1 H, CH_2), 2.42 (ddd, ^2J = 13.5, ^3J = 10.7, ^3J = 4.1 Hz, 1 H, CH_2), 2.76 (m, ^3J = 8.5, ^3J = 7.1, ^3J = 6.8, ^3J = 6.1, ^3J = 5.6 Hz, 1 H, 4-H), 3.33 (dd, ^3J = 6.8, ^3J = 5.6 Hz, 1 H, 3-H), 3.82 (d, ^2J = 13.2 Hz, 1 H, NCH_2), 3.86 (d, ^2J = 13.2 Hz, 1 H, NCH_2'), 3.97 (dd, ^2J = 8.9, ^3J = 6.1 Hz, 1 H, 5-H), 4.32 (dd, ^2J = 8.9, ^3J = 7.1 Hz, 1 H, 5-H'), 4.41 (dd, ^2J = 11.2, ^3J = 8.5 Hz, 1 H, CO–OCH_2), 4.63 (dd, ^2J = 11.2, ^3J = 5.6 Hz, 1 H, CO–OCH_2'), 4.82 (d, ^3J = 5.6 Hz, 1 H, 2-H), 7.04–7.40 (2 m, 10 H, Ar–H).

The spectrum of **12** showed no additional signals, indicating that it was diastereomerically pure and hence **11 Ag** and **7 Ag** were enantiomerically pure with respect to the NMR method.

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