De Novo Synthesis of Racemic Spirocyclopropane-Annelated 2-Deoxyhexose Derivatives[‡]

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Keywords: Carbohydrates / Cyclopropane derivatives / Cycloaddition / High-pressure chemistry

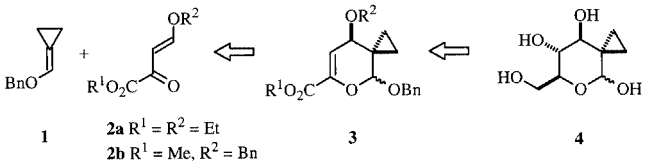
High-pressure-induced inverse-electron-demand hetero-Diels–Alder reactions of ethyl *trans*-4-ethoxy-2-oxo-3-butenoate (**2a**) and methyl *trans*-4-benzyloxy-2-oxo-3-butenoate (**2b**) with benzyl (cyclopropylidenemethyl) ether (**1**) each yielded mixtures of two separable diastereomeric esters **7a** (64%) and **7b** (80%) which, in three subsequent steps, led to the 3-ethylated and 3-benzylated α- and β-anomeric benzyl spiro[2-deoxy-(D,L)-*arabino*-hexopyranoside-2,1′-cyclopropane] α-**10a**,**b** and β-**10a**,**b**, respectively. The relative configuration of β-**10a** was proved by an X-ray crystal structure analysis. Deprotection of β-**10b** was achieved by Pd-catalyzed hydrogenation in dimethylacetamide leading to spiro[2-deoxy-α/β-2-(D,L)-*arabino*-hexopyranoside-2,1′-cyclopropane] (**4**).

Introduction

The chemical modification of natural compounds has long since become a commonly used approach for the formation of novel biologically active molecules with different pharmacological characteristics. The desperate search for effective anticancer and anti-HIV therapeutic agents has greatly stimulated research on specifically altered sugars.[1] Cyclopropanated[2,3] or spirocyclopropane-annelated sugar derivatives, as well as their nucleosides, are of potential interest with respect to their physiological activity because the strain energy contained in the cyclopropane moiety is expected to induce an enhanced reactivity of such compounds and/or of their metabolic intermediates and thus may provoke them to act as enzyme inhibitors. To the best of our knowledge, only a few syntheses of spirocyclopropane-annelated sugars or sugar derivatives have been developed.[4] One of these methodologies involves the transformation of natural sugars or their derivatives.[4a−4e] Another approach consists of the stepwise assembly of the sugar moiety using an aldol condensation of a sterically congested cyclopropanecarboxylic acid ester.[4f] An attractive synthetic procedure for the preparation of carbohydrate derivatives — an inverse-electron-demand hetero-Diels−Alder reaction of enol ethers with α,β-unsaturated carbonyl compounds — has been known for more than 50 years[5] and has been used many times for the synthesis of both racemic and enantiopure sugars and their derivatives.[6] Diels−Alder reactions of methylenecyclopropane derivatives under normal or high pressure have previously been studied.[7a−7e] Here we wish to report the de novo synthesis of some racemic 2-spirocyclopropane-annelated 2-deoxy-*arabino*-hexopyranoside derivatives.

Results and Discussion

This approach to the 2-deoxy-*arabino*-hexopyranoside skeleton utilizes an inverse-electron-demand hetero-Diels−Alder cycloaddition of an enol ether to an β,γ-unsaturated α-keto ester as the key step (Scheme 1).



Scheme 1

[‡] Cyclopropyl Building Blocks for Organic Synthesis, 83. Part 82: T. Voigt, H. Winsel, A. de Meijere, *Synlett* **2002**, 1362−1364. Part 81: D. Frank, S. I. Kozhushkov, T. Labahn, A. de Meijere, *Tetrahedron* **2002**, *58*, 7001−7007.

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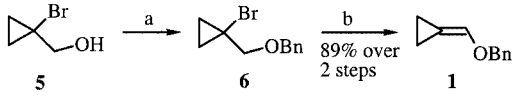
The starting material, benzyl (cyclopropylidenemethyl) ether (**1**), was obtained in two steps from (1-bromocyclopropyl)methanol (**5**),[8] which was benzylated and then dehydrobrominated by treatment with potassium *tert*-butoxide in good overall yield[9,10] (Scheme 2). Two appropriate heterodienes of type **2** — ethyl *trans*-4-ethoxy-2-oxo-3-butenoate (**2a**) and methyl *trans*-4-benzyloxy-2-oxo-3-butenoate (**2b**) — were prepared according to published procedures.[11,12]



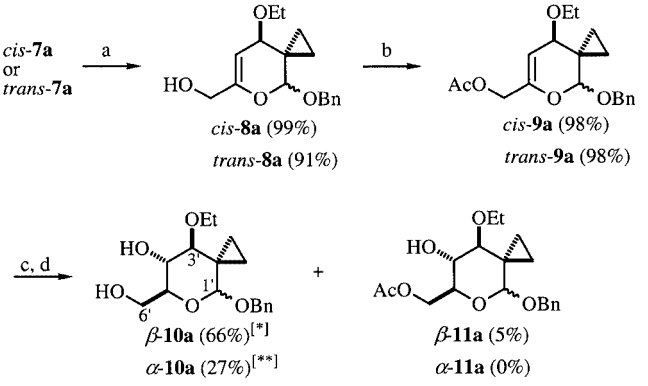
Scheme 2. Preparation of benzyl (cyclopropylidenemethyl) ether (**1**): a) $PhCH_2Br$, NaH, nBu_4NI (cat.), THF, 0 → 25 °C, then 25 °C, 70 h; b) $tBuOK$, DMSO, 10 → 25 °C, then 25 °C, 2 h

To begin with, the stereochemical aspects of the cycloadditions of the enol ether **1** to heterodienes of type **2** were studied with the ethoxy derivative **2a**. In view of the thermal instability of the α-ketocarboxylate **2a**, as well as the steric encumbrance of **1** with its trisubstituted double bond, application of high pressure proved to be the method of choice to accelerate the Diels−Alder reaction between the two.[13] When pressurized to 10 kbar in anhydrous dichloromethane, **2a** reacted smoothly with the enol ether **1** at 25 °C and, after 20 h, gave the ester **7a** as a 3:1 mixture of the *cis*- and *trans*-diastereomers in 53% isolated yield (Scheme 3). Higher reaction temperatures (32−50 °C) and longer reaction times (30−70 h) increased the yield to 62%, but led to slightly diminished diastereoselectivities (Table 1). Anhydrous acetonitrile also turned out to be a good solvent: the highest yield of **7a** (64%) was achieved at 50 °C and 10 kbar after 30 h. Even higher temperatures and longer reaction times were of no advantage and resulted only in enhanced oligomerisation of the heterodiene **2a**. The two diastereomers *cis*- and *trans*-**7a** were easily separated by column chromatography on silica gel. The *cis*-configuration could be assigned for the major diastereomer *cis*-**7a** by a simple NOESY experiment, since it showed a nuclear Overhauser effect between 4-H and 8-H, whereas that for *trans*-**7a** did not.[14]

Table 1. Conditions and yields of the hetero-Diels−Alder reaction of the diene **2a** with enol ether **1** (1.2 equiv.) at 10 kbar

Solvent	T [°C]	Time [h]	Yield of **7a** (%)	Ratio *cis*/*trans*
CH_2Cl_2	25	20	53	3.0
CH_2Cl_2	32	44	57	2.8
CH_2Cl_2	40	70	62	2.1
MeCN	40	70	60	2.1
MeCN	50	30	64	2.2

The ester *cis*-**7a** was reduced with $LiAlH_4$ in diethyl ether to give the alcohol *cis*-**8a**, which was transformed into the acetate *cis*-**9a** by treatment with neat acetic anhydride in the presence of DMAP (Scheme 4). Hydroboration of *cis*-**9a** with $BH_3{\cdot}SMe_2$ followed by oxidative workup (H_2O_2) led to a completely diastereoselective[15a−15d] formation of 1,3-diprotected spiro[2-deoxy-β-(D,L)-*arabino*-hexopyranoside-2,1′-cyclopropane] (β-**10a**) in 66% yield along with some of the acetate β-**11a** (5%) arising from incomplete hydrolysis during the basic workup. An X-ray crystallographic analysis of a single crystal of β-**10a** was performed in order to confirm that the relative configuration corresponds to that of 2-deoxy-β-(D,L)-*arabino*-hexopyranose (Figure 1). In a similar manner the cycloadduct *trans*-**7a** could be transformed into the corresponding 1,3-diprotected spiro[2-deoxy-α-(D,L)-*arabino*-hexopyranoside-2,1′-cyclopropane] (α-**10a**). However,



Scheme 4. Preparation of spiro[2-deoxy-α/β-(D,L)-*arabino*-hexopyranoside-2,1′-cyclopropane]: a) $LiAlH_4$, Et_2O, 0 °C, 2.5 h; b) Ac_2O, DMAP, pyridine, 0 → 25 °C, then 25 °C, 3 h; c) $BH_3{\cdot}SMe_2$, THF, 0 → 25 °C, then 25 °C, 5.5 h; d) EtOH, NaOH, H_2O_2, 0 °C, then 75 °C, 30 min. [*] 8% of unchanged *cis*-**9a** was reisolated. [**] 15% of unchanged *trans*-**9a** was reisolated

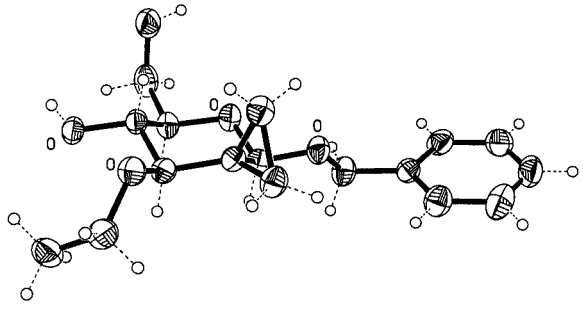
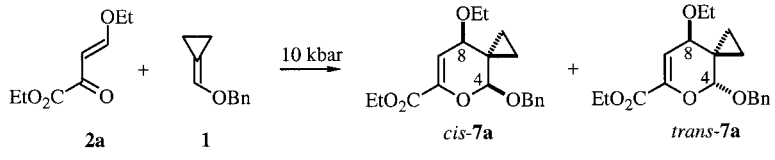


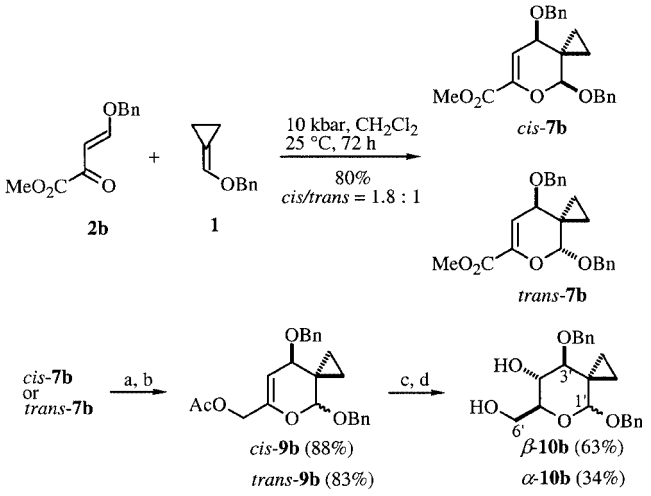
Figure 1. X-ray crystal structure of compound *rac*-β-**10a**[16]



Scheme 3. Inverse-electron-demand hetero-Diels−Alder reaction of heterodiene **2a** with the strained enol ether **1**. For details see Table 1

hydroboration of *trans*-**9a** turned out to be more difficult; for unknown reasons, it required prolonged reaction times as well as repeated additions of the borane complex and gave a significantly lower yield (27%) of α-**10a**.

Since it would obviously be advantageous to deprotect both hydroxy groups in a key intermediate of type **10** in one step, for example by hydrogenolysis, the benzyloxy-substituted heterodiene **2b**[12] was employed in the [4+2] cycloaddition with the enol ether **1** (Scheme 5). At 10 kbar in anhydrous dichloromethane at 25 °C the reaction took place to give, after 72 h, the glycal ester **7b** as an easily separable mixture of the *cis*- and *trans*-diastereomers in 80% yield (ratio 1.8:1). Like *cis*/*trans*-**7a**, the cycloadducts *cis*-**7b** and *trans*-**7b** were transformed into the corresponding 1,3-diprotected racemic spiro[2-deoxy-*arabino*-hexopyranoside-2,1′-cyclopropane] derivatives β-**10b** and α-**10b**. Since alcohols of type **8** are unstable under these conditions (Scheme 4), they were *O*-acetylated without purification. H,H-COSY and H,C-HMQC-2D NMR spectra measurements for β-**10b** confirmed the structure of this compound.



Scheme 5. Hetero-Diels–Alder reaction of diene **2b** with the enol ether **1** and further transformations: a) $LiAlH_4$, Et_2O, 0 °C, 2.5 h; b) Ac_2O, DMAP, pyridine, 0 → 25 °C, then 25 °C, 3 h; c) $BH_3{\cdot}SMe_2$, THF, 0 → 25 °C, then 25 °C, 18 h; d) EtOH, NaOH, H_2O_2, 0 °C, then 75 °C, 1.5 h

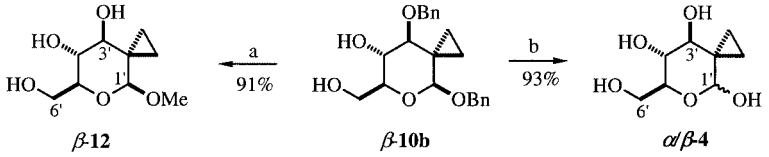
Attempted debenzylation of β-**10b** by palladium-catalyzed hydrogenation in methanol surprisingly gave the methyl hexopyranoside β-**12** in 91% yield (Scheme 6). The formation of alkyl glycosides from aldoses and alcohols is well-known, but usually occurs under acidic conditions only. The spirocyclopropanated aldose β-**10b** apparently undergoes this 1-*O*′-methylation particularly easily even under neutral conditions because the adjacent cyclopropyl group helps to stabilize a developing positive charge at the anomeric center.[17a,17b]

The methyl hexopyranoside **12** was formed as a single diastereomer, as the ^{13}C NMR spectrum showed only a single set of signals. This could be identified as the β-anomer by comparison of its spectrum with that of methyl β-D-glucoside. For **12**, the chemical shift of carbon atom C-1 is δ = 104.9 ppm and for methyl β-D-glucoside it has been reported to be δ = 104.5 ppm (δ = 100.5 ppm for methyl α-D-glucoside).[18] ^{13}C NMR spectra with and without proton decoupling have been measured for **12**. The direct coupling constant $^1J^{13}_{C,H}$ between the anomeric carbon atom and the proton was found to be 165 Hz. It is known that changes in the substituent at C-2 position in the pyranose ring do not affect the $^1J^{13}_{C,H}$ value for the majority of 2-deoxy-D-*arabino*-hexose derivatives, and the measured value is typical for a β-D-glucoside.[18]

While an attempted deprotection of β-**10b** in water failed, it was accomplished by hydrogenolysis in the presence of 10% Pd/C in dimethylacetamide (DMA). Unfortunately, it proved difficult to remove the last trace of DMA by lyophilisation and subsequent drying under reduced pressure. The 2-deoxypyranoside **4** was obtained as a mixture of α- and β-anomers in a 15:85 ratio. The relative configurations of the anomers were assigned on the basis of their ^{13}C NMR spectroscopic data as in the case of the methyl hexopyranoside β-**12**.

Compound **4** was tested as a 10^{-3} M solution in H_2O against two α-fucosidases (bovine epididymis, human placenta), five α-galactosidases (*E. coli*, bovine liver, *Aspergillus niger*, *Aspergillus rizae*, jack bean), five α-glucosidases (maltase from yeast and from rice; isomaltase from baker's yeast; amyloglucosidase from *Aspergillus niger* and from rhizopus mold), two β-glucosidases (from almond and from *Caldocelium saccharolyticum*), two α-mannosidases (jack bean, almond), one β-mannosidase (*Helix pomatia*), one β-xylosidase (*Aspergillus niger*), one α-*N*-acetylgalactosaminidase (chicken liver), three β-*N*-acetylglucosaminidases (jack bean, bovine epididymis A and B), at optimal values of pH. Unfortunately, none of these enzymes were inhibited at this concentration.[19]

In summary, a straightforward synthesis of the 3-*O*′-protected and totally deprotected 2-spirocyclopropane-annelated deoxysugars has been achieved utilizing an inverse electron-demand hetero-Diels–Alder cycloaddition as the key step. Further synthetic elaboration of the cyclopropane moiety may afford new routes to other 2-substituted 2-deoxysugars.



Scheme 6. Hydrogenation of β-**10b**: a) H_2, 10% Pd/C, MeOH, 20 °C, 20 min; b) H_2, 10% Pd/C, dimethylacetamide, 20 °C, 16 h

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 250 at 250 (^{1}H) and 62.9 [^{13}C, additional DEPT (Distortionless Enhancement by Polarisation Transfer)] MHz or a Varian VXR 500 S instrument at 500 (^{1}H) MHz in $CDCl_3$, C_6D_6, [D_6]DMSO, D_2O solution. ^{1}H chemical shifts are relative to the internal reference [δ = 7.26 (for $CHCl_3$), 7.16 (for [D_5]benzene), 4.65 (for HDO), 2.49 (for [D_5]DMSO)]; δ in ppm, *J* in Hz. ^{13}C chemical shifts are relative to the solvent resonance [δ = 77.0 (for $CDCl_3$), 128.0 (for [D_6]benzene), 39.7 (for [D_6]DMSO)]. MS (EI): Finnigan MAT 95 spectrometer (70 eV). HRMS: Varian MAT 311 A. IR: Bruker IFS 66 (FT-IR). M.p.: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey−Nagel precoated sheets, 0.25 mm G/UV_{254} silica. Starting materials: anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl, DMSO from CaH_2, and dichloromethane from P_4O_{10}. All other chemicals were used as commercially available (Merck, Acros, Bayer, Hoechst, Degussa AG, and Hüls AG). All reactions were performed under argon. Attempted elemental and HPLC analyses to prove bulk purities for compounds **1**, *cis*-**7b**, *trans*-**7b**, *trans*-**9b** all failed. However, these compounds were found to be at least ≥ 95% pure according to their ^{1}H and ^{13}C NMR spectra as well as thin layer chromatography.

Benzyl (Cyclopropylidenemethyl) Ether (1): NaH (60% suspension in mineral oil, 8.4 g, 211 mmol) was added in small portions to an ice-cooled solution of (1-bromocyclopropyl)methanol (**5**; 30.2 g, 200 mmol), benzyl bromide (34.2 g, 200 mmol) and tetra-*n*-butylammonium iodide (1.0 g, 2.7 mmol) in THF (200 mL) with stirring during 1 h. The reaction mixture was allowed to warm to ambient temperature and stirred for 70 h, then water (50 mL) was added, and THF was removed by evaporation under reduced pressure. The residue was taken up in water (200 mL) and the aqueous solution extracted with pentane (1 × 200, 2 × 100 mL). The pentane solution was washed with water (4 × 100 mL) and brine (100 mL), dried with $MgSO_4$ and concentrated under reduced pressure at room temperature to give the bromo ether **6** (50.3 g) as a colorless oil. Without further purification, the crude bromoether **6** was added to a solution of *t*BuOK (28.0 g, 250 mmol) in anhydrous DMSO (160 mL) during 30 min with stirring and cooling with a water bath. After stirring for 2 h at ambient temperature, the mixture was diluted with pentane (250 mL) and ice-cold water (600 mL). The water phase was extracted with pentane (3 × 100 mL), the combined pentane solutions were washed with water (5 × 100 mL) and brine (300 mL), and dried over Na_2SO_4. Pentane was removed under reduced pressure, and the residue was distilled over a 20 cm Vigreux column to give enol ether **1** (28.6 g, 89%) as a colorless liquid, b. p. 53−55 °C (0.2 Torr). IR (film): $\tilde{\nu}$ = 3032 cm^{-1}, 2980, 1766, 1183. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.02−1.09 (m, 2 H), 1.22−1.29 (m, 2 H), 5.01 (s, 2 H), 6.74 (m, 1 H), 7.26−7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 0.8, 4.8, 70.7 (CH_2), 94.4 (C), 127.4 (CH, 2C), 127.7 (CH), 128.4 (CH, 2C), 135.7 (CH), 138.0 (C) ppm. MS (EI): *m*/*z* (%) = 160 (5) [M^+], 145 (8), 131 (5), 116 (2), 91 (100) [$C_7H_7^+$], 65 (26).

Ethyl *cis*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-carboxylate (*trans*-7a) and ethyl *trans*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-carboxylate (*cis*-7a): A solution of **1** (192 mg, 1.20 mmol) and **2a** (172 mg, 1.00 mmol) in acetonitrile (1 mL) was kept in a sealed Teflon tube for 30 h at 50 °C and 10 kbar pressure. The mixture was concentrated under reduced pressure, and the residue was subjected to chromatography (8 g of silica gel; 27 × 1 cm column) eluting with pentane/diethyl ether 5:1 to give two fractions.

Fraction I: *trans*-**7a** (68 mg, 20%, R_f = 0.31). IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 2978, 1731, 1646. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.48 (m, 2 H), 0.70 (m, 1 H), 0.88 (m, 1 H), 1.15 (t, *J* = 7.0 Hz, 3 H), 1.32 (t, *J* = 7.0 Hz, 3 H), 3.23 (d, *J* = 3.0 Hz, 1 H), 3.46 (dq, *J* = 9.0, 7.0 Hz, 1 H), 3.66 (dq, *J* = 9.0, 7.0 Hz, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.78 (s, 1 H), 4.89 (d, *J* = 12.0 Hz, 1 H), 6.38 (d, *J* = 3.0 Hz, 1 H), 7.32 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.4, 5.5 (CH_2), 14.1, 15.4 (CH_3), 21.8 (C), 61.3, 64.9, 70.4 (CH_2), 71.5, 102.2, 111.1 (CH), 127.7 (CH, 3 × C), 128.3 (CH, 2 × C), 137.2, 142.2 (C), 162.6 (C=O) ppm. MS (EI): *m*/*z* (%) = 332 (<0.1) [M^+], 199 (4), 173 (8), 145 (100), 117 (49), 99 (27), 91 (26) [$C_7H_7^+$], 71 (78).

Fraction II: *cis*-**7a** (145 mg, 44%, R_f = 0.15). IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 2976, 2871, 1732, 1647. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.45 (m, 1 H), 0.63 (m, 1 H), 0.78 (m, 1 H), 1.05 (m, 1 H), 1.22 (t, *J* = 7.4 Hz, 3 H), 1.32 (t, *J* = 7.5 Hz, 3 H), 3.29 (d, *J* = 5.5 Hz, 1 H), 3.58 (dq, *J* = 9.0, 7.4 Hz, 1 H), 3.66 (dq, *J* = 9.0, 7.4 Hz, 1 H), 4.25 (q, *J* = 7.5 Hz, 2 H), 4.40 (s, 1 H), 4.64 (d, *J* = 13.2 Hz, 1 H), 4.83 (d, *J* = 13.2 Hz, 1 H), 6.38 (d, *J* = 5.5 Hz, 1 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.5, 11.0 (CH_2), 14.2, 15.5 (CH_3), 22.7 (C), 61.3, 64.6, 69.8 (CH_2), 73.4, 101.6, 110.2, 127.4 (CH), 127.7 (CH, 2 C), 128.2 (CH, 2 C), 137.4, 141.9 (C), 162.8 (C=O) ppm. MS (EI): *m*/*z* (%) = 332 (0.1) [M^+], 259 (9), 241 (13), 180 (4), 108 (9), 91 (100) [$C_7H_7^+$], 84 (27).

[*cis*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-yl]methanol (*cis*-8a): A solution of *cis*-**7a** (543 mg, 1.63 mmol) in diethyl ether (5 mL) was added dropwise at 0 °C to a suspension of lithium aluminum hydride (34 mg, 0.90 mmol) in diethyl ether (5 mL). The mixture was stirred for 2.5 h at this temperature, then water (0.5 mL) and saturated sodium sulfate solution (5 mL) were added carefully. The mixture was diluted with Et_2O (50 mL), the aqueous phase was extracted with diethyl ether (3 × 20 mL), the combined ether fractions were dried ($MgSO_4$) and concentrated under reduced pressure to give *cis*-**8a** (468 mg, 99%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3416 cm^{-1}, 3065, 2976, 1683, 1479. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.40 (m, 1 H), 0.55 (m, 1 H), 0.70 (m, 1 H), 0.98 (m, 1 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 3.10 (br. s, 1 H), 3.19 (d, *J* = 4.5 Hz, 1 H), 3.50 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.58 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.92 (s, 2 H), 4.29 (s, 1 H), 4.59 (d, *J* = 12.5 Hz, 1 H), 4.76 (d, *J* = 12.5 Hz, 1 H), 5.18 (d, *J* = 4.5 Hz, 1 H), 7.28 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.4, 10.4 (CH_2), 15.3 (CH_3), 22.4 (C), 62.0, 63.7, 69.4 (CH_2), 73.5, 97.4, 101.2, 127.1 (CH), 127.3 (CH, 2 C), 127.9 (CH, 2 C), 137.6, 151.8 (C) ppm. MS (EI): *m*/*z* (%) = 290 (0.1) [M^+], 259 (2), 181 (56), 108 (100) [$PhCH_2OH^+$], 107 (77) [$PhCH_2O^+$], 91 (98) [$C_7H_7^+$], 79 (94) [$C_6H_7^+$]. HRMS (EI) for $C_{17}H_{22}O_4$: calcd. 290.1518; found 290.1518.

[*trans*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-yl]methanol (*trans*-8a): A solution of *trans*-**7a** (849 mg, 2.55 mmol) in diethyl ether (10 mL) was added dropwise at 0 °C to a suspension of lithium aluminum hydride (54 mg, 1.42 mmol) in diethyl ether (10 mL). The mixture was stirred for 2.5 h at this temperature, then water (0.5 mL) and saturated sodium sulfate solution (5 mL) were added carefully. The mixture was diluted with diethyl ether (30 mL), the water phase was extracted with Et_2O (3 × 20 mL), the combined ether fractions were dried ($MgSO_4$) and concentrated under reduced pressure to give *trans*-**8a** (673 mg, 91%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.40 (m, 1 H), 0.80 (m, 3 H), 1.19 (t, *J* = 7.0 Hz, 3 H), 2.58 (br. s, 1 H), 3.49 (d, *J* = 4.0 Hz, 1 H), 3.48 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.58 (dq, *J* = 9.5, 7.0 Hz, 1 H), 4.05 (s, 2 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.88 (d, *J* = 12.0 Hz, 1 H), 5.03 (s, 1 H), 5.16 (d, *J* = 4.0 Hz, 1 H), 7.32 (m, 5

H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.4, 6.3 (CH_2), 15.4 (CH_3), 22.9 (C), 62.3, 64.0, 70.6 (CH_2), 73.9, 97.7, 100.2 (CH), 127.5 (CH, 2 C), 127.6 (CH), 128.2 (CH, 2 C), 137.4, 152.9 (C) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 259 (1), 147 (38), 133 (18), 108 (31) [$PhCH_2OH^+$], 107 (25) [$PhCH_2O^+$], 91 (100) [$C_7H_7^+$], 79 (39) [$C_6H_7^+$].

[*cis*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-yl]methyl Acetate (*cis*-9a): Acetic anhydride (1.08 g, 10.6 mmol) and DMAP (12 mg, 0.1 mmol) were added at 0 °C to a solution of *cis*-**8a** (600 mg, 2.07 mmol) in pyridine (2 mL). The resulting clear solution was stirred at 25 °C for 3 h and concentrated under reduced pressure as much as possible. The residue was additionally dried for 1 h under reduced pressure (10^{-3} Torr), then taken up in diethyl ether (40 mL), the ethereal solution was washed with saturated sodium bicarbonate solution (5 × 10 mL) and brine (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give *cis*-**9a** (674 mg, 98%) as a colorless oil. IR (film): ṽ = 3064 cm^{-1}, 3007, 2973, 1743 (C=O), 1681. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.46 (m, 1 H), 0.59 (m, 1 H), 0.73 (m, 1 H), 1.02 (m, 1 H), 1.17 (t, *J* = 7.0 Hz, 3 H), 2.06 (s, 3 H), 3.19 (d, *J* = 4.5 Hz, 1 H), 3.52 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.57 (dq, *J* = 9.5, 7.0 Hz, 1 H), 4.39 (s, 1 H), 4.39 (d, *J* = 13.0 Hz, 1 H), 4.48 (d, *J* = 13.0 Hz, 1 H), 4.58 (d, *J* = 12.5 Hz, 1 H), 4.79 (d, *J* = 12.5 Hz, 1 H), 5.27 (d, *J* = 4.5 Hz, 1 H), 7.28 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.4, 10.7 (CH_2), 15.4, 20.6 (CH_3), 22.5 (C), 63.6, 63.9, 69.3 (CH_2), 73.4, 101.1, 101.2, 127.2 (CH), 127.4 (CH, 2 C), 128.0 (CH, 2 C), 137.5, 147.4 (C), 170.2 (C=O) ppm. MS (EI): *m*/*z* (%) = 332 (2) [M^+], 331 (2) [M^+ − H], 259 (3), 225 (2), 166 (2), 135 (4), 91 (100) [$C_7H_7^+$]. HRMS (EI) for $C_{19}H_{24}O_5$: calcd. 332.1623; found 332.1623.

[*trans*-4-(Benzyloxy)-8-ethoxy-5-oxaspiro[2.5]oct-6-ene-6-yl]methyl Acetate (*trans*-9a): The *trans*-isomer of *cis*-**9a** was prepared analogously starting from *trans*-**8a** (650 mg, 2.24 mmol) in 98% yield (729 mg) as a colorless oil. IR (film): ṽ = 3066 cm^{-1}, 3006, 2975, 1742 (C=O), 1681. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.46 (m, 1 H), 0.72 (m, 2 H), 0.83 (m, 1 H), 1.17 (t, *J* = 7.0 Hz, 3 H), 2.11 (s, 3 H), 3.49 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.53 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.62 (d, *J* = 4.0 Hz, 1 H), 4.51 (s, 2 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 4.87 (d, *J* = 12.0 Hz, 1 H), 4.89 (s, 1 H), 5.18 (d, *J* = 4.0 Hz, 1 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.4, 6.0 (CH_2), 15.4, 20.8 (CH_3), 22.5 (C), 63.5, 64.3, 70.2 (CH_2), 73.0, 100.6, 101.4 (CH), 127.6 (CH, 3 C), 128.2 (CH, 2 C), 137.3, 148.3 (C), 170.4 (C=O) ppm. MS (CI): *m*/*z* (%) = 350 (44) [M + NH_4^+], 304 (56) [M + NH_4^+ − EtOH], 287 (100) [M^+ − EtO].

β-11a: Borane−dimethyl sulfide complex (2 M in THF, 0.60 mL, 1.20 mmol) was added dropwise at 0 °C to a solution of *cis*-**9a** (858 mg, 2.58 mmol) in THF (9 mL). The mixture was stirred at 25 °C, and two further portions of BH_3·Me_2S (0.60 mL, 1.20 mmol and 0.30 mL, 0.60 mmol) were added after 2 h and an additional 1.5 h, respectively. The mixture was stirred for another 2 h, then EtOH (3 mL) was added carefully at 0 °C followed by a solution of H_2O_2 (30% in water, 0.31 mL, 3.0 mmol) and NaOH solution (1 M in water, 3.0 mL, 3.0 mmol). The mixture was heated under reflux for 30 min, cooled and concentrated under reduced pressure, the residue was shaken with diethyl ether (100 mL), the ether solution was washed with brine (7 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (20 g of silica gel, 21 × 2 cm column) eluting with diethyl ether to give three fractions.
Fraction I: *cis*-**9a** (68 mg, 8%, R_f = 0.76) as a colorless oil.
Fraction II: **β-11a** (40 mg, 5%, R_f = 0.54) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.48 (m, 1 H), 0.59 (m, 2 H), 0.83 (m, 1 H), 1.15 (t, *J* = 7.0 Hz, 3 H), 2.14 (s, 3 H), 3.00 (br. s, 1 H), 3.42 (d, *J* = 8.0 Hz, 1 H), 3.53 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.57 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.62−3.75 (m, 1 H), 3.72 (dd, *J* = 8.0, 7.0 Hz, 1 H), 4.38 (m, 1 H), 4.51 (m, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.70 (s, 1 H), 4.88 (d, *J* = 12.0 Hz, 1 H), 7.32 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 1.9, 3.8 (CH_2), 15.4, 20.9 (CH_3), 24.8 (C), 64.0, 69.3, 70.4 (CH_2), 71.0, 74.1, 80.9, 99.7 (CH), 127.7 (CH, 3 C), 128.3 (CH, 2 C), 137.3 (C), 171.9 (C=O) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 333 (<0.1), 287 (1), 243 (10), 183 (5), 137 (10), 91 (100) [$C_7H_7^+$], 65 (14).
Fraction III: β-**10a** (524 mg, 66%, R_f = 0.26) as a colorless solid, m.p. 95 °C. IR (KBr): ṽ = 3429 cm^{-1}, 3068, 2969, 1456, 1097. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.46 (m, 1 H), 0.60 (m, 2 H), 0.79 (m, 1 H), 1.14 (t, *J* = 7.3 Hz, 3 H), 2.78 (br. s, 2 H), 3.44 (d, *J* = 8.1 Hz, 1 H), 3.48 (dq, *J* = 9.5, 7.3 Hz, 1 H), 3.52 (dq, *J* = 9.5, 7.3 Hz, 1 H), 3.56−3.70 (m, 1 H), 3.62 (dd, *J* = 8.1, 7.0 Hz, 1 H), 3.82 (m, 1 H), 3.95 (m, 1 H), 4.58 (d, *J* = 12.4 Hz, 1 H), 4.79 (s, 1 H), 4.85 (d, *J* = 12.4 Hz, 1 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 1.7, 3.6 (CH_2), 15.4 (CH_3), 24.9 (C), 62.8, 69.1, 70.7 (CH_2), 71.6, 75.6, 81.0, 99.9 (CH), 127.6 (CH, 3 C), 128.3 (CH, 2 C), 137.3 (C) ppm. MS (EI): *m*/*z* (%) = 308 (0.1) [M^+], 251 (14), 169 (10), 99 (16), 91 (100) [$C_7H_7^+$]. HRMS (EI) for $C_{17}H_{24}O_5$: calcd. 308.1623; found 308.1623.

α-10a: Borane−dimethyl sulfide complex (2 M in THF, 0.42 mL, 0.84 mmol) was added dropwise at 0 °C to a solution of *trans*-**9a** (700 mg, 2.11 mmol) in THF (9 mL). The mixture was stirred at 25 °C, and two further portions of BH_3·Me_2S (0.40 mL, 0.80 mmol and 0.42 mL, 0.84 mmol) were added after 21 h and an additional 2 h, respectively. The mixture was stirred for an additional 3 h, then EtOH (3 mL) was added carefully at 0 °C followed by a solution of H_2O_2 (30% in water, 0.22 mL, 2.1 mmol) and of NaOH (1 M in water, 2.1 mL, 2.1 mmol). The mixture was heated under reflux for 1 h, cooled and concentrated under reduced pressure, the residue was shaken with diethyl ether (100 mL), the ether solution was washed with brine (7 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (20 g of silica gel, 21 × 2 cm column) eluting with diethyl ether to give two fractions.
Fraction I: *trans*-**9a** (103 mg, 15%, R_f = 0.73) as a colorless oil.
Fraction II: α-**10a** (174 mg, 27%, R_f = 0.32) as a colorless solid, m.p. 77 °C. IR (KBr): ṽ = 3430 cm^{-1}, 3088, 2974, 1458, 1023. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.28 (m, 1 H), 0.38 (m, 1 H), 0.67 (m, 1 H), 0.76 (m, 1 H), 1.13 (t, *J* = 7.0 Hz, 3 H), 2.70−3.30 (br. s, 2 H), 3.59 (d, *J* = 7.0 Hz, 1 H), 3.66 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.70 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.71 (m, 1 H), 3.82 (m, 1 H), 3.87 (d, *J* = 3.0 Hz, 2 H), 4.00 (s, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 7.31 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 4.3, 5.2 (CH_2), 15.4 (CH_3), 24.5 (C), 62.4, 68.6, 68.9 (CH_2), 71.5, 72.8, 77.9, 103.8, 127.6 (CH), 127.8, 128.3 (CH, 2 C), 137.5 (C) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 307 (0.1) [M^+ − H], 262 (1), 217 (4), 201 (22), 127 (17), 91 (100) [$C_7H_7^+$].

Methyl *trans*-4,8-Dibenzyloxy-5-oxaspiro[2.5]oct-6-ene-6-carboxylate (*trans*-7b) and Methyl *cis*-4,8-Dibenzyloxy-5-oxaspiro[2.5]-oct-6-ene-6-carboxylate (*cis*-7b): A solution of **1** (0.96 g, 6.0 mmol) and **2b** (1.10 g, 5.0 mmol) in dichloromethane (4 mL) was kept in a sealed Teflon tube for 72 h at 25 °C and 10 kbar pressure. The mixture was concentrated under reduced pressure, and the residue was subjected to chromatography (100 g of silica gel, 24 × 3.5 cm column) eluting with pentane/diethyl ether 2:1 to give two fractions.
Fraction I: *trans*-**7b** (532 mg, 28%, R_f = 0.46) as a colorless oil. IR (film): ṽ = 3064 cm^{-1}, 3030, 3007, 1734, 1645. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.60 (m, 2 H), 0.75 (m, 1 H), 0.93 (m, 1

H), 3.83 (s, 3 H), 4.01 (d, J = 3.3 Hz, 1 H), 4.50 (d, J = 11.7 Hz, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 11.7 Hz, 1 H), 4.87 (s, 1 H), 4.91 (d, J = 12.0 Hz, 1 H), 6.31 (d, J = 3.3 Hz, 1 H), 7.28−7.39 (m, 10 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.6, 5.8 (CH_2), 22.0 (C), 52.3 (CH_3), 70.6, 71.0 (CH_2), 71.5, 102.1, 110.6, 127.5 (CH), 127.6, 127.7, 127.8, 128.3 (CH, 2 C), 128.4 (CH), 137.2, 138.0, 142.5 (C), 163.1 (C=O) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 194 (5), 166 (12), 107 (17), 91 (100) [$C_7H_7^+$].

Fraction II: *cis*-**7b** (990 mg, 52%, R_f = 0.34) as a colorless oil. IR (film): $\tilde{\nu}$ = 3063 cm^{-1}, 3029, 3007, 1734, 1648. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.42 (m, 1 H), 0.69 (m, 1 H), 0.82 (m, 1 H), 1.05 (m, 1 H), 3.38 (dd, J = 4.6, 0.5 Hz, 1 H), 3.80 (s, 3 H), 4.42 (d, J = 0.5 Hz, 1 H), 4.60 (d, J = 12.1 Hz, 1 H), 4.68 (d, J = 12.5 Hz, 1 H), 4.73 (d, J = 12.1 Hz, 1 H), 4.86 (d, J = 12.5 Hz, 1 H), 6.39 (d, J = 4.6 Hz, 1 H), 7.28−7.40 (m, 10 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.8, 11.2 (CH_2), 22.7 (C), 52.4 (CH_3), 70.0, 70.4 (CH_2), 72.2, 101.9, 109.9, 127.5 (CH), 127.6, 127.7, 127.8 (CH, 2 C), 128.2 (CH), 128.3 (CH, 2 C), 137.4, 138.44, 142.0 (C), 163.2 (C=O) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 321 (1), 289 (3), 215 (4), 166 (8), 91 (100) [$C_7H_7^+$].

(*cis*-4,8-Dibenzyloxy-5-oxaspiro[2.5]oct-6-ene-6-yl)methyl Acetate (*cis*-9b): A solution of lithium aluminum hydride (1.37 M in Et_2O, 2.07 mL, 2.84 mmol) was added dropwise with stirring at 0 °C within 5 min to a solution of *cis*-**7b** (1.80 g, 4.73 mmol) in diethyl ether (20 mL). The mixture was stirred at this temperature for 2.5 h, then water (0.11 mL), a 3 M NaOH solution (0.11 mL) and water again (0.33 mL) were added. After stirring for 30 min, the suspension was filtered with suction, the filter cake was washed with diethyl ether (3 × 20 mL), the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in pyridine (5 mL), and to this solution were added acetic anhydride (2.48 g, 24.3 mmol) and DMAP (12 mg, 0.1 mmol). The resulting clear solution was stirred for 3 h at 25 °C and concentrated under reduced pressure as much as possible. The residue was dissolved in diethyl ether (50 mL), washed with saturated $NaHCO_3$ solution (4 × 10 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give *cis*-**9b** (1.64 g, 88%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3030, 2934, 2864, 1743, 1681. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.41 (m, 1 H), 0.59 (m, 1 H), 0.76 (m, 1 H), 1.02 (m, 1 H), 2.07 (s, 3 H), 3.29 (d, J = 4.5 Hz, 1 H), 4.30 (s, 1 H), 4.42 (d, J = 12.8 Hz, 1 H), 4.51 (d, J = 12.8 Hz, 1 H), 4.59 (d, J = 12.3 Hz, 1 H), 4.63 (d, J = 12.5 Hz, 1 H), 4.68 (d, J = 12.3 Hz, 1 H), 4.85 (d, J = 12.5 Hz, 1 H), 5.28 (d, J = 4.5 Hz, 1 H), 7.22−7.40 (m, 10 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.8, 11.3 (CH_2), 20.9 (CH_3), 22.8 (C), 63.8, 69.6, 70.1 (CH_2), 72.6, 100.9, 101.4, 127.4, 127.5 (CH), 127.7 (CH, 2 C), 127.8 (CH, 2 C), 128.2 (CH, 2 C), 128.3 (CH, 2 C), 137.7, 138.9, 148.0 (C), 170.5 (C=O) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 303 (1), 287 (3), 215 (6), 197 (15), 91 (100) [$C_7H_7^+$]. $C_{24}H_{26}O_5$ (394.47) calcd. C 73.08, H 6.64; found C 73.94, H 6.25.

(*trans*-4,8-Dibenzyloxy-5-oxaspiro[2.5]oct-6-ene-6-yl)methyl Acetate (*trans*-9b): The *trans*-isomer of *cis*-**9b** was prepared analogously starting from *trans*-**7b** (1.58 g, 4.15 mmol) in 83% yield (1.35 g) as a colorless oil. IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3030, 2934, 2866, 1741, 1675. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.45 (m, 1 H), 0.81 (m, 3 H), 2.11 (s, 3 H), 3.67 (d, J = 3.8 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.53 (s, 2 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.62 (d, J = 11.8 Hz, 1 H), 4.88 (d, J = 12.0 Hz, 1 H), 4.99 (s, 1 H), 5.20 (d, J = 3.8 Hz, 1 H), 7.27−7.39 (m, 10 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.9, 6.4 (CH_2), 20.9 (CH_3), 22.7 (C), 63.6, 70.5, 70.6 (CH_2), 73.2, 100.4, 100.8 (CH), 127.6 (CH, 3 C), 127.7, 127.8 (CH, 2 C), 128.3 (CH, 3 C), 137.3, 138.4, 149.0 (C), 170.5 (C=O) ppm. MS (EI): *m*/*z* (%) = [M^+] not observed, 287 (2), 244 (2), 181 (5), 91 (100) [$C_7H_7^+$].

β-10b: Borane−dimethyl sulfide complex (2 M in THF, 1.00 mL, 2.00 mmol) was added dropwise at 0 °C to a solution of *cis*-**9b** (1.58 g, 4.01 mmol) in THF (10 mL). The mixture was stirred at 25 °C, and two further portions of BH_3·Me_2S (1.00 mL, 2.00 mmol and 0.50 mL, 1.00 mmol) were added after 11 h and an additional 5 h, respectively. The mixture was stirred for an additional 3 h, then EtOH (5 mL) was added carefully at 0 °C followed by a solution of H_2O_2 (30% in water, 1.70 mL, 16.64 mmol) and of NaOH (3 M in water, 1.5 mL, 4.50 mmol). The mixture was heated under reflux for 1 h, then a solution of NaOH (2.00 mL, 6.00 mmol) and water (5.0 mL) were added, and the heating was continued for another 30 min. The cooled mixture was concentrated under reduced pressure, the residue was shaken with diethyl ether (150 mL), the ether solution was washed with brine (5 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (80 g of silica gel, 28 × 3 cm column) eluting with dichloromethane/acetone 5:1 to give β-**10b** (930 mg, 63%, R_f = 0.35) as a colorless solid. A small portion of this product was recrystallized from benzene to give colorless crystals, m.p. 93−95 °C. IR (KBr): $\tilde{\nu}$ = 3301 cm^{-1}, 3089, 3064, 3026, 3014, 2916, 2874, 1497, 1364, 1082, 1016. ^{1}H NMR (300 MHz, C_6D_6): δ = 0.62 (m, 1 H), 0.77 (m, 1 H), 0.93 (m, 1 H), 1.15 (m, 1 H), 2.17 (t, J = 3.7 Hz, 1 H), 2.45 (d, J = 3.9 Hz, 1 H), 3.27 (ddd, J = 8.8, 7.0, 4.5 Hz, 1 H), 3.39 (d, J = 8.8 Hz, 1 H), 3.63 (dt, J = 8.8, 3.9 Hz, 1 H), 3.86 (m, 2 H), 4.35 (d, J = 12.0 Hz, 1 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.53 (s, 1 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 7.03−7.24 (m, 10 H) ppm. ^{13}C NMR (75.5 MHz, C_6D_6): δ = 2.6, 4.1 (CH_2), 25.5 (C), 63.2, 70.6 (CH_2), 72.9 (CH), 75.4 (CH_2), 76.0, 81.2, 100.1 (CH), 127.7 (CH, 3 C), 127.8, 127.9 (CH, 2 C), 128.6 (CH), 128.7 (CH, 2 C), 138.3, 139.2 (C) ppm. MS (EI): *m*/*z* (%) = 370 (<0.1) [M^+], 369 (6) [$M - H^+$], 342 (12), 321 (8), 263 (7), 198 (8), 156 (11), 91 (100) [$C_7H_7^+$]. HRMS (EI) for $C_{22}H_{26}O_5$: calcd. 370.1780; found 370.1780. $C_{22}H_{26}O_5$ (370.45) calcd. C 71.33, H 7.07; found C 71.09, H 6.98.

α-10b: The α-isomer of β-**10b** was prepared analogously starting from *trans*-**9b** (1.31 g, 3.32 mmol). Chromatographic purification (80 g of silica gel, 28 × 3 cm column) eluting with dichloromethane/acetone (10:1) gave α-**10b** (420 mg, 34%, R_f = 0.20) as a colorless solid. A small portion of this product was recrystallized from hexane/diethyl ether to give colorless crystals, m.p. 86−89 °C. IR (KBr): $\tilde{\nu}$ = 3475 cm^{-1}, 3085, 3066, 3031, 3005, 2927, 2877, 1497, 1454, 1402, 1367, 1129, 1013. ^{1}H NMR (250 MHz, C_6D_6): δ = 0.24 (m, 1 H), 0.39 (m, 1 H), 0.81 (m, 1 H), 1.02 (m, 1 H), 2.37 (br. s, 1 H), 2.70 (d, J = 3.9 Hz, 1 H), 3.79 (dt, J = 8.8, 3.9 Hz, 1 H), 3.87−4.06 (m, 3 H), 3.95 (s, 1 H), 4.15 (d, J = 8.8 Hz, 1 H), 4.30 (d, J = 12.1 Hz, 1 H), 4.37 (d, J = 11.8 Hz, 1 H), 4.62 (d, J = 11.8 Hz, 1 H), 4.63 (d, J = 12.1 Hz, 1 H), 7.08−7.37 (m, 10 H) ppm. ^{13}C NMR (62.9 MHz, C_6D_6): δ = 4.8, 5.8 (CH_2), 25.1 (C), 63.2, 68.9 (CH_2), 73.0, 73.5 (CH), 75.4 (CH_2), 78.6, 104.3 (CH), 127.6, 127.8, 127.9 (CH, 2 C), 128.2 (CH), 128.5 (CH, 2 C), 128.6 (CH), 138.3, 139.3 (C) ppm. MS (EI): *m*/*z* (%) = 370 (< 0.1) [M^+], 279 (6), 231 (8), 156 (10), 91 (100) [$C_7H_7^+$]. HRMS (EI) for $C_{22}H_{26}O_5$: calcd. 370.1780; found 370.1780. $C_{22}H_{26}O_5$ (370.45) calcd. C 71.33, H 7.07; found C 71.37, H 6.84.

β-12: The protected sugar β-**10b** (278 mg, 0.75 mmol) in methanol (50 mL) was hydrogenated in the presence of 10% Pd/C (50 mg) at 20 °C and 1 bar for 20 min. The catalyst was filtered off, and the solution was concentrated under reduced pressure. The residue was then lyophilized twice to give β-**12** (140 mg, 91%) as a colorless

glass. IR (KBr): $\tilde{\nu}$ = 3422 cm^{-1}, 3006, 2902, 2835, 1102, 1030. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 3.6, 4.7 (CH_2), 25.4 (C), 54.0 (CH_3), 61.4 (CH_2), 68.5, 71.0, 74.1, 105.0 (CH) ppm. MS (CI, NH_3): *m/z* (%) = 426 (<0.1) [2M + NH_4^+], 222 (23) [M + NH_4^+], 190 (100) [M + NH_4^+ − CH_3OH], 173 (36) [M^+ − CH_3O], 102 (54).

α-4: A solution of β-**10b** (150 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (DMA) (15 mL) was hydrogenated in the presence of 10% Pd/C (75 mg) at 20 °C and 1 bar for 16 h. The catalyst was filtered off, and the solution was concentrated under reduced pressure. The residue was lyophilized twice, then dried for one week under high vacuum (10^{-3} Torr) to give α/β-**4** (81 mg) as a colorless glass which still contained 12 mol % of DMA, yield of α/β-**4** 93%. IR (KBr): $\tilde{\nu}$ [α/β-**4**] = 3474 cm^{-1}, 3009, 2928, 1616, 1420, 1087, 1019. ^{13}C NMR (62.9 MHz, D_2O): δ (β-**4**) = 4.1, 5.5 (CH_2), 26.1 (C), 62.0 (CH_2), 69.7, 71.5, 74.1, 99.6 (CH); δ (α-**4**) = 1.0, 3.4 (CH_2), 26.1 (C), 62.0 (CH_2), 71.2, 72.8, 77.6, 95.6 (CH) ppm. MS (CI, NH_3) [α/β-**4**]: *m/z* (%) = 398 (0.5) [2M + NH_4^+], 380 (1) [2M + NH_4^+ − H_2O], 208 (31) [M + NH_4^+], 190 (100) [M + NH_4^+ − H_2O], 173 (36) [M^+ − OH], 105 (29).

Acknowledgments

This work was financially supported by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg "Kinetics and Selectivity of Chemical Processes in Compressed Fluid Phases"), and the Fonds der Chemischen Industrie as well as by BASF, Bayer, Degussa, and Hüls AG through generous gifts of chemicals. T. H. is indebted to the Hermann-Schlosser-Stiftung for a graduate fellowship. The authors are grateful to Dr. Burkhard Knieriem for his careful proof reading of the final manuscript. M. T. B. thanks the European Community for a postdoctoral grant (No. ERBCHBGCT 940731). The authors are indebted to Prof. Dr. P. Vogel, LGSA, Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne (Switzerland), for the biological testing of compound **4**.

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[16] **Crystal Structure Determination of *rac*-β-10a**: Data were collected on a Stoe AED2 four-circle diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-96, G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467) and refined versus F^2 by the least-squares method with all data (SHELXS-96, *Program for Crystal Structure Refinement*, University of Göttingen, **1996**). *R* values: $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. Single crystal crystallized from diethyl ether, colorless, monoclinic, space group $P2_1/c$; $Z = 4$, a = 12.844(3) Å, b = 13.791(3) Å, c = 9.871(2) Å, β = 112.46(3)°, V = 1615.8(6) $Å^3$; $\rho_{calcd.}$ = 1.268 Mg/m^3. 4159 Reflections, 2083 unique observed [$I > 2\sigma(I)$], were measured at −80 °C. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined on calculated positions by using a riding method. $R1$ = 0.0602, $wR2$ = 0.1760 (all data) for 201 parameters. Crystallographic data of β-**10a** have been deposited as supplementary publication no. CCDC-114680 with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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Received June 21, 2002
[O02350]