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O,O-Acetal Formation of *exo*-Annelated Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol with Lactic Acid and Phenyllactic Acid Derivatives

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Summary. Acetals of a series of substituted lactic acid derivatives were formed with enantiopure lactol **1**. ^{1}H and ^{13}C NMR spectroscopic data of the anomerically pure O,O-acetals are compared in order to assign the absolute configuration of the O-protected lactic acid derivatives and for the determination of enantiomeric excesses. The results are supported by molecular modeling studies.

Keywords. Acetalization; Lactic esters; Lactamides; Enantiomeric excess; Enantiomeric selectivity.

O,O-Acetalbildung des *exo*-anellierten Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ols mit Milchsäure- und Phenylmilchsäurederivaten

Zusammenfassung. Substituierte Milchsäurederivate wurden mit enantiomerenreinem Lactol **1** acetalisiert. Die ^{1}H- und ^{13}C-NMR-Daten der dabei erhaltenenen anomerenreinen O,O-Acetale sind zur Bestimmung von Enantiomerenüberschüssen und der absoluten Konfiguration geeignet. Die Resultate der Konformationsanalyse werden durch Kraftfeldrechnungen unterstützt.

Introduction

The terpenoid carbohydrate models **1** and **2** are valuable tools as enantiopure hydroxyl protecting groups [1], for the separation of racemic alcohols, and for the determination of the enantiomeric purity and the absolute configuration of secondary alcohols [2]. The thermodynamically controlled preferential formation of one diastereoisomer can be explained by a simple conformational analysis of the two possible structures by considering steric and stereoelectronic effects for bulky

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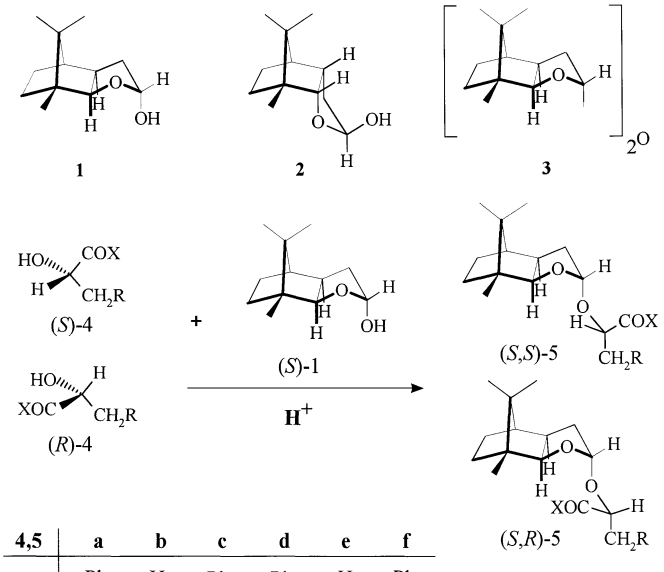
and planar substituents, respectively. This has been described in detail elsewhere [3] and is supported by the solid-state structures of various acetalized alcohols [4].

We now have extended the investigation of the suitability of the title lactol **1** in the acetal formation of functionalized secondary alcohols and examined the reaction of α-hydroxy carboxylic acid derivatives with **1** on a preparative scale. Additionally, a simple procedure for the determination of enantiomeric excess of α-hydroxy acid derivatives by *in situ* acetalization in the NMR tube was elaborated, taking into account their increasing importance in medicinal chemistry [5]. We anticipated only small diastereoselectivities for the carboxylates, these groups being not only stereoelectronically active but also exhibiting the properties of a bulky substituent. However, some evidence has been reported for the participation of this functional group in stereoelectronic interactions [6]. Hence, we acetalized a series of model compounds (**4a–f**; [7]) and determined the enantioselectivity of the reaction by NMR tube experiments at room temperature.

Results and Discussion

The diastereomeric acetals (*S*,*S*)-**5**/(*S*,*R*)-**5a–f** (for convenience, only the chiral descriptors for the anomeric center of the ring system and the lactic acid derivative are given) were formed by acid catalyzed (*p*-toluene sulfonic acid) reaction of racemic **4a–f** with **3** (the easier to handle dimer of **1**) in dichloromethane on a preparative scale and in chloroform-d_1 in the NMR tube. They were isolated by flash chromatography on triethylamine impregnated silica gel in up to 90% yield. Under these reaction conditions, the thermodynamic product ratio is observed [8]. As two of the diastereomeric products did not show a sufficient separation on TLC, the corresponding acetals (*S*,*S*)-**5b–e** were synthesized starting from enantiopure



4,5	a	b	c	d	e	f
R	Ph	H	Ph	Ph	H	Ph
X	OH	OEt	OMe	OBn	NMe_2	NMe_2

Scheme 1

Table 1. Characteristic ^{1}H and ^{13}C NMR signals of the diastereomeric O,O-acetals (*S*,*S*)-**5**/(*S*,*R*)-**5a–f** (in $CDCl_3$; δ in ppm relative to internal *TMS*)

	(*S*,*S*)-**5a**	(*S*,*R*)-**5a**	(*S*,*S*)-**5b**	(*S*,*R*)-**5b**	(*S*,*S*)-**5c**	(*S*,*R*)-**5c**	(*S*,*S*)-**5d**	(*S*,*R*)-**5d**	(*S*,*S*)-**5e**	(*S*,*R*)-**5e**	(*S*,*S*)-**5f**	(*S*,*R*)-**5f**
H-2	5.19	4.95	5.17	5.14	5.15	4.95	5.18	4.97	5.04	5.18	5.02	5.02
H-7a	2.54	3.98	3.87	3.98	2.53	3.88	2.57	3.89	3.89	3.82	2.98	3.75
H*	4.48	4.23	4.34	3.97	4.42	4.08	4.50	4.17	4.60	4.27	4.66	4.46
C-2			103.8	105.9	102.7	106.7	102.9	106.6	103.4	104.5	102.3	105.7
C-7a			91.4	91.4	90.6	91.6	90.7	91.5	91.4	91.6	90.9	91.3
C*			69.3	72.6	73.3	77.9	73.4	77.8	68.2	69.3	71.9	74.3
C=O			173.5	174.0	172.8	173.4	172.3	172.7	172.7	172.8	171.7	172.1
$\Delta C_{C=O}$[a]			−2.2	−1.7	−1.7	−1.1	−1.6	−1.2	−2.0	−2.1	−2.0	−1.6
C_b			19.0	18.4	39.1	39.1	39.1	39.1	18.5	17.3	39.1	39.0
ΔC_bb			−1.3	−1.9	−1.5	−1.5	−1.3	−1.3	−2.1	−3.3	−2.9	−3.0
$\Delta\delta C^C$			+0.9	−0.2	+0.2	−0.4	+0.3	−0.1	−0.1	−1.2	−0.9	−1.4
Selectivity[d]	1.15	: 1	1.0	: 1	1.40	: 1	1.25	: 1	1.0	: 1	1.25	: 1

[a] $\Delta C_{C=O} = \delta_{C=O}$ ((*S*,*S*)-**5**/(*S*,*R*)-**5a–e**) − $\delta_{C=O}$(**4a–e**); [b] $\Delta C_b = \delta C_b$((*S*,*S*)-**5**/(*S*,*R*)-**5a–e**) − δC_b(**4a–e**); [c] $\Delta\delta C = \Delta C_b - \Delta C_{C=O}$; [d] estimated error: ±0.03

(*S*)-**4b–e** for the unambiguous assignment of the NMR data. The characteristic signals of the diastereomers are summarized in Table 1.

NMR spectroscopy of lactic ester derivatives

The chemical shifts of the H-2 protons (acetal position) follow the general trend observed earlier [2–4], *i.e.* those of the ester derivatives (*S*,*S*)-**5a–d** are shifted downfield compared to those of (*S*,*R*)-**5a–d** which are effected by the deshielding ester carbonyl group. On the other hand, the H-7a protons in the *endo*-bridgehead position are shifted to rather high field in the phenyllactic acid derivatives (*S*,*S*)-**5a**,**c**,**d** (up to 1.5 ppm). This can be understood assuming the phenyl group being located below the benzofuran ring system in the (*S*,*S*) forms. This preferred conformation of the (*S*,*S*) type acetals is supported by force field calculations [9] of the diastereomeric acetals (*S*,*S*)-**5**/(*S*,*R*)-**5d**; the most stable conformations are shown in Fig. 1. For (*S*,*S*)-**5d**, an interatomic distance of about 2.9 Å for the 7a-proton and the phenyl moiety is found. Additionally, the proton in the 6a-(*endo*)-position of the 4,7-methano-benzofuran framework is shielded by the phenyl ring and resonates at 0.5–0.8 ppm in (*S*,*S*)-**5a**,**c**,**d**. Interestingly, the benzyl ester group

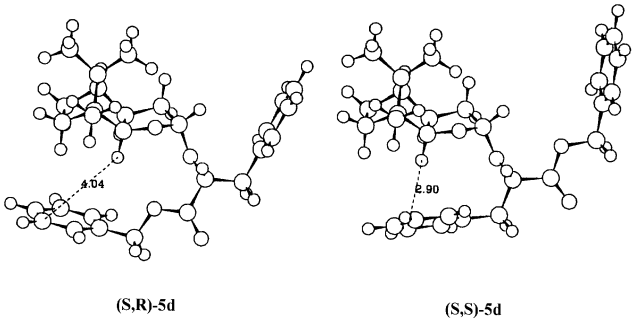


Fig. 1. Most stable conformations of the O,O-acetals (*S*,*S*)-**5d**/(*S*,*R*)-**5d** (distance in Å)

does not show any influence on the chemical shifts of the characteristic protons, as can be clearly seen from the nearly identical shifts of the diastereomeric methyl ester acetals (*S*,*S*)-**5**/(*S*,*R*)-**5c**. In all examples as well as in all O,O-acetals reported earlier [4] the resonances of the protons at the chiral center of the lactic acid derivatives (*S*,*S*)-**5** are found downfield by 0.2 to 0.4 ppm due to *syn*-periplanarity with the endocyclic oxygen. This unique feature can be employed for the assignment of the absolute configuration of functionalized secondary alcohols. However, the racemic alcohol must be available as well, and the procedure is handicapped by the sometimes complex splitting pattern of the proton at the chiral center.

The carbon shifts of the O,O-acetals listed in Table 1 allow an unambiguous assignment of the absolute configuration of the α-hydroxy acid derivative. In all cases, the acetal carbon atom of (*S*,*S*)-**5b–d** is found 2.1 to 4.0 ppm upfield from the corresponding resonances of (*S*,*R*)-**5b–d**, a tendency which can be observed for the chiral carbon atom of the lactic acid derivative ($\Delta\delta = 1.1$–4.0 ppm) as well. This upfield shift is – although to a smaller degree – consistently observed for the carbon atoms at the 7a-ring position and for the carbonyl carbon atom. We applied one of the methods described earlier for the determination of the absolute configuration of secondary alcohols with two alkyl groups of different size [4e] by looking at the carbon shift differences in γ-position to the chiral center of the acetal (C-2) and comparing these numbers with the carbon resonances of the starting alcohols **4** ($\Delta\delta$C in Table 1). Correct values were obtained for the ester acetals (*S*,*S*)-**5**/(*S*,*R*)-**5b–d** (a positive sign $\Delta\delta$C implies that the chiral centers of the acetal carbon and the lactic acid derivative have the same descriptor; if a negative sign is obtained, different descriptors are deduced.

NMR spectroscopy of lactamide derivatives

The general features observed in the ^{1}H NMR spectra of ester acetals (*S*,*S*)-**5**/(*S*,*R*)-**5a–d** are found in the spectra of amides (*S*,*S*)-**5**/(*S*,*R*)-**5e**, **f** as well, with only one exception: the H-2 protons do not show a downfield shift in the (*S*,*S*) configurated diastereoisomers (*S*,*S*)-**5**. There is, however, no evidence at all that the amide group adopts a different conformation. The carbon shifts show nearly identical sets of signals for the diastereomeric acetals when compared to the ester acetals as indicated by the C*-H protons with a downfield shift for (*S*,*S*)-**5e** and (*S*,*S*)-**5f**, too. It might thus be concluded that the amide group does not exhibit the same deshielding effects as the ester carbonyl group. It is known that the amide group lacks a general and uniform anisotropic effect [10].

When applying the calculation described above for the carbon signals in the determination of the absolute configuration, it is clearly noticable that this procedure does not work for the amide acetals (*S*,*S*)-**5**/(*S*,*R*)-**5e** and (*S*,*S*)-**5**/(*S*,*R*)-**5f**. Obviously, the differences between the carbon shifts of C_b in the α-hydroxy amide and its acetalized form are too large; therefore, negative values are calculated for $\Delta\delta$C in all cases.

Selectivities

Selectivities were determined in the NMR tube experiments by reaction of **3** under acid catalysis with 2.2 to 2.5 equivalents of the racemic acid derivative **4a–f** at

room temperature and subsequent integration of the H-2 doublets of the diastereomeric acetals. The values given in Table 1 are averages of up to 4 independent experiments under the conditions described in the experimental part. No measurable effect could be observed when slightly changing **4a**–**f**:**3** ratios. Neither were the selectivities in any way influenced by the amounts of **4** and **1** in the reaction mixture, nor did they change with time when the (*S*,*S*)-**5**:(*S*,*R*)-**5** ratio was determined repeatedly; in other words, no kineticially controlled product ratio was observed. With all phenyllactic acid derivatives, a very modest preference for the (*S*,*S*) type acetals could be found.

The nonbonding interactions between the methyl group and the 4,7-methanobenzofuran ring system in the lactic acid derivatives (*S*,*S*)-**5**/(*S*,*R*)-**5b** and (*S*,*S*)-**5**/(*S*,*R*)-**5e** are obviously too small to have an observable effect on the different stabilities of the diastereomeric acetals. Thus, when taking all selectivities observed for functionalized secondary alcohols with methyl groups as bulky substituents into consideration [4], the following order of *exo*-anomeric stabilization of stereoelectronically active substituents can be established: $Ph \approx C{\equiv}CH > C{\equiv}N > C\text{-}O > C\text{-}S \gg CO_2R \geqslant CONR_2$.

Conclusions

The results given above demonstrate the feasibility of assigning the absolute configuration of lactic ester derivatives, especially by employing ^{13}C NMR spectroscopy, even in cases when only one enantiomer is available. In N,N-disubstituted lactamide derivatives, this assignment requires the racemic α-hydroxy lactamide derivative for comparison as well. The small diastereoselectivities observed indicate a rather small participation of carboxylic acid derivatives in n_{oxygen}-$\sigma^*_{C=O}$ interactions.

Experimental

General

300 MHz ^1H NMR spectra were recorded on a Bruker ARX 300 (VTU, 300 K), ^{13}C NMR spectra (50.3 MHz) on a Bruker AC 200 spectrometer at ambient temperature. Optical rotations were measured on a Perkin Elmer 141 Polarimeter. Elemental analyses were carried out by the microelemental analysis service of the chemistry department of the University of Frankfurt. TLC was performed on commercially available plates (Merck, silica gel 60); visualization of the compounds was performed with either UV light or oxidation with a solution of $(NH_4)_6Mo_7O_{24}$ and $Ce(SO_4)_2$ in diluted sulfuric acid and subsequent heating. The TLC plates were deactivated with a solution of petrolether/ether/triethylamine (10/3/1, v/v) prior to use. Flash chromatography was performed on commercial silica gel (Merck 60, 0.040–0.063); column fillings were performed with the above solvent mixture and reactivated with the solvent employed for separation.

Starting materials

(*S*)- and *rac*-**4a** were conveniently prepared by treatment of (*S*)- and *rac*-phenyl alanine with nitric acid [11]; (*S*)-**4b** was commercially available (Fluka); *rac*-**4b** was obtained by esterification of racemic lactic acid with ethanol [12]; (*S*)- and *rac*-**4c** and **4d** were obtained from the sodium salts of

(*S*)- and *rac*-**4a** by reaction with methyl iodide and benzyl bromide, respectively [11, 13]; (*S*)- and *rac*-**4e** were obtained by treatment of the ethyl esters with dimethylamine [14], (*S*)- and *rac*-**4f** by reaction of **4c** with N,N-dimethylamine [15].

*General procedure for the synthesis of (S,S)-***5**/(S,R)-**5b–e**

200 mg (0.53 mmol) of (2*S*-(2α(2R^*,3a′S^*,4′S^*,7′S^*,7a′S^*),3aα,4β,7β,7aα))-2,2′-oxy*bis*(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran) (**3**) and 2.5 mmol of either (*S*)- or *rac*-**4b–e** were stirred with 3–5 mg of *p*-toluenesulfonic acid and *ca.* 1 g of molecular sieve (4 Å) in 10 ml of dichloromethane for 3 h at room temperature. Then, about 0.3 ml of triethylamine were added to the reaction mixture, the solution was filtered, and the solvents were evaporated *in vacuo*. The remainder was immediately subjected to flash chromatography employing a column of 30 cm length and 3 cm internal diameter filled with *ca.* 50 g of silica. The reaction of (*S*)- and *rac*-**4a** was performed on the NMR tube scale. In the cases of acetals (*S,S*)-**5**/(*S,R*)-**5b** and (*S,S*)-**5**/(*S,R*)-**5d**, no separation was achieved under the employed conditions, and the NMR data were evaluated from the diastereomeric mixtures. Experimental setup for the NMR tube experiments: 5.0 mg (13 mmol) of **3** and 66 mmol of *rac*-**4a–d** were dissolved in 0.5 ml of chloroform-d_1, and a very small crystal of *p*-toluenesulfonic acid was added.

Ethyl (2S-(2α*(*R^**),3a*α*,4*β*,7*β*,7a*α*))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-propanoate ((S,S)-***5b***)*

From (*S*)-**4b**; 286 mg (85%); colorless liquid; $R_f = 0.64$ (*PE*:*E* = 5:1); $\alpha_D^{22} = -123.5$ ($c = 0.179$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): 6 = 5.17 (d, 1H, $^3J = 4.9$ Hz, H-2), 4.34 (q, 1H, $^3J = 7.1$ Hz, C*-H), 4.17 (AB-part of an ABX_3-system, 2H, OEt), 3.87 (d, 1H, $^3J = 7.4$ Hz, H-7a), 1.38 (d, 3H, $^3J = 7.0$ Hz, C*-CH^3), 1.28 (t, 3H, $^3J = 7.1$ Hz, OEt), 1.30–2.30 (m, 8H, H-3, H-3a, H-4, H-5,H-6), 0.78/0.95/0.98 (3×s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.5$ (C=O), 103.8 (C-2), 91.5 (C-7a), 69.3 (C*), 60.7 (OEt), 48.4 (C-4), 47.6 (C-7), 47.0 (C-8), 45.8 (C-3a), 38.6 (C-3), 32.4 (C-6), 28.9 (C-5), 22.9/20.4/11.6 (ring-CH_3), 19.0 (C*-CH_3), 14.2 (OEt) ppm; $C_{17}H_{28}O_4$ (296.4); calc.: C 68.89, H 9.52; found: C 68.63, H 9.31.

Ethyl (2S-(2α*(*S^**),3a*α*,4*β*,7*β*,7a*α*))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-propanoate ((S,R)-***5b***)*

$R_f = 0.64$ (*PE*:*E* = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.14$ (d, 1H, $^3J = 4.9$ Hz, H-2), 3.98 (q, 1H, $^3J = 7.1$ Hz, C*-H), 4.17 (AB-part of an ABX_3-system, 2H, OEt), 3.97 (d, 1H, $^3J = 7.4$ Hz, H-7a), 1.34 (d, 3H, $^3J = 6.7$ Hz, C*-CH_3), 1.29 (t, 3H, $^3J = 7.0$ Hz, OEt) 1.30–2.30 (m, 8H, H-3, H-3a, H-4, H-5, H-6), 0.76/0.90/0.96 (3×s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 174.0$ (C=O), 105.9 (C-2), 91.4 (C-7a), 72.5 (C*), 60.5 (OEt), 48.6 (C-4), 47.5 (C-7), 47.0 (C-8), 45.8 (C-3a), 38.8 (C-3), 32.3 (C-6), 28.8 (C-5), 22.8/20.4/11.5 (ring-CH_3), 18.4 (C*-CH_3), 14.2 (OEt) ppm.

Methyl (2S-2α*(*R^**),3a*α*,4*β*,7*β*,7a*α*))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl propanoate ((S,S)-***5c***)*

From (*S*)-**4c**; 302 mg (79%); colorless liquid; $R_f = 0.47$ (*PE*:*E* = 5:1); $\alpha_D^{22} = -97.8$ ($c = 0.300$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.15$–7.30 (m, 5H, Phenyl-H), 5.15 (d, 1H, $^3J = 4.3$ Hz, H-2), 4.42 (X-part of an ABX system, 1H, $^3J = 3.6$, 10.2 Hz, C*-H), 3.73 (s, 3H, OCH_3), 3.13/2.85 (AB-part of an ABX system, 2H, $^3J = 3.6$, 10.2 Hz, $^2J = 13.6$ Hz, CH_2Ph), 2.53 (d, 1H, $^3J = 7.5$ Hz, H-7a), 0.90–2.20 (m, 7H, H-3, H-3a, H-4, H-5, H-6b), 0.71/0.77/0.85 (3 × s, 9H, ring-CH_3), 0.60–0.80 (m, 1H, 6aa) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.8$ (C=O), 137.9 (C-Ph(1)), 129.7

(C-Ph(3)), 128.1 (C-Ph(2)), 126.4 (C-Ph(4)), 90.6 (C-7a), 73.3 (C*), 51.9 (OCH_3), 48.2 (C-4), 47.5 (C-7), 46.9 (C-8), 45.6 (C-3a), 39.1 (CH_2Ph), 38.6 (C-3), 32.1 (C-6), 28.8 (C-5), 22.8/20.4/11.4 (ring-CH_3) ppm; $C_{22}H_{30}O_4$ (358.5); calc.: C 73.71, H 8.44; found: C 74.01, H 8.69.

Methyl (2S-2α(S),3aα,4β,7β,7aα))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl propanoate ((S,R)-***5c**

Colorless liquid; $R_f = 0.51$ (*PE*:*E* = 5:1); $\alpha_D^{22} = -74.4$ ($c = 0.882$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.15$–7.30 (m, 5H, Phenyl-H), 4.95 (d, 1H, $^3J = 5.1$ Hz, H-2), 4.08 (X-part of an ABX system, 1H, $^3J = 6.3$, 7.8 Hz, C*-H), 3.88 (d, 1H, $^3J = 7.6$ Hz, H-7a), 3.67 (s, 3H, OCH_3), 2.94 (m, AB-part of an ABX system, 2H, CH_2Ph), 1.30–2.30 (m, 8H, H-3, H-3a, H-4, H-5, H-6), 0.76/0.85/0.89 (3 × s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.4$ (C=O), 137.0 (C-Ph(1)), 129.4 (C-Ph(3)), 128.3 (C-Ph(2)), 126.6 (C-Ph(4)), 106.7 (C-2), 91.6 (C-7a), 77.9 (C*) 51.7 (OCH_3) 48.6 (C-4), 47.5 (C-7), 46.8 (C-8), 45.7 (C-3a), 39.1 ($PhCH_2$), 38.4 (C-3), 32.3 (C-6), 28.9 (C-5), 22.8/20.4/11.3 (ring-CH_3) ppm; $C_{22}H_{30}O_4$ (358.5); calc.: C 73.71, H 8.44; found: C 74.00, H 8.72.

Phenylmethyl (2S-2α(R),3aα,4β,7β,7aα))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl propanoate ((S,S)-***5d**)

From (*S*)-**4d**; 417 mg (90%); Colorless liquid; $R_f = 0.57$ (*PE*:*E* = 5:1), $\alpha_D^{22} = -113.8$ (c = 0.322 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.10$–7.45 (m, 10H, Phenyl-H), 5.22/5.17 (ABq, 2H, $^2J = 12.3$ Hz, OCH_2), 5.20 (d, 1H, $^3J \approx 4.7$ Hz, H-2), 4.50 (X-part of an ABX system, 1H, $^3J = 3.8$, 10.1 Hz, C*-H), 2.90/3.16 (AB-part of an ABX system, 2H, $^3J = 3.8$, 10.1 Hz, $^2J = 13.6$ Hz, CH_2Ph), 2.59 (d, 1H, $^3J = 7.1$ Hz, H-7a), 0.80–2.20 (m, 7H, H-3, H-3a, H-4, H-5, H-6b), 075/0.81/0.88 (3 × s, 9H, ring-CH_3), 0.60–0.75 (m, 1H, 6aa) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.3$ (C=O), 137.9 (C-Ph)(1)), 135.7 (C-Ph)(1)), 129.0 (C-Ph(3)), 128.6 (C-Ph(3)), 128.4 (C-Ph(2)), 128.4 (C-Ph(2)), 128.2 (C-Ph(4)), 126.5 (C-Ph(4)), 102.9 (C-2), 90.7 (C-7a), 73.4 (C*), 66.6 (OCH_2), 48.2 (C-4), 47.1 (C-7), 46.9 (C-8), 45.7 (C-3a), 39.1 (CH_2Ph), 38.5 (C-3), 32.2(C-6), 28.8 (C-5), 22.8/20.5/11.4 (ring-CH_3) ppm; $C_{28}H_{34}O_4$ (434.6); calc.: C 77.39, H 7.89; found: C 77.18, H 7.94.

Phenylmethyl (2S-2α(S),3aα,4β,7β,7aα))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl propanate ((S,R)-***5d**)

$R_f = 0.57$ (*PE*:*E* = 5:1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.10$–7.40 (m, 10H, Phenyl-H), 5.12 (s, 2H, OCH_2), 4.97 (d, 1H, $^3J = 7.6$ Hz, H-2), 4.17 (t, 1H, $^3J \approx 7.0$ Hz, C*-H), 3.91 (d, 1H, $^3J = 7.6$ Hz, H-7a), 2.90 (d, 2H, $^3J = 7.0$ Hz, CH_2Ph), 0.80–2.50 (8H, H-3, H-3a, H-4, H-5, H-6), 0.79/0.88/0.90 (3×s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.7$ (C = O), 137.8 (C-Ph(1)), 136.9 (C-Ph(1)), 129.7 (C-Ph(3)), 129.4 (C-Ph(3)), 128.3 (C-Ph(2)), 128.1 (C-Ph(2)), 128.0 (C-Ph(4)), 126.6 (C-Ph(4)), 106.6 (C-2), 91.5 (C-7a), 77.8 (C*), 66.4 (OCH_2), 48.6 (C-4), 47.5 (C-7), 46.9 (C-8), 45.6 (C-3a), 39.1 (CH_2Ph), 38.6 (C-3), 32.2 (C-6) 28.8 (C-3), 22.8/20.4/11.4 (ring-CH_3) ppm.

(2S-(2α(R),3aα,4β,7β,7aα))-N,N-Dimethyl-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)propanamide ((S,S)-***5e**)

94 mg (30%) from *rac*-**4e**; colorless liquid; $R_f = 0.31$ (Et_2O): $\alpha_D^{22} = -157.1$ ($c = 0.271$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.05$ (d, 1H, $^3J = 5.0$ Hz, H-2), 4.60 (q, 1H, $^3J = 6.8$ Hz, C*-H), 3.89 (d, 1H, $^3J = 7.4$ Hz, H-7a), 2.98/3.08 (2×s, 6H, N-CH_3), 1.40–2.20 (m, 8H, H-3, H-3a, H-4, H-5, H-6), 1.35 (d, 3H, $^3J = 6.9$ Hz, C*-CH_3), 0.80/0.94/1.00 (3 × s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.3$ (C=O), 103.4 (C-2), 91.4 (C-7a), 68.2 (C*), 48.4 (C-4), 47.6 (C-7),

464.9 (C-8), 45.9 (C-3a) 38.6 (C-3), 35.9/36.8 (N-CH_3), 32.4 (C-6), 28.9 (C-5), 22.8/20.4/11.6 (ring-CH_3), 18.5 (C^*-CH_3) ppm; $C_{17}H_{29}O_3N$ (295.4); calc.: C 69.12, H 9.89, N 4.74; found: C 69.09, H 10.02, N 4.95.

(2S-2α(S),3aα,4β,7β,7aα))-N,N-Dimethyl-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)propanamide ((S,R)-***5e**

85 mg (27%) from *rac-***4e**; colorless liquid; $R_f = 0.37$ (Et_2O); $\alpha_D^{22} = -88.8$ ($c = 0.376$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.18$ (d, 1H, $^3J = 4.9$ Hz, H-2), 3.82 (q, 1H, $^3J = 6.5$ Hz, C^*-H), 3.82 (d, 1H, $^3J = 7.6$ Hz, H-7a), 2.95/3.07 (2×s, 6H, N-CH_3), 1.40–2.20 (m, 8H, H-3, H-3a, H-4, H-5, H-6), 1.33 (d, 3H, $^3J = 6.5$ Hz, C^*-CH_3), 0.79/0.93/0.99 (3 × s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.8$ (C=O), 104.5 (C-2), 91.6 (C-7a), 69.3 (C^*), 48.6 (C-4), 47.6 (C-7), 46.9 (C-8), 45.9 (C-3a), 38.7 (C-3), 36.0/36.9 (N-CH_3), 32.4 (C-6), 28.9 (C-5), 22.8/20.4/11.5 (ring-CH_3), 17.3 (C^*-CH_3) ppm; $C_{17}H_{29}O_3N$ (295.4); calc.: C 69.12, H 9.89, N 4.74; found: C 68.97, H 10.06, N 4.94.

N,N-Dimethyl (2S-(2α(R),3aα,4β,7β,7aα))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl-propanamide ((S,S)-***5f**)

162 mg (41%) from *rac-***4f**; colorless liquid; $R_f = 0.40$ (Et_2O); $\alpha_D^{22} = -98.3$ ($c = 1.230$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.15$–7.50 (m, 5H, Phenyl-H), 5.02 (d, 1H, $^3J = 4.7$ Hz, H-2), 4.66 (t, 1H, $^3J = 7.1$ Hz, C^*-H), 2.98 (d, 1H, $^3J = 6.7$ Hz, H-7a), 2.86–2.96 (m, 2H, CH_2Ph), 2.91/2.92 (2 × s, 6H, N-CH_3), 1.30–2.20 (m, 7H, H-3, H-3a, H-4, H-5, H-6b), 0.87/0.83/0.73 (3 × s, 9H, ring-CH_3), 0.60–0.80 (m, 1H, 6a) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 171.7$ (C=O), 137.9 (C-Ph(1)), 129.6 (C-Ph(3)), 128.1 (C-Ph(2)), 126.5 (C-Ph(4)), 102.3 (C-2), 90.9 (C-7a), 71.9 (C^*), 48.2 (C-4), 47.2 (C-7), 46.9 (C-8), 45.8 (C-3a), 39.1 (CH_2Ph), 38.5/36.8 (N-CH_3), 32.3 (C-6), 28.8 (C-5), 22.8/20.5/11.4 (ring-CH_3) ppm; $C_{23}H_{33}O_3N$ (371.5); calc.: C 74.36, H 8.94, N 3.77; found: C 74.59, H 8.76, N 3.65.

N,N-Dimethyl (2S-(2α(S),3aα,4β,7β,7aα))-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yloxy)-3-phenyl-propanamide ((S,R)-***5f**)

115 mg (29%) from *rac-***4f**; colorless liquid; $R_f = 0.57$ (Et_2O); $\alpha_D^{22} = -111.7$ ($c = 0.606$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.16$–7.26 (m, 5H, Phenyl-H), 5.05 (d, 1H, $^3J = 5.0$ Hz, H-2), 4.46 (t, 1H, $^3J = 7.1$ Hz, C^*-H), 3.75 (d, 1H, $^3J = 7.5$ Hz, H-7a), 2.97 (AB-part of an ABX system, 2H, $^3J = 7.1$ Hz, $^2J = 13.0$ Hz, CH_2Ph), 2.87/2.83 (2 × s, 6H, N-CH_3), 0.90–2.30 (m, 8H, H-3, H-3a, H-4, H-5, H-6), 0.87/0.86/0.75 (3 × s, 9H, ring-CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 172.1$ (C=O), 137.3 (C-Ph(1)), 129.4 (C-Ph(3)), 128.1 (C-Ph(2)), 126.4 (C-Ph(4)), 105.7 (C-2), 91.2 (C-7a), 74.3 (C^*), 48.6 (C-4), 47.4 (C-7), 46.9 (C-8), 45.7 (C-3a), 39.0 (CH_2Ph), 36.7/35.8 (N-CH_3), 32.1 (C-6), 28.7 (C-5), 22.8/20.5/11.4 (ring-CH_3) ppm; $C_{23}H_{33}O_3N$ (371.5); calc.: C 74.36, H 8.94, N 3.77; found: C 74.07, H 9.20, N 3.78.

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