Asymmetric Synthesis of 1-Aryl-1,2,3,4-tetrahydroisoquinolines, 2[◇]

Preparation of Chiral 2-(2-Bromobenzyl)-1,3-dioxolanes and Their Addition to Acylimines☆

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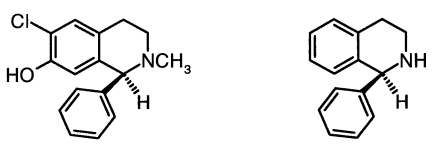
A series of enantiomerically pure 2-(2-bromobenzyl)-1,3-dioxolanes **10** has been prepared by transacetalization of the dimethyl acetal **8** or the enol ether **7** with enantiomerically pure C_2 symmetric 1,2-diols. We investigated the ability of the chiral 1,3-dioxolane moiety to control the diastereoselectivity during the addition of the aryllithium intermediates **18** to the acylimines **17**. Those reactive aryllithium species were generated by bromine/lithium exchange at the bromo acetals **10**. In this series the best diastereoselectivity was obtained by addition of the aryllithium intermediate **18b** to the acylimine **17a** to yield the diastereomeric addition products **19c**/**20c** in a ratio of 72:28. After separation, the main diastereomer **19c** was cyclized to afford the dihydroisoquinoline (*R*)-**21**, which was then hydrogenated to give the NMDA antagonistic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**2**. The chiral auxiliary, the diol **9b**, cleaved during the cylization of **19c**, could be recovered in 89% yield.

Introduction

1,2,3,4-Tetrahydroisoquinolines of synthetic, plant and mammalian origin have been intensively studied because of their manifold pharmacological properties, e.g. fibrinolytic, antiviral, tranquilizing, muscle relaxant, hypotensive, hallucinogenic, positive inotropic effects.[2] Our interest has been focused on 1-aryl-1,2,3,4-tetrahydroisoquinolines possessing antagonistic effects at dopamine D_1 and NMDA receptors (NMDA: *N*-methyl-D-aspartate). Thus, tetrahydroisoquinolinol (±)-**1** binds with high affinity (K_i = 12.5 nM) and selectivity to the D_1 receptors,[3] whereas the isoquinoline (±)-**2** interacts with the phencyclidine binding site of the NMDA receptors.[4] In both cases the enantiomers with the (*S*) configuration, (*S*)-**1** and (*S*)-**2**, exhibit higher affinity than their mirror images (*R*)-**1** and (*R*)-**2**.[3][5]

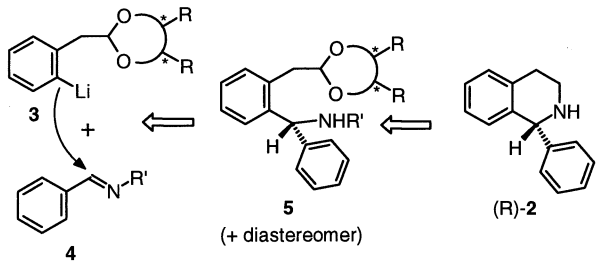
Scheme 1



(S)-**1** (S)-**2**

We therefore planned to devise a novel asymmetric synthesis to obtain enantiomerically pure 1-aryl-1,2,3,4-tetrahydroisoquinolines. In contrast to the established asymmetric syntheses of 1-aryltetrahydroisoquinolines, which utilize complete isoquinoline ring systems for the introduction of the chirality in position 1,[5][6][7][8][9] we followed another strategy. In the first step an aryllithium intermediate (**3**) was generated by halogen/metal exchange of an appropriate aryl halide, and this should be added to imine derivatives (**4**) to give the addition products **5**. The diastereoselectivity during this addition should be controlled by the chiral acetal moiety of **3**. Hydrolysis of the acetal, with recovery of the chiral auxiliary, and subsequent cyclization should complete the synthesis of the enantiomerically pure 1-phenyltetrahydroisoquinoline (*R*)-**2**.

Scheme 2



Preparation of the Enantiomerically Pure 2-(2-Bromobenzyl)-1,3-dioxolanes 10

The starting material for the preparation of the dioxolanes **10** is (2-bromophenyl)acetaldehyde dimethyl acetal (**8**), which has been obtained by a two-step homologization of 2-bromobenzaldehyde (**6**) consisting of a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride and subsequent addition of methanol to the resulting enol ether

[◇] Part 1: Ref.[1].

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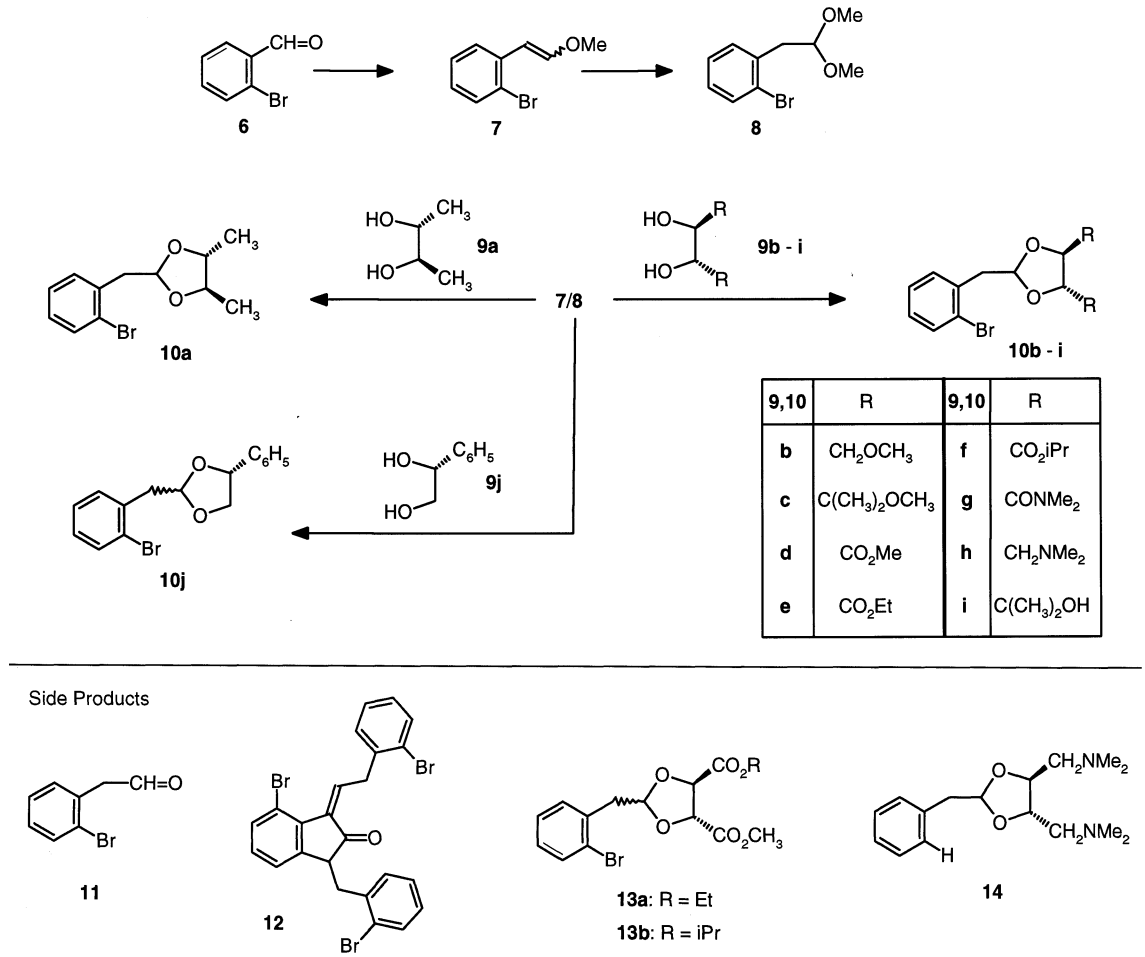
Scheme 3



9,10	R	9,10	R
b	CH_2OCH_3	f	CO_2iPr
c	$C(CH_3)_2OCH_3$	g	$CONMe_2$
d	CO_2Me	h	CH_2NMe_2
e	CO_2Et	i	$C(CH_3)_2OH$

7.[10] Transacetalization of the dimethyl acetal **8** with the enantiomerically pure C_2 symmetric 1,2-diols **9a**, **9b**[11] and **9c**[12] in the presence of *p*-toluenesulfonic acid, furnished the 2-(2-bromobenzyl)-1,3-dioxolanes **10a–c** in 80–89% yield. The reaction sequence could be shortened by reacting the diols **9a–c** with the enol ether **7** to give the dioxolanes **10a–c** in comparable yields (79–90%). Alternatively, the branched acetal **10c** was prepared by derivatization of the diester **10d**: Reaction of **10d** with an excess of methylmagnesium iodide provided the diol **10i,** which was alkylated with methyl iodide to give the dimethyl ether **10c**. In the case of **10c** the derivatization of the diester **10d** is not a better method than the direct reaction of the dimethyl acetal **8** or the enol ether **7** with the diol **9c**. However, this sequence may be advantageous in the preparation of sterically more demanding acetals.

The transacetalization of the dimethyl acetal **8** with the dimethyl tartrate **9d** required refluxing toluene instead of THF to provide the dimethyl dicarboxylate **10d** (50% yield) along with the (2-bromophenyl)acetaldehyde **11** and the indanone **12** as side products. Removal of the liberated methanol with molecular sieves (4 Å) in a Soxhlet apparatus shortened the reaction time from seven days to three days and, moreover, raised the yield of **10d** to 63%. Starting with the enol ether **7** instead of the dimethyl acetal **8** led to a further improvement in the yield (72%). Although the reaction conditions were optimized, only low yields of the diethyl dicarboxylate **10e** (22%) and the diisopropyl dicarboxylate **10f** (24%) were obtained. Side reactions leading to the phenylacetaldehyde **11**, the indanone **12** and the transesterified products **13a** and **13b** (mixture of diastereomers) are responsible for the low yields.

In contrast to the diols **9a–f**, the tartaramide **9g** and the diaminodiol **9h** did not react with the dimethyl acetal **8** or the enol ether **7** to yield the dioxolanes **10g** and **10h**. Therefore, the diamide **10g** was prepared by aminolysis of the dimethyl dicarboxylate **10d** with an excess of dimethylamine. However, reduction of the diamide **10g** with $LiAlH_4$ furnished the debrominated diamine **14** instead of the bromo derivative **10h**.

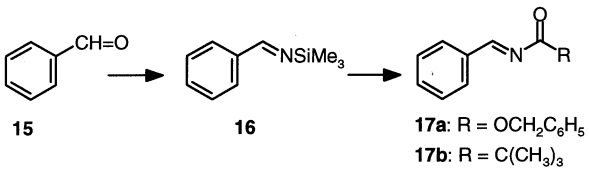
Transacetalization of the dimethyl acetal **8** with the non-C_2-symmetric diol **9j** (the reduction product of (*R*)-(−)-mandelic acid) led to a 65:35 mixture of the diastereomers *cis*-**10j** and *trans*-**10j**. However, all attempts to separate the diastereomers *cis*-**10j** and *trans*-**10j** by fractional crystallization or flash chromatography failed. Since the 1,3-dioxolane moiety of **10j** should control the diastereoselectivity the dia-

stereomeric mixture of *cis*-**10j** and *trans*-**10j** is not suitable as starting material for asymmetric syntheses.

Addition of the Lithiated Dioxolanes 18 to the Acylimines 17

The required acylimines **17** were obtained by an aza-analogous Peterson olefination of benzaldehyde (**15**) with lithium bis(trimethylsilyl)amide[13] and subsequent acylation of the silylimine **16** with acyl chlorides.[14] Thus, **17a** with the easily cleavable benzyloxycarbonyl residue and **17b** with the sterically demanding pivaloyl residue were prepared.

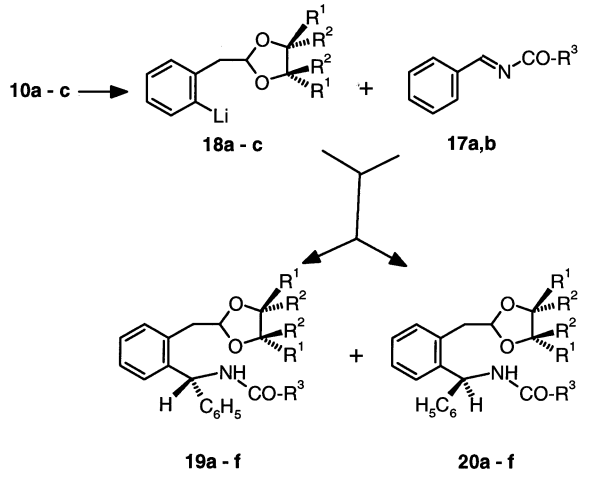
Scheme 4



The aryllithium intermediates **18a**−**g** were generated by treatment of the 2-(2-bromobenzyl)-1,3-dioxolanes **10a**−**g** with *n*-butyllithium at −100°C. However, only the methyl and the methoxyalkyl substituted 1,3-dioxolanes **18a**−**c** reacted with the acylimines **17a, b** to give the addition products **19/20** in good yields. In contrast, the reaction (5 h, −100°C) of the lithiobenzyl-1,3-dioxolanes **18d**−**g**, bearing ester or amide substituents, with the acylimine **17b** led to complex mixtures of products. The same result was obtained after a reaction time of 2 h (−100°C) and after raising the reaction temperature to −20°C or +20°C.

As the addition of **18a**−**c** to the acylimines **17a,b** resulted in good yields of **19/20** we investigated the analogous addition of the aryllithium intermediates **18a**−**c** to the silylimine **16**, which should give an unprotected primary amine. But, all attempts to perform the addition to the silylimine **16** failed. Only debrominated derivatives of **10a**−**c** and benzaldehyde were detected in the product mixture.

Scheme 5



The results of the addition of the aryllithium intermediates **18a**−**c** to the acylimines **17a, b** are summarized in Table 1. Because of the opposite configuration of the dimethyldioxolane **10a** the corresponding diastereoselectivities (entries 1 and 2) are reversed in comparison with entries 3−6. Table 1 shows comparable diastereoselectivities in the entries 1/2, in the entries 3/4, and in the entries 5/6. This leads to the conclusion that the diastereomeric ratio is not influenced appreciably by the acylimine component. The substitution pattern of the dioxolane ring, however, can influence the diastereoselectivity to a greater extent. Thus, enlargement of the methyl substituent in **18a** to a methoxymethyl substituent (**18b**) improved the diastereomeric ratio from 62:38 (**20a/19a**, entry 1) to 72:28 (**19c/20c**, entry 3). Surprisingly, a further expansion of the dioxolane substituents [**18c**, $R^1 = C(CH_3)_2OCH_3$] led to complete loss of the diastereoselectivity (**19e/20e** = 51:49, entry 5).

Table 1. Results of the addition of **18a**−**c** to **17a**, **b**

Entry	R^1	R^2	R^3	diastereomeric ratio	yield
1	H	CH_3	OBn	**19a** : **20a** = 38 : 62	71 %
2	H	CH_3	$C(CH_3)_3$	**19b** : **20b** = 36 : 64	76 %
3	CH_2OCH_3	H	OBn	**19c** : **20c** = 72 : 28	72 %
4	CH_2OCH_3	H	$C(CH_3)_3$	**19d** : **29d** = 68 : 32	78 %
5	$C(CH_3)_2OCH_3$	H	OBn	**19e** : **20e** = 51 : 49	63 %
6	$C(CH_3)_2OCH_3$	H	$C(CH_3)_3$	**19f** : **20f** = 55 : 45	66%

The diastereomeric ratios **19/20** were determined by integration of characteristic signals in the 400 MHz ^{1}H-NMR spectra of the unpurified addition products **19/20**. For example, the ^{1}H-NMR spectrum of the crude addition product of **18b** to **17a** (entry 3) shows two doublets at δ = 6.29 (**19c**) and δ = 6.26 (**20c**) in the ratio 72:28 for the proton $Ph_2CH-NHCO_2Bn$. Since the combination of **18b** and **17a** led to the best diastereoselectivity in this series (entry 3), the diastereomeric ratio **19c/20c** was confirmed by a HPLC analysis to be 72.1:27.9.

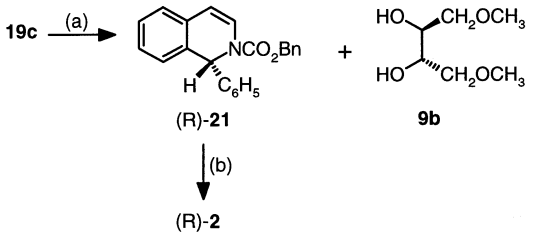
The separation of the diastereomers **19** and **20** turned out to be very problematic. After many attempts, the diastereomers **19c** and **20c** were successfully separated by flash chromatography (**19c**: R_f = 0.18; **20c**: R_f = 0.16).

Synthesis of the 1-Phenyltetrahydroisoquinoline (*R*)-2 and Determination of the Absolute Configuration

Heating a methanolic solution of the main diastereomer **19c** with an excess of *p*-toluenesulfonic acid afforded the dihydroisoquinoline (*R*)-**21** and the chiral auxiliary **9b**, which were isolated in 82% and 89% yield, respectively. Finally, the tetrahydroisoquinoline (*R*)-**2** was obtained by catalytic hydrogenation of the dihydroisoquinoline (*R*)-**21**.

The specific optical rotation $[\alpha]_{589}^{20}$ of the isolated 1-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**2** was determined to be −10.12 (*c* = 0.60 in $CHCl_3$). Yamato and coworkers assigned the (*S*)-configuration to the laevorotatory enantiomer (−)-**2** ($[\alpha]_{589}^{24}$ = −10.2, *c* = 0.17 in $CHCl_3$) by comparison of the 1-phenyltetrahydroisoquinoline (−)-**2** with 1-

Scheme 6



(a) *p*-Toluenesulfonic acid, methanol, 16 h, 65°C, (*R*)-**21**: 82%, **9b**: 89%. − (b) H_2, 1.7 bar, Pd/C, methanol, 4 h, room temp., 45%.

alkylated tetrahydroisoquinolines.[8a] However, very recently Wanner and coworkers reinvestigated the absolute configuration of the 1-phenyl-1,2,3,4-tetrahydroisoquinolines (+)-**2** and (−)-**2**. The X-ray analysis of (+)-**2**, which is acylated with an enantiomerically pure carboxylic acid, unequivocally revealed the dextrorotatory enantiomer (+)-**2** to have the (*S*) configuration.[15] Thus, the (*R*) configuration has to be assigned to the dihydroisoquinoline (*R*)-(+)-**21** and the new stereogenic center of the addition product **19c**.[16]

The stereochemical assignment of the compounds in Table 1 is deduced from the ^{1}H-NMR spectra. The signal for the proton $Ph_2CH-NHCOR^3$ of the main diastereomer is always shifted downfield in relation to the analogous signal of the minor diastereomer. Thus, the addition of **18b, c** led to main diastereomers with (*R*) configuration (entries 3−6), whereas (*S*) configuration is assigned to the main diastereomers obtained in the addition of **18a** with the opposite configuration in the acetal moiety (entries 1 and 2).

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Experimental Section

General: Unless otherwise stated, moisture sensitive reactions were conducted under dry nitrogen. − THF was distilled from sodium benzophenone ketyl prior to use. − Flash chromatography (FC)[17]: Silica gel 60, 0.040−0.063 mm (Merck). − HPLC: Column filled with silica gel (5 µm particles, LiChrosorb Si 60, Merck); pump L-6200 (Merck), pressure 40 bar, rate 1 ml/min; L-4250-UV/VIS-detector (Hitachi), λ = 254 nm; eluent petroleum ether/diethyl ether (60:40). − Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected. − Optical rotation: Polarimeter 241 (Perkin-Elmer); 1.0 dm tube; concentration *c* [g/100 ml]; temperature 20°C. − Elemental analyses: CHN elemental analyzer Rapid (Heraeus). − MS: Mass spectrometer 5989A (Hewlett Packard); CI = chemical ionization. − IR: IR spectrophotometer 1600 FT-IR and 2000 FT-IR (Perkin-Elmer). − ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): GSX FT NMR spectrometer (Jeol), tetramethylsilane as internal standard, δ in ppm.

General Procedure 1 (GP1). − Preparation of 1,3-Dioxolanes **10a−j** *by Transacetalization of* **7** *or* **8** *with Diols* **9**: A mixture of **7** or **8**, *p*-toluenesulfonic acid (200 mg per 10 mmol **7** or **8**), the corresponding diol **9** (ca. 1.1 equiv.) and the appropriate solvent (THF or toluene) was heated to reflux in a Soxhlet apparatus filled with molecular sieves (4 Å) to remove methanol. After three days the solution was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$ and then with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by FC or distillation.

General Procedure 2 (GP2). − Bromine/Lithium Exchange at the Aryl Bromides **10a−c** *and Subsequent Reaction with the Acylimines* **17a, b**: An enantiomerically pure aryl bromide **10** was dissolved in THF (20 ml) and cooled to −100°C. A solution of *n*-butyllithium (1.6 mol/l in *n*-hexane, 1.05 equiv.) was added and the reaction mixture was stirred for 15 min at −100°C. A solution of an acylimine **17** (1.05 equiv.) in THF (10 ml) was added. The reaction mixture was stirred for 6 h at −85 to −100°C and then a saturated solution of NH_4Cl (20 ml) was added. The organic layer was separated, dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by FC. Before carrying out the purification procedure, ^{1}H-NMR spectra were recorded to determine the diastereomeric ratio of the crude products.

(4R,5R)-(−)-2-(2-Bromobenzyl)-4,5-dimethyl-1,3-dioxolane (**10a**): (a) According to *GP1* a solution of **8** (5.00 g, 20.4 mmol) and **9a** (2.02 g, 22.4 mmol) in THF (100 ml) was heated to reflux. The residue was purified by distillation. Colourless oil, b.p.$_{0.018}$ = 70−75°C, yield 4.43 g (80.0%), $[\alpha]_{589}$ = −60.0 (*c* = 1.00 in $CHCl_3$). − $C_{12}H_{15}BrO_2$ (271.2): calcd. C 53.2 H 5.58 Br 29.5 found C 53.4 H 5.93 Br 29.4. − MS; *m/z*: 272/270 [$M^{\cdot+}$], 200/198 [M − $CH_3COC_2H_5$]. − IR (film): $\tilde{\nu}$ = 1473 cm^{-1} (C=C), 1145 (C−O), 1114 (C−O), 1076 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, *J* = 3.7 Hz, 3 H, CHC*H*$_3$), 1.27 (d, *J* = 4.4 Hz, 3 H, CHC*H*$_3$), 3.09 (dd, *J* = 13.2/5.1 Hz, 1 H, aryl-C*H*$_2$), 3.14 (dd, *J* = 13.2/4.4 Hz, 1 H, aryl-C*H*$_2$), 3.60 (m, 2 H, 4-H and 5-H), 5.32 (dd, *J* = 5.1/4.4 Hz, 1 H, 2-H), 7.08 (td, *J* = 8.1/1.5 Hz, 1 H, 5-H arom.), 7.22 (td, *J* = 8.1/1.5 Hz, 1 H, 4-H arom.), 7.34 (dd, *J* = 8.1/1.5 Hz, 1 H, 6-H arom.), 7.52 (dd, *J* = 8.1/1.5 Hz, 1 H, 3-H arom.). − ^{13}C NMR ($CDCl_3$): δ = 16.9 (q, CH*C*H$_3$), 17.0 (q, CH*C*H$_3$), 41.6 (t, aryl-*C*H$_2$), 78.1 (d, C-4), 79.7 (d, C-5), 102.1 (d, C-2), 125.0 (s, C-1 arom.), 127.2 (d, C-6 arom.), 128.2 (d, C-5 arom.), 132.0 (d, C-4 arom.), 132.6 (d, C-3 arom.), 136.0 (s, C-2 arom.). (b) As described for (a), **7** (5.00 g, 23.5 mmol) was reacted with **9a** (2.31 g, 25.7 mmol). Yield 5.70 g (89.5%).

(4S,5S)-(+)-2-(2-Bromobenzyl)-4,5-bis(methoxymethyl)-1,3-dioxolane (**10b**): (a) According to *GP1* a solution of **8** (6.20 g, 25.3 mmol) and **9b**[11] (4.00 g, 26.7 mmol) in THF (95 ml) was heated to reflux. The residue was purified by distillation. Colourless oil, b.p.$_{0.014}$ = 113−117°C, yield 7.40 g (88.3%), $[\alpha]_{589}$ = +3.20 (*c* = 1.00 in $CHCl_3$). − $C_{14}H_{19}BrO_4$ (331.2): calcd. C 50.8 H 5.78 found C 50.9 H 5.69. − MS (CI); *m/z*: 333/331 [M + H^+]. − IR (film): $\tilde{\nu}$ = 2926 cm^{-1} (C−H), 1473 (C=C), 1136 (C−O), 1106 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 3.14 (dd, *J* = 13.9/5.1.4 Hz, 1 H, aryl-C*H*$_2$), 3.18 (dd, *J* = 13.9/4.4 Hz, 1 H, aryl-C*H*$_2$), 3.38 (s, 3 H, OC*H*$_3$), 3.40 (s, 3 H, OC*H*$_3$), 3.49 (m, 4 H, 2 × C*H*$_2$OCH$_3$), 3.98 (m, 2 H, 4-H and 5-H), 5.35 (dd, *J* = 5.1/4.4 Hz, 1 H, 2-H), 7.09 (td, *J* = 8.1/2.2 Hz, 1 H, 5-H arom.), 7.25 (td, *J* = 8.1/2.2 Hz, 1 H, 4-H arom.), 7.36 (dd, *J* = 8.1/1.5 Hz, 1 H, 6-H arom.), 7.53 (dd, *J* = 8.1/1.5 Hz, 1 H, 3-H arom.). − ^{13}C NMR ($CDCl_3$): δ = 40.9 (t, aryl-*C*H$_2$), 59.3 (q, O*C*H$_3$), 59.4 (q, O*C*H$_3$), 72.8 (t, *C*H$_2$OCH$_3$), 73.0 (t, *C*H$_2$OCH$_3$), 77.2 (d, C-4), 77.8 (d, C-5), 103.5 (d, C-2), 125.1 (s, C-1 arom.), 127.3 (d, C-6 arom.), 128.3 (d, C-5 arom.), 132.1 (d, C-4 arom.), 132.6 (d, C-3 arom.), 135.7 (s, C-2 arom.). (b) As described for (a), **7** (5.00 g, 23.5 mmol) was reacted with **9b** (3.66 g, 24.4 mmol). Yield 6.66 g (85.7%).

(4R,5R)-(+)-2-(2-Bromobenzyl)-4,5-bis(2-methoxypropan-2-yl)-1,3-dioxolane (**10c**): (a) According to *GP1* a solution of **8** (6.10 g, 24.9 mmol) and **9c**[12] (5.42 g, 26.3 mmol) in THF (100 ml) was

heated to reflux. The residue was purified by FC (diameter of the column 5 cm, petroleum ether/ethyl acetate, 90:10, 50 ml fractions, R_f = 0.72). Pale yellow oil, yield 7.77 g (80.6%), $[\alpha]_{589}$ = +4.24 (*c* = 1.00 in $CHCl_3$). − $C_{18}H_{27}BrO_4$ (387.3): calcd. C 55.8 H 7.03 found C 56.0 H 6.88. − MS; *m/z*: 373/371 [$M^{\cdot+}$ − CH_3], 217 [$M^{\cdot+}$ − $BrC_6H_4CH_2$]. − IR (film): $\tilde{\nu}$ = 2855 cm^{-1} (O*C*H_3), 1471 (C=C), 1135 (C−O), 1032 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.11 [s, 3 H, C(CH_3)$_2$OCH$_3$], 1.12 [s, 3 H, C(CH_3)$_2$OCH$_3$], 1.21 [s, 3 H, C(CH_3)$_2$OCH$_3$], 1.22 [s, 3 H, C(CH_3)$_2$OCH$_3$], 3.05 (dd, *J* = 13.9/5.9 Hz, 1 H, aryl-CH_2), 3.20 (m, 7 H, aryl-CH_2 and 2 × OCH_3), 3.90 (d, *J* = 3.7 Hz, 1 H, 4-H), 4.04 (d, *J* = 2.9 Hz, 1 H, 5-H), 5.48 (t, *J* = 5.9 Hz, 1 H, 2-H), 7.07 (td, *J* = 8.1/1.5 Hz, 1 H, 5-H arom.), 7.25 (td, *J* = 8.1/1.5 Hz, 1 H, 4-H arom.), 7.36 (dd, *J* = 8.1/1.5 Hz, 1 H, 6-H arom.), 7.53 (dd, *J* = 8.1/1.5 Hz, 1 H, 3-H arom.). − ^{13}C NMR ($CDCl_3$): δ = 21.0 [q, C(*C*H_3)$_2$OCH$_3$], 21.3 [q, C(*C*H_3)$_2$OCH$_3$], 22.1 [q, C(*C*H_3)$_2$OCH$_3$], 22.2 [q, C(*C*H_3)$_2$OCH$_3$], 41.2 (t, aryl-*C*H_2), 49.2 (q, O*C*H_3), 49.5 (q, O*C*H_3), 75.8 [s, *C*(CH$_3$)$_2$OCH$_3$], 77.2 [s, *C*(CH$_3$)$_2$OCH$_3$], 82.0 (d, C-4), 84.0 (d, C-5), 104.6 (d, C-2), 125.1 (s, C-1 arom.), 127.2 (d, C-6 arom.), 128.1 (d, C-5 arom.), 131.9 (d, C-4 arom.), 132.6 (d, C-3 arom.), 136.4 (s, C-2 arom.). (b) As described for (a), **7** (5.00 g, 23.5 mmol) was reacted with **9c** (5.70 g, 24.7 mmol). Yield 7.15 g (78.7%). (c) A solution of methyl iodide (4.76 g, 33.5 mmol) and unpurified **10i** (4.00 g, 11.1 mmol) in THF (60 ml) was added at room temperature to a suspension of NaH (95%, 0.85 g, 33.3 mmol) in THF (100 ml). The reaction mixture was heated under reflux for 18 h. Water (200 ml) was added, the organic layer was separated, dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by FC [see method (a) above]. Pale yellow oil, yield 3.66 g (84.9%), $[\alpha]_{589}$ = +4.22 (*c* = 1.00 in $CHCl_3$).

(−)-Dimethyl (4R,5R)-2-(2-Bromobenzyl)-1,3-dioxolane-4,5-dicarboxylate (**10d**): (a) According to *GP1* a solution of **8** (5.00 g, 20.4 mmol) and **9d** (4.00 g, 22.5 mmol) in toluene (100 ml) was heated to reflux. The residue was purified by FC (diameter of the column 4 cm, petroleum ether/ethyl acetate, 85:15, 25 ml fractions). **11** and **12** (R_f = 0.45): Colourless oil, yield 1.40 g, ratio **11/12** ca. 1:1. **10d** (R_f = 0.20): Pale yellow oil, yield 4.64 g (63.3%), $[\alpha]_{589}$ = −44.8 (*c* = 1.00 in $CHCl_3$). − $C_{14}H_{15}BrO_6$ (359.2): calcd. C 46.8 H 4.21 Br 22.2 found C 46.9 H 4.01 Br 22.3. − MS (CI); *m/z*: 361/359 [M + H^+]. − IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1223 (C−O), 1140 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 3.20−3.24 (m, 2 H, aryl−CH_2), 3.73 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, CO_2CH_3), 4.67 (d, *J* = 3.7 Hz, 1 H, 5-H), 4.80 (d, *J* = 3.7 Hz, 1 H, 4-H), 5.51 (t, *J* = 5.1 Hz, 1 H, 2-H), 7.11 (t, *J* = 8.1 Hz, 1 H, 5-H arom.), 7.26 (t, *J* = 8.1 Hz, 1 H, 4-H arom.), 7.42 (d, *J* = 8.1 Hz, 1 H, 6-H arom.), 7.55 (d, *J* = 8.1 Hz, 1 H, 3-H arom.). − ^{1}H NOE ($CDCl_3$, pulse delay = 8 s, 37.5 dB): Irrad. at δ = 4.67 (5-H), NOE at δ = 3.73, 3.76, 4.80, and 5.51; irrad. at δ = 4.80 (4-H), NOE at δ = 3.73, 3.76, and 4.67; irrad.at δ = 5.51 (2-H), NOE at δ = 3.20, 3.24, and 4.67. − ^{13}C NMR ($CDCl_3$): δ = 40.6 (t, aryl−*C*H_2), 52.8 (q, CO_2CH_3), 52.9 (q, CO_2CH_3), 76.7 (d, C-4), 76.9 (d, C-5), 106.4 (d, C-2), 124.9 (s, C-1 arom.), 127.5 (d, C-6 arom.), 128.6 (d, C-5 arom.), 132.2 (d, C-4 arom.), 132.7 (d, C-3 arom.), 134.9 (s, C-2 arom.), 169.7 (s, CO_2CH_3), 169.9 (s, CO_2CH_3). (b) As described for (a), **7** (4.36 g, 20.5 mmol) was reacted with **9d** (4.00 g, 22.5 mmol). Yield 6.08 g (82.7%).

(+)-Diethyl (4R,5R)-2-(2-Bromobenzyl)-1,3-dioxolane-4,5-dicarboxylate (**10e**): According to *GP1* a solution of **8** (3.00 g, 12.2 mmol) and **9e** (2.61 g, 12.7 mmol) in toluene (60 ml) was heated to reflux. The residue was purified by FC (diameter of the column 3 cm, petroleum ether/ethyl acetate, 85:15, 15 ml fractions). **11** and **12** (R_f = 0.45): Colourless oil, ratio **11/12** ca. 1:1. **10e** (R_f = 0.32): Pale yellow oil, yield 1.08 g (22.8%); $[\alpha]_{589}$ = +2.40 (*c* = 1.00 in $CHCl_3$). − $C_{16}H_{19}BrO_6$ (387.2): calcd. C 49.6 H 4.95 found C 49.4 H 4.91. − MS; *m/z*: 388/386 [M^+], 315/313 [$M^{\cdot+}$ − $CO_2CH_2CH_3$]. − IR (film): $\tilde{\nu}$ = 1755 cm^{-1} (C=O), 1221 (C−O), 1140 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.3 Hz, 3 H, OCH$_2$CH_3), 1.31 (t, *J* = 7.3 Hz, 3 H, OCH$_2$CH_3), 3.16−3.28 (m, 2 H, aryl-CH_2), 4.25 ("q", *J* = 7.3 Hz, 4 H, 2 × OCH_2CH$_3$), 4.68 (d, *J* = 3.7 Hz, 1 H, 4-H), 4.81 (d, *J* = 3.7 Hz, 1 H, 5-H), 5.53 (dd, *J* = 5.9/4.4 Hz, 1 H, 2-H), 7.09 (td, *J* = 8.1/1.5 Hz, 1 H, 5-H arom.), 7.25 (td, *J* = 8.1/1.5 Hz, 1 H, 4-H arom.), 7.42 (dd, *J* = 7.3/2.2 Hz, 1 H, 6-H arom.), 7.53 (d, *J* = 8.1 Hz, 1 H, 2-H arom.). **13a** (R_f = 0.29): Pale yellow oil (not pure), yield 0.42 g.

(+)-Diisopropyl (2R,3R)-2-(2-Bromobenzyl)-1,3-dioxolane-4,5-dicarboxylate (**10f**) *and 4-Isopropyl 5-Methyl 2-(2-bromobenzyl)-1,3-dioxolane-4,5-dicarboxylate* (**13b**): According to *GP1* a solution of **8** (3.00 g, 12.2 mmol) and **9f** (3.44 g, 14.7 mmol) in toluene (60 ml) was heated to reflux. The residue was purified by FC (diameter of the column 3 cm, petroleum ether/ethyl acetate 85:15, 25 ml fractions). **10f** (R_f = 0.35): Colourless oil, yield 1.12 g (22.0%); $[\alpha]_{589}$ = +1.20 (*c* = 1.00 in $CHCl_3$). − $C_{18}H_{23}BrO_6$ (415.2): calcd. C 52.1 H 5.58 found C 51.9 H 5.40. − MS; *m/z*: 416/414 [$M^{\cdot+}$]. − IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (C=O), 1264 (C−O), 1140 (C−O), 1104 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.25 [d, *J* = 5.9 Hz, 6 H, 2 × OCH(CH_3)$_2$], 1.29 [d, *J* = 5.9 Hz, 6 H, 2 × OCH(CH_3)$_2$], 3.24 (dd, *J* = 13.9/5.9 Hz, 1 H, aryl−CH_2), 3.33 (dd, *J* = 13.9/4.4 Hz, 1 H, aryl−CH_2), 4.68 (d, *J* = 3.7 Hz, 1 H, 4-H), 4.80 (d, *J* = 3.7 Hz, 1 H, 5-H), 5.12 ["sept", *J* = 5.9 Hz, 2 H, 2 × OC*H*(CH$_3$)$_2$], 5.59 (dd, *J* = 5.9/4.4 Hz, 1 H, 2-H), 7.09 (td, *J* = 8.1/1.5 Hz, 1 H, 5-H arom.), 7.26 (td, *J* = 7.3/1.5 Hz, 1 H, 4-H arom.), 7.42 (dd, *J* = 8.1/1.5 Hz, 1 H, 6-H arom.), 7.53 (d, *J* = 8.1 Hz, 1 H, 3-H arom.). **13b** (R_f = 0.30): Colourless oil, yield 1.05 g (22.1%). − $C_{16}H_{19}BrO_6$ (387.2): calcd. C 49.6 H 4.95 found C 49.4 H 4.77. − MS (CI); *m/z*: 389/387 [M + H^+]. − IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (C=O), 1264 (C−O), 1140 (C−O), 1104 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.28 [d, *J* = 5.9 Hz, 6 × 0.5 H, OCH(CH_3)$_2$], 1.33 [d, *J* = 5.9 Hz, 6 × 0.5 H, OCH(CH_3)$_2$], 3.23−3.35 (m, 2 H, aryl−CH_2), 3.80 (s, 3 × 0.5 H, CO_2CH_3), 3.83 (s, 3 × 0.5 H, CO_2CH_3), 4.67−4.70 (m, 1 H, 4-H or 5-H), 4.79−4.83 (m, 1 H, 5-H or 4-H), 5.07−5.17 [m, 1 H, OC*H*(CH$_3$)$_2$], 5.59 (dd, *J* = 5.9/4.4 Hz, 1 H, 2-H), 7.09 (td, *J* = 8.1/1.5 Hz, 1 H, 5-H arom.), 7.26 (td, *J* = 7.3/1.5 Hz, 1 H, 4-H arom.), 7.42 (dd, *J* = 8.1/1.5 Hz, 1 H, 6-H arom.), 7.53 (d, *J* = 8.1 Hz, 1 H, 3-H arom.). Ratio of diastereomers 1:1.

(4R,5R)-(+)-2-(2-Bromobenzyl)-N,N,N′,N′-tetramethyl-1,3-dioxolane-4,5-dicarboxamide (**10g**): A mixture of **10d** (5.00 g, 13.9 mmol), dimethylamine (100.0 ml, 33% in ethanol) and ethanol (30 ml) was stirred for 48 h at room temperature. The solvent was evaporated in vacuo and the residue was purified by FC (diameter of the column 4 cm, petroleum ether/ethyl acetate 50:50, 20 ml fractions, R_f = 0.36). Pale yellow oil, yield 4.93 g (92.0%), $[\alpha]_{589}$ = +3.60 (*c* = 1.11 in $CHCl_3$). − $C_{16}H_{21}BrN_2O_4$ (385.3): calcd. C 49.9 H 5.49 N 7.23 Br 20.7 found C 49.6 H 5.67 N 7.05 Br 20.8. − MS (CI); *m/z*: 387/385 [M + H^+]. − IR (film): $\tilde{\nu}$ = 1720 cm^{-1} (C=O), 1223 (C−O), 1140 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 2.95 [s, 3 H, CON(CH_3)$_2$], 2.97 [s, 3 H, CON(CH_3)$_2$], 3.13 [s, 3 H, CON(CH_3)$_2$], 3.15 [s, 3 H, CON(CH_3)$_2$], 3.20 (d, *J* = 5.1 Hz, 2 H, aryl-CH_2), 5.19 (d, *J* = 5.9 Hz, 1 H, 5-H), 5.30 (d, *J* = 5.9 Hz, 1 H, 4-H), 5.46 (t, *J* = 5.1 Hz, 1 H, 2-H), 7.09 (t, *J* = 8.1 Hz, 1 H, 5-H arom.), 7.24 (t, *J* = 8.1 Hz, 1 H, 4-H arom.), 7.32 (d, *J* = 8.1 Hz, 1 H, 6-H arom.), 7.53 (d, *J* = 8.1 Hz, 1 H, 3-H arom.).

(4R,5R)-2-(2-Bromobenzyl)-α,α,α′,α′-tetramethyl-1,3-dioxolane-4,5-dimethanol (**10i**): A solution of methyl iodide (15.6 g, 0.11 mol) in diethyl ether (50 ml) was slowly added to a suspension of Mg (2.66 g, 0.11 mol) in diethyl ether (150 ml) (generation of

methylmagnesium iodide). After complete addition of the methyl iodide solution the reaction mixture was refluxed for 30 min. The mixture was cooled to 0°C and a solution of **10d** (5.00 g, 13.9 mmol) in THF (60 ml) was added and the reaction mixture was stirred for 2 h at room temperature. A saturated solution of NH_4Cl (300 ml) was added, the organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 150 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated in vacuo. Without further purification the residual diol **10i** was employed for methylation to give **10c**. **10i**: Colourless oil, yield 4.90 g (98.0%). − $C_{16}H_{23}BrO_4$ (359.3). − MS (CI); *m/z*: 361/359 [M + H^+]. − IR (film): $\tilde{\nu}$ = 3384 cm^{-1} (OH), 2975 (CH), 1138 (C−O), 1031 (C−O). − ^1H NMR ($CDCl_3$): δ = 1.11 [s, 3 H, C(CH_3)$_2$OH], 1.12 [s, 3 H, C(CH_3)$_2$OH], 1.17 [s, 3 H, C(CH_3)$_2$OH], 1.18 [s, 3 H, C(CH_3)$_2$OH], 2.29 (m, 2 H, 2 × OH, H/D exchange), 3.02 (dd, *J* = 14.1/4.3 Hz, 1 H, aryl-CH_2), 3.16 (dd, *J* = 14.1/4.3 Hz, 1 H, aryl-CH_2), 3.70 (d, *J* = 5.1 Hz, 1 H, 4-H), 3.82 (d, *J* = 5.1 Hz, 1 H, 5-H), 5.36 (t, *J* = 4.3 Hz, 1 H, 2-H), 7.03 (td, *J* = 7.7/1.3 Hz, 1 H, 5-H arom.), 7.18 (td, *J* = 7.71/1.3 Hz, 1 H, 4-H arom.), 7.27 (dd, *J* = 7.7/1.3 Hz, 1 H, 6-H arom.), 7.48 (d, *J* = 7.7 Hz, 1 H, 3-H arom.).

cis-(2S,4R)- and trans-(2R,4R)-2-(2-Bromobenzyl)-4-phenyl-1,3-dioxolane (*cis*-**10j** and *trans*-**10j**): (a) According to *GP1* a solution of **8** (2.00 g, 8.16 mmol) and **9j** (1.24 g, 8.98 mmol) in THF (50 ml) was heated to reflux. The residue was purified by FC (diameter of the column 4 cm, petroleum ether/ethyl acetate 90:10, 20 ml fractions, R_f = 0.70). Pale yellow oil, yield 2.46 g (94.6%). − $C_{16}H_{15}BrO_2$ (319.2): calcd. C 60.2 H 4.74 found C 60.1 H 4.65. − MS; *m/z*: 320/318 [$M^{\cdot+}$], 200/198 [$M^{\cdot+}$ − C_6H_5−CO−CH_3]. − IR (film): $\tilde{\nu}$ = 1132 cm^{-1} (C−O), 1028 (C−O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.15−3.35 (m, 2 H, aryl-CH_2), 3.67−3.74 (m, 1 H, 5-H), 4.20 (dd, *J* = 14.7/7.3 Hz, 0.65 H, 5-H), 4.40 (dd, *J* = 14.1/8.1 Hz, 0.35 H, 5-H), 5.02 (dd, *J* = 7.3/6.6 Hz, 0.65 H, 4-H), 5.07 (dd, *J* = 8.1/6.6 Hz, 0.35 H, 4-H), 5.35 (t, *J* = 5.1 Hz, 0.65 H, 2-H), 5.56 (t, *J* = 5.1 Hz, 0.35 H, 2-H), 7.06−7.58 (m, 9 H, arom.). − ^1H NOE ($CDCl_3$, pulse delay = 8 s, 37.5 dB): Irrad. at δ = 5.35 ppm (2-H, *cis*-**10j**), NOE at δ = 3.15−3.35, 4.20, and 5.02 ppm; irrad. at δ = 5.56 ppm (2-H, *trans*-**10j**), NOE at δ = 3.15−3.35 and 3.67−3.74 ppm. The ^1H-NMR spectrum of the unpurified product reveals the signals for *cis*-**10j** and *trans*-**10j** in the ratio 65:35. (b) As described for (a), **7** (1.50 g, 7.04 mmol) was reacted with **9j** (1.07 g, 7.74 mmol). Yield 2.11 g (93.7%).

(4S,5S)-2-Benzyl-4,5-bis(dimethylaminomethyl)-1,3-dioxolane (**14**): A solution of **10g** (5.00 g, 13.0 mmol) in THF (50 ml) was slowly added to a suspension of $LiAlH_4$ (1.23 g, 32.3 mmol) in THF (100 ml) and the reaction mixture was heated under reflux for 18 h. The excess $LiAlH_4$ was cautiously (cooling to 0°C) hydrolyzed with water (2.5 ml), 2 N NaOH (5 ml) and water (5 ml). The reaction mixture was filtered, the organic solvent was evaporated in vacuo, and the residue was purified by FC (diameter of the column 3.5 cm, petroleum ether/ethyl acetate 50:50, 20 ml fractions, R_f = 0.25). Pale yellow oil, yield 3.43 g (95.0%). − MS (CI); *m/z*: 279 [M + H^+]. − IR (film): $\tilde{\nu}$ = 1135 cm^{-1} (C−O), 1031 (C−O). − ^1H NMR ($CDCl_3$): δ = 2.78 [s, 6 H, N(CH_3)$_2$], 2.80 [s, 6 H, N(CH_3)$_2$], 2.86 (m_c, 2 H, aryl-CH_2), 3.49 (m, 2 H, 4-H and 5-H), 4.24 (m_c, 4 H, 2 × CH_2NMe$_2$), 5.76 (t, *J* = 4.4 Hz, 1 H, 2-H), 6.72−6.84 (m, 5 H, arom.).

Benzyl N-{(αR) and (αS)-2-[(4R,5R)-4,5-Dimethyl-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}carbamate (**19a** and **20a**): According to *GP2*, **10a** (120 mg, 0.44 mmol) was reacted with **17a** (117 mg, 0.49 mmol). FC: Diameter of the column 2 cm, petroleum ether/ethyl acetate (80:20), 10 ml fractions, R_f = 0.23. Colourless oil, yield 135 mg (71.0%). − $C_{27}H_{29}NO_4$ (431.5): calcd. C 75.2 H 6.77 N 3.25 found C 75.0 H 7.02 N 3.13. − MS (CI); *m/z*: 432 [M + H^+]. − IR (film): $\tilde{\nu}$ = 3321 cm^{-1} (NH), 1720 (C=O), 1261 (C−O), 1232 (C−O). − ^1H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 5.9 Hz, 3 × 0.38 H, CHCH_3), 1.06 (d, *J* = 5.9 Hz, 3 × 0.38 H; CHCH_3), 1.08 (d, *J* = 5.9 Hz, 3 × 0.62 H, CHCH_3), 1.10 (d, *J* = 5.9 Hz, 3 × 0.62 H, CHCH_3), 2.72−2.84 (m, 2 H, aryl-CH_2), 3.33−3.49 (m, 2 H, 4-H and 5-H), 5.04 (d, *J* = 11.7 Hz, 1 H, PhCH_2O), 5.08 (d, *J* = 11.7 Hz, 1 H, PhCH_2O), 5.15 (t, *J* = 3.7 Hz, 1 H, 2-H), 6.16 (d, *J* = 8.1 Hz, 0.62 H, aryl-C*H*-NH, s after H/D exchange), 6.21 (d, *J* = 8.1 Hz, 0.38 H, aryl-C*H*-NH, s after H/D exchange), 6.29 (d, *J* = 7.3 Hz, 0.38 H, aryl-CH-N*H*, H/D exchange), 6.38 (d, *J* = 7.3 Hz, 0.62 H, aryl-CH-N*H*, H/D exchange), 7.01−7.33 (m, 14 H, arom.). − The ^1H-NMR spectra before and after purification by FC reveal a diastereomeric ratio of **19a/20a** = 38:62.

N-{(αR) and (αS)-2-[(4R,5R)-4,5-Dimethyl-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}-2,2-dimethylpropionamide (**19b** and **20b**): According to *GP2*, **10a** (120 mg, 0.44 mmol) was reacted with **17b** (92.6 mg, 0.49 mmol). FC: Diameter of the column 2 cm, petroleum ether/ethyl acetate (80:20), 10 ml fractions, R_f = 0.28. Colourless oil, yield 128 mg (76.0%). − $C_{24}H_{31}NO_3$ (381.5): calcd. C 75.6 H 8.19 N 3.67 found C 75.6 H 8.01 N 3.80. − MS; *m/z*: 381 [M^+], 324 [M^+ − C(CH_3)$_3$]. − IR (film): $\tilde{\nu}$ = 3298 cm^{-1} (NH), 1633 (C=O), 115 (C−O). − ^1H NMR ($CDCl_3$): δ = 1.14 (d, *J* = 5.9 Hz, 3 × 0.64 H, CHCH_3), 1.17 (d, *J* = 6.6 Hz, 3 × 0.36 H, CHCH_3), 1.20 (d, *J* = 5.9 Hz, 3 × 0.36 H, CHCH_3), 1.22 (d, *J* = 5.9 Hz, 3 × 0.64 H, CHCH_3), 1.24 [s, 9 H, C(CH_3)$_3$], 2.87−3.06 (m, 2 H, aryl-CH_2), 3.48−3.59 (m, 2 H, 4-H and 5-H), 5.22 (dd, *J* = 5.9/3.7 Hz, 0.64 H, 2-H), 5.25 (dd, *J* = 5.9/3.7 Hz, 0.36 H, 2-H), 6.27 (d, *J* = 7.3 Hz, 0.36 H, aryl−C*H*−NH, s after H/D-exchange), 6.32 (d, *J* = 8.1 Hz, 0.64 H, aryl−C*H*−NH, s after H/D-exchange), 6.53 (d, *J* = 8.1 Hz, 0.64 H, aryl−CH−N*H*, H/D-exchange), 6.59 (d, *J* = 7.3 Hz, 0.36 H, aryl−CH−N*H*, H/D-exchange), 7.08−7.34 (m, 9 H, arom.). The ^1H-NMR spectra before and after purification by FC reveal a diastereomeric ratio of **19b/20b** = 36:64.

(+)-Benzyl N-{(αR)-2-[(4S,5S)-4,5-Bis(methoxymethyl)-1,3-dioxolan-2-ylmethyl]-α-phenyl-benzyl}carbamate (**19c**) *and (+)-Benzyl N-{(αS)-2-[(4S,5S)-4,5-Bis(methoxymethyl)-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}carbamate* (**20c**): According to *GP2*, **10b** (300 mg, 0.91 mmol) was reacted with **17a** (230 mg, 0.96 mmol). The HPLC analysis (eluent petroleum ether/diethyl ether, 60:40) of the crude product (320 mg, 71.9%); showed a diastereomeric ratio **19c** (retention time 11.4 min):**20c** (retention time 13.9 min) of 72.1:27.9; according to the ^1H NMR: **19c/20c** 72:28. The separation of the diastereomers **19c** and **20c** was achieved by FC: Diameter of the column 2 cm, petroleum ether/diethyl ether 60:40, 10 ml fractions). **19c** (R_f = 0.18): Colourless oil, yield 100 mg (22.5%), $[\alpha]_{589}$ = +1.80 (*c* = 0.83 in $CHCl_3$). − $C_{29}H_{33}NO_6$ (491.6): calcd. C 70.9 H 6.77 N 2.85 found C 70.5 H 6.99 N 3.01. − MS (CI); *m/z*: 492 [M + H^+]. − IR (film): $\tilde{\nu}$ = 3324 cm^{-1} (NH), 1716 (C=O), 1135 (C−O), 1105 (C−O). − ^1H NMR ($CDCl_3$): δ = 2.92−2.95 (m, 2 H, aryl-CH_2), 3.24−3.44 (m, 10 H, 2 × CH_2−OCH_3), 3.91−3.94 (m, 2 H, 4-H and 5-H), 5.07−5.23 (m, 3 H, 2-H and PhCH_2O), 6.20 (d, *J* = 7.3 Hz, 1 H, aryl-CH-N*H*, H/D-exchange), 6.29 (d, *J* = 7.3 Hz, 1 H, aryl−C*H*−NH, s after H/D-exchange), 7.05−7.35 (m, 14 H, arom.). **20c** (R_f = 0.16): Colourless oil, yield 60 mg (13.5%), $[\alpha]_{589}$ = +11.1 (*c* = 0.71 in $CHCl_3$). − $C_{29}H_{33}NO_6$ (491.6): calcd. C 70.9 H 6.77 N 2.85 found C 70.6 H 6.45 N 2.54. − MS (CI); *m/z*: 492 [M + H^+]. − IR (film): $\tilde{\nu}$ = 3324 cm^{-1} (NH), 1135 (C−O), 1105 (C−O). − ^1H NMR ($CDCl_3$): δ = 2.96−2.98 (m, 2 H, aryl-CH_2), 3.24−3.44 (m, 10 H, 2 × CH_2−OCH_3), 3.89−3.92 (m, 2 H, 4-H and 5-H), 5.08−5.21 (m, 3

H, 2-H and PhCH_2O), 6.26 (d, J = 7.3 Hz, 1 H, aryl−CH−NH, s after H/D exchange), 6.55 (d, J = 7.3 Hz, 1 H, aryl−CH−NH, H/D exchange), 7.04−7.40 (m, 14 H, arom.). In addition to the pure diastereomers, 160 mg (36%) of a diastereomeric mixture was isolated.

N-{(αR) and (αS)-2-[(4S,5S)-4,5-Bis(methoxymethyl)-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}-2,2-dimethylpropionamide (**19d** and **20d**): According to *GP2*, **10b** (200 mg, 0.60 mmol) was reacted with **17b** (123 mg, 0.65 mmol). FC: Diameter of the column 3 cm, petroleum ether/ethyl acetate (85:15), 13 ml fractions, R_f = 0.28. Colourless oil, yield 210 mg (78.8%). − $C_{26}H_{35}NO_5$ (441.6): calcd. C 70.7 H 7.99 N 3.17 found C 70.3 H 8.54 N 3.18. − MS; *m/z*: 426 [M^+ − CH_3]. − IR (film): $\tilde{\nu}$ = 3319 cm^{-1} (NH), 1650 (C=O), 1131 (C−O). − H NMR ($CDCl_3$): δ = 1.16 [s, 9 H, C(CH_3)$_3$], 2.91−2.93 (m, 2 H, aryl−CH_2), 3.23−3.40 (m, 10 H, 2 × CH_2−OCH_3), 3.84−3.87 (m, 2 H, 4-H and 5-H), 5.15 (dd, J = 5.1/3.7 Hz, 0.68 H, 2-H), 5.19 (dd, J = 5.9/3.7 Hz, 0.32 H, 2-H), 6.14 (d, J = 7.3 Hz, 0.32 H, aryl−CH−NH, s after H/D exchange), 6.27 (d, J = 7.3 Hz, 0.68 H, aryl−CH−NH, s after H/D exchange), 6.42 (d, J = 7.3 Hz, 0.68 H, aryl−CH−NH, H/D exchange), 6.48 (d, J = 7.3 Hz, 0.32 H, aryl−CH−NH, H/D exchange), 6.93−7.26 (m, 9 H, arom.). The ^{1}H-NMR spectra before and after purification by FC reveal a diastereomeric ratio of **19d/20d** = 68:32.

Benzyl N-{(αR) and (αS)-2-[(4R,5R)-4,5-Bis(2-methoxypropan-2-yl)-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}carbamate (**19e** and **20e**): According to *GP2*, **10c** (116 mg, 0.30 mmol) was reacted with **17a** (76.5 mg, 0.32 mmol). FC: Diameter of the column 2 cm, petroleum ether/ethyl acetate (90:10), 10 ml fractions, R_f = 0.25. Colourless oil, yield 90 mg (54.8). − $C_{33}H_{41}NO_6$ (547.7): calcd. C 72.4 H 7.55 N 2.56 found C 72.4 H 7.77 N 2.30. − MS; *m/z*: 397 [M^+ − $NHCO_2Bn$]. − IR (film): $\tilde{\nu}$ = 3299 cm^{-1} (NH), 1714 (C=O, 1136 (C−O), 1098 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 0.92 [s, 3 × 0.49 H, C(CH_3)$_2$OCH_3], 0.96 [s, 3 × 0.51 H, C(CH_3)$_2$OCH_3], 1.02 [s, 3 H, C(CH_3)$_2$OCH_3], 1.09 [s, 3 × 0.51 H, C(CH_3)$_2$OCH_3], 1.13 [s, 3 × 0.49 H, C(CH_3)$_2$OCH_3], 1.15 [s, 3 H, C(CH_3)$_2$OCH_3], 2.90−3.26 (m, 8 H, aryl−CH_2 and 2 × OCH_3), 3.75−3.81 (m, 1 H, 4-H), 4.00−4.04 (m, 1 H, 5-H), 5.10−5.14 (m, 2 H, PhCH_2O), 5.30 (t, J = 4.4 Hz, 0.49 H, 2-H), 5.39 (t, J = 4.4 Hz, 0.51 H, 2-H), 6.07 (d, J = 8.1 Hz, 0.51 H, aryl−CH−NH, H/D exchange), 6.09 (d, J = 8.1 Hz, 0.49 H, aryl−CH−NH, H/D exchange), 6.14 (d, J = 8.1 Hz, 0.49 H, aryl−CH−NH, s after H/D exchange), 6.29 (d, J = 8.1 Hz, 0.51 H, aryl−CH−NH, s after H/D exchange), 7.11−7.36 (m, 14 H, arom.). The ^{1}H-NMR spectra before and after purification by FC reveal a diastereomeric ratio of **19e/20e** = 51:49.

N-{(αR) and (αS)-2-[(4R,5R)-4,5-Bis(2-methoxypropan-2-yl)-1,3-dioxolan-2-ylmethyl]-α-phenylbenzyl}-2,2-dimethylpropionamide (**19f** and **20f**): According to *GP2*, **10c** (116 mg, 0.30 mmol) was reacted with **17b** (60 mg, 0.32 mmol). FC: Diameter of the column 2 cm, petroleum ether/ethyl acetate (90:10), 10 ml fractions, R_f = 0.25. Colourless oil, yield 100 mg (67.0%). − $C_{30}H_{43}NO_5$ (497.7): calcd. C 72.4 H 8.10 N 2.81 found C 72.0 H 8.36 N 2.92. − MS (CI); *m/z*: 498 [M + H^+]. − IR (film): $\tilde{\nu}$ = 3299 cm^{-1} (NH), 1714 (C=O), 1136 (C−O), 1098 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 1.06 [s, 3 × 0.45 H, C(CH_3)$_2$OCH_3], 1.13 [s, 3 × 0.55 H, C(CH_3)$_2$OCH_3], 1.16 [s, 3 H, C(CH_3)$_2$OCH_3], 1.22 [s, 3 × 0.45 H, C(CH_3)$_2$OCH_3], 1.25 [s, 3 × 0.55 H, C(CH_3)$_2$OCH_3], 1.27 [s, 3 × 0.45 H, C(CH_3)$_2$OCH_3], 1.28 [s, 3 × 0.55 H, C(CH_3)$_2$OCH_3], 1.30 [s, 9 × 0.45 H, C(CH_3)$_3$], 1.31 [s, 9 × 0.55 H, C(CH_3)$_3$], 2.91−3.11 (m, 2 H, aryl−CH_2), 3.19 (s, 3 × 0.55 H, OCH_3), 3.22 (s, 3 × 0.55 H, OCH_3), 3.24 (s, 3 × 0.45 H, OCH_3), 3.29 (s, 3 × 0.45 H, OCH_3), 3.88 (d, J = 2.9 Hz, 0.45 H, 4-H), 3.92 (d, J = 3.7 Hz, 0.45 H, 5-H), 4.10 (d, J = 2.2 Hz, 0.55 H, 4-H), 4.11 (d, J = 1.5 Hz, 0.55 H, 5-H), 5.34 (t, J = 5.1 Hz, 0.55 H, 2-H), 5.48 (dd, J = 5.1/3.7 Hz, 0.45 H, 2-H), 6.17 (d, J = 7.3 Hz, 0.45 H, aryl−CH−NH, H/D exchange), 6.30 (d, J = 7.3 Hz, 0.55 H, aryl−CH−NH, H/D exchange), 6.57 (d, J = 7.3 Hz, 0.55 H, aryl−CH−NH, s after H/D exchange), 6.64 (d, J = 7.3 Hz, 0.45 H, aryl−CH−NH, s after H/D exchange), 7.05−7.38 (m, 9 H, arom.). The ^{1}H-NMR spectra before and after purification by FC reveal a diastereomeric ratio of **19f/20f** = 55:45.

(R)-(+)-Benzyl 1-Phenyl-1,2-dihydroisoquinoline-2-carboxylate [(*R*)-**21**)]: A solution of **19c** (88 mg, 0.18 mmol) and *p*-toluenesulfonic acid monohydrate (78.8 mg, 0.41 mmol) in methanol (20 ml) was heated under reflux for 16 h. A saturated solution of $NaHCO_3$ (20 ml) and CH_2Cl_2 (20 ml) were added, the organic layer was separated, dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by FC (diameter of the column 2 cm, petroleum ether/ethyl acetate, 85:15, R_f = 0.78). After complete elution of (*R*)-**21** the chiral auxiliary **9b** was eluted with petroleum ether/ethyl acetate 50:50. (*R*)-**21**: Pale yellow oil, yield 51.4 mg (82.3%), $[\alpha]_{589}$ = +83.0 (c = 1.04 in $CHCl_3$). − $C_{23}H_{19}NO_2$ (341.4): calcd. C 80.9 H 5.61 N 4.10 found C 80.7 H 5.81 N 4.08. − MS (CI); *m/z*: 342 [M + H^+]. − IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1635 (*C*=*C*−N), 1232 (C−O), 1120 (C−O). − ^{1}H NMR ($CDCl_3$): δ = 5.20−5.24 (m, 2 H, PhCH_2O), 5.85 (d, J = 7.3 Hz, 0.68 H, 4-H), 5.92 (d, J = 7.3 Hz, 0.32 H, 4-H), 6.32 (s, 0.32 H, 1-H), 6.52 (s, 0.68 H, 1-H), 6.89 (d, J = 7.3 Hz, 0.32 H, 3-H), 7.07−7.34 (m, 14 H, arom. and 1 × 0.68 H, 3-H). Ratio of R_2N−*C*=O rotamers 68:32. − ^{13}C NMR ($CDCl_3$): δ = 58.1 (d, C-1, main rotamer), 59.1 (d, C-1, minor rotamer), 68.1 (t, Ph*C*H_2O), 108.7 (d, C-4, minor rotamer), 108.9 (d, C-4, main rotamer), 124.7 (d, C-3, main rotamer), 125.0 (d, C arom.), 125.2 (d, C-3, minor rotamer), 125.7 (d, C arom.), 126.5 (d, C arom.), 127.1 (d, C arom.), 127.2 (d, C arom.), 127.3 (d, C arom.), 127.4 (d, C arom.), 127.7 (d, C arom.), 127.9 (d, C arom.), 128.1 (d, C arom.), 128.3 (d, C arom.), 128.4 (d, C arom.), 128.6 (d, C arom.), 128.7 (d, C arom.), 130.0 (s, C arom., minor rotamer), 130.2 (s, C arom., main rotamer), 131.6 (s, C arom., main rotamer), 131.9 (s, C arom., minor rotamer), 135.7 (s, C arom., minor rotamer), 135.8 (s, C arom., main rotamer), 141.8 (s, C arom., main rotamer), 142.5 (s, C arom., minor rotamer), 153.1 (s, N*C*O_2Bn, main rotamer), 153.6 (s, N*C*O_2Bn, minor rotamer). **9b**: Colourless oil, yield 23.7 mg (89.2%).

(R)-(−)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-**2**]: Pd/C catalyst (10%, 10 mg) was added to a solution of (*R*)-**21** (40 mg, 0.12 mmol) in methanol (20 ml). The reaction mixture was stirred for 4 h under a hydrogen amosphere (1.7 bar H_2) at room temperature. The mixture was filtered (celite), the filtrate was concentrated in vacuo and the residue was purified by FC (diameter of the column 2 cm, CH_2Cl_2/methanol 90:10, 10 ml fractions, R_f = 0.25). Colourless oil, yield 10.9 mg (44.6%), $[\alpha]_{589}$ = −10.12 (c = 0.60 in $CHCl_3$) [ref.[8a][15]: $[\alpha]_{589}$ = −10.2 (c = 0.17 in $CHCl_3$)]. For spectroscopic data see ref.[8a].

☆ Dedicated to Prof. Dr. *H.-D. Stachel* on the occasion of his 70th birthday.

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