Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4811–4830

TETRAHEDRON: *ASYMMETRY*

[1,2]-Wittig rearrangement of acetals. Part 1: Investigation about structural requirements

Peter Gärtner,[a,*] Martin F. Letschnig,[a] Max Knollmüller [a] and Horst Völlenkle [b]

[a] *Institute of Organic Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*

[b] *Institute of Mineralogy, Crystallography and Structural Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*

Received 10 November 1999; accepted 6 December 1999

Abstract

Acetals of different alcohols with (+)-camphor derived enantiomerically pure 7,8,8-trimethyl-4,7-methanobenzofuran-2-ol were prepared and subjected to conditions favorable for a [1,2]-Wittig rearrangement. Results with regard to conversion, yield and stereochemical course depending on the structure of the starting material are discussed. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The [1,2]-Wittig rearrangement[1] is a classic class of carbanion rearrangement which has been reviewed[2] extensively, and most recently on the occasion of Wittig′s 100th birthday anniversary.[3] Although this lithium base induced rearrangement has been known for more than 50 years only the [2,3]-Wittig sigmatropic version of allyl ethers enjoys wide synthetic application.[2c,4] The synthetic utilization of the [1,2]-shift usually suffers from low yields and a limited range of substrates.[5] However, from a stereochemical point of view the reaction is quite interesting, because, despite the fact that it is nowadays recognized that the reaction proceeds via a radical dissociation–recombination process,[1–3] the stereogenicities of the two proradical centers are retained to an appreciable extent, i.e. retention of configuration at the migrating carbon and inversion at the lithium bearing terminus under non-chelation or retention under chelation controlled conditions.[2,3,6] With regard to structure–reactivity relationships it has been established that at either the carbanion terminus or the migrating group a radical-stabilizing factor is required.[6f] Thus, it was envisaged that acetal systems such as O-glycosides would easily undergo the [1,2]-Wittig rearrangement,[7] providing an easy access to C-glycosides.

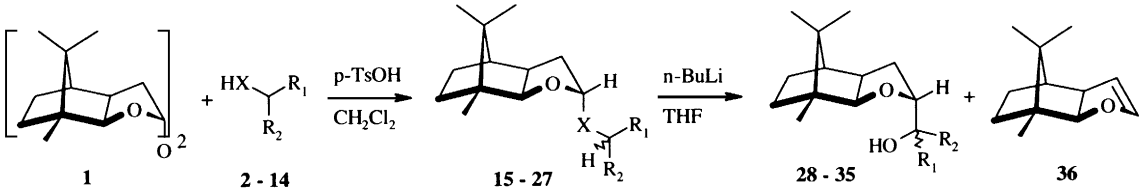
* Corresponding author. Fax: +43-1-58801-154-92; e-mail: pgaertne@mail.zserv.tuwien.ac.at

0957-4166/99/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(99)00562-5

During our own investigations on the application of acetals as chiral ligands for organometallics we had observed such rearrangements.[8] Being interested in the compounds produced by this reaction as new ligands and because at this time little was known about acetals in [1,2]-Wittig rearrangements — in the meantime some excellent work[2d,3,9] by other groups has been performed as well — we started to investigate this reaction in more detail. This first part deals with the influence of the structure of the acetal on the conversion, yield and stereochemical course.

2. Results and discussion

The acetals **15**–**27** which were selected as starting materials for the [1,2]-Wittig rearrangement were synthesized from anhydrolactol **1** and either alcohols **2**–**13** or thiol **14** following the standard acid catalyzed procedure (Scheme 1, Table 1).[10]

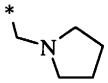
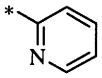
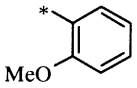
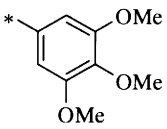
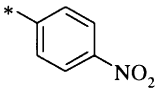


Scheme 1. Synthesis and [1,2]-Wittig rearrangement of the acetals **15**–**27**

The selection of **2**–**14** was based on considerations aimed at achieving a high divergence in the aglycon part of the molecule. Thus, with compounds **15**–**22** we wanted to see what happens if the space required by one of the ligands at the lithium bearing terminus increases and how this is modified by a second aryl-ligand **21**, with compounds **23**–**26** we wanted to check what the influence of the electronic properties of the aryl-ligand itself is, acetals **22**–**25** should give us some insight into the effect of additional centers for complex formation, and finally with **27** we wanted to look whether the rearrangement can be carried out with O,S-acetals as well. For compounds **16**–**20** and **22** which were formed as a mixture of two diastereomers in a ratio of about 2:1 according to the expected 'enantiomer-selectivity'[11] the mixtures obtained after chromatography were used in this study. The configuration of the major diastereoisomer was determined from characteristic shift differences in the ^{1}H NMR spectra compared with the minor isomer according to the b-pl-H rule.[11,12] Results on the influence of the absolute configuration of the aglycon part will be published soon.

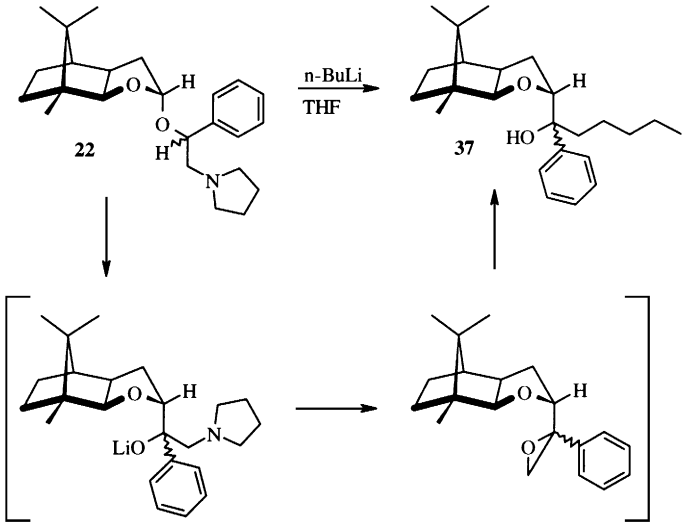
For the sake of comparability the [1,2]-Wittig rearrangement of all acetals **15**–**27** was carried out under standardized conditions which have turned out to be the best in most of the cases. A systematic investigation with regard to different reaction conditions will be the main task of the next paper in this series. Thus, a solution of each of the acetals **15**–**27** in tetrahydrofuran was treated with *n*-butyllithium (3 equiv.) at room temperature for 3 h to give the rearranged benzylalcohols **28**–**35** as a mixture of two diastereomers (de=12–65%). Diastereomeric ratios were determined by chromatography or by comparison of integrals in the ^{1}H NMR spectra. With the other acetals **19**, **20**, **22**, **26**, **27** no rearranged product could be isolated, but for different reasons. The highly hindered acetals **19** and **20** did not react at all, probably due to steric congestions in the course of the rearrangement. However, the starting material was recovered quantitatively. The β-pyrrolidinyl substituted acetal **22** did not give the expected β-pyrrolidinyl substituted benzylalcohol but instead furnished alcohol **37** which bore an alkyl group as the sole substituent. This was rationalized by the pathway outlined in Scheme 2 where acetal **22** was deprotonated and rearranged as usual. However, in the following reaction cascade the alkoxide

Table 1
Summary of the [1,2]-Wittig rearrangement of the acetals **15–27**

Compound	R_1	R_2	X	de [%] of 16 - 20, 22[a]	Yield of 28 - 35 [%]	de [%] of 28 - 35[a]	Yield of 36 [%]	Rec. 15 - 27 [%]
2, 15, 28	Ph	H	O	-	55	24 (S)	21	0
3, 16, 29	Ph	Me	O	14 (S)	26	50 (S)	3	64
4, 17, 30	Ph	Et	O	37 (S)	6	12 (S)	0	88
5, 18, 31	Ph	n-Bu	O	67 (S)	4	20 (S)	0	95
6, 19	Ph	i-Pr	O	67 (S)	-	-	0	100
7, 20	Ph	t-Bu	O	-	-	-	0	100
8, 21, 32	Ph	Ph	O	-	41	-	0	0
9, 22	Ph		O	16 (R)	-[b]	-	15	12
10, 23, 33		H	O	-	12	65 (S)[c]	14	0
11, 24, 34		H	O	-	67	34 (R)	22	2
12, 25, 35		H	O	-	42	28 (S)[c]	25	13
13, 26		H	O	-	-	-	-	0
14, 27	Ph	H	S	-	-	-	2	30

[a] In parentheses the absolute configuration of the chiral center in question is given for the diastereomer in excess. [b] Rearranged product was further converted (vide infra (Scheme 2)). [c] De value was not determined by chromatography but by comparison of the integrals in the ^1H NMR spectra.

replaced the pyrrolidine in a nucleophilic substitution to afford an epoxide and eventually, this epoxide was attacked by butyllithium to yield the lithium salt of **37**.



Scheme 2. Reaction pathway for the rearrangement of the acetal **22**

Compound **26** in which the benzylic protons should be more acidic due to the nitro group on the aromatic ring was converted completely. In the complex reaction mixture we were not able to detect any trace of the anticipated rearrangement product. With thioacetal **27**, 70% of the starting material was not recovered after treatment with butyllithium. However, the only reaction product which could be isolated was a small amount of enol ether **36**. This observation may be attributed to the fact that the desulfurizative lithiation[6c] is faster than the Wittig rearrangement which was already found to be retarded when thio ethers were used as starting materials.[4a]

As far as the stereochemistry of the former acetal center is concerned, it is assumed that the reaction proceeds as usual with retention of configuration[2d,3,9] although there was one example[9] reported recently which violates this principle. This was confirmed in our study by analyzing ^{13}C NMR data for those carbons of the methanobenzofuran system which should be influenced most, i.e. C-3a and C-7a (Table 2).

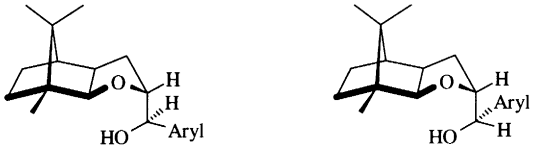
The interpretation of this data is not easy, because in the region where one would expect the signal for C-3a there appears a further doublet which belongs to C-4. Thus, data for this carbon were also included in the analysis. Anyway, as can be seen from Table 2 the data is consistent to a large extent, especially for the rearranged products bearing an additional alkyl- or aryl-ligand at the newly formed alcohol center (**29**–**32**, **37**) and it is therefore highly probable that all rearranged products have the same configuration at C-2. With compounds **28**, **33**–**35** the shifts for C-3a and C-7a of isomer **A** are in satisfactory agreement, but for the diastereomer **B** these signals are shifted upfield near to the range in which they were usually observed for the starting acetals. This may be due to the fact that the hydrogen which is bound to the alcohol carbon in these compounds allows conformations which are not populated if there is an alkyl- or aryl-ligand located in this position.

The relative configuration of the newly formed alcohol center of the major diastereomer was determined by comparing coupling constants in the ^{1}H NMR spectra and by characteristic shift differences in the ^{13}C NMR spectra which should be a result of the γ-effect. It is well known[13] that in β-alkoxy alcohols in which no additional functional group for hydrogen bond formation exists the vicinal coupling constant between the hydrogen at the alcohol carbon and the hydrogen at the alkoxy center is bigger in

Table 2
Comparison of ^{13}C NMR data for C-3a and C-7a of the methanobenzofuran system of the rearranged products **28–35**, **37** (2 stereoisomeric alcohols A and B) with the corresponding data of the starting materials **15–27** (for acetals of secondary alcohols 2 stereoisomers)

Compound	$\delta_{C\text{-}3a}$ [ppm] A / B	$\delta_{C\text{-}4}$ [ppm] A / B	$\delta_{C\text{-}7a}$ [ppm] A / B	Compound	$\delta_{C\text{-}3a}$ [ppm]	$\delta_{C\text{-}4}$ [ppm]	$\delta_{C\text{-}7a}$ [ppm]
28	47.3 / 49.2	48.5 / 48.6	90.8 / 94.2	**15**	46.0	48.4	91.2
29	49.0 / 49.3	48.1 / 48.6	94.1 / 94.7	**16**	46.1 / 46.0	48.4/48.5	91.0 / 91.0
30	49.4 / 49.3	48.4 / 48.7	94.5 / 94.7	**17**	45.9 / 46.1	48.4	91.0 / 91.1
31	49.4 / 49.3	48.4 / 48.6	94.5 / 94.8	**18**	45.9 / 46.1	48.3	91.0 / 91.1
32	49.4	48.7	95.0	**19**	45.9 / 46.1	48.4	91.0 / 91.1
33	47.7 / 49.0	48.9 / 48.4	92.2 / 93.3	**20**	46.2 / 46.1	48.6 / 48.8	91.2 / 91.2
34	47.9 / 49.2	48.9 / 48.7	91.1 / 93.8	**21**	46.0	48.5	91.3
35	47.6 / 49.2	48.9 / 48.6	91.2 / 94.1	**22**	45.9 / 46.0	48.4	91.0 / 91.2
37	49.4 / 49.3	48.4 / 48.6	94.5 / 94.7	**23**	45.5	48.1	91.0
				24	46.0	48.5	91.1
				25	46.0	48.5	91.3
				26	45.8	48.4	91.5
				27	47.0	48.4	84.2

the *syn*- than in the corresponding *anti*-isomer. Thus, we analyzed this coupling constant for the *syn*- and *anti*-isomers of **28**, **33–35** (Fig. 1, Table 3).



syn
28A, 33A - 35A

anti
28B, 33B - 35B

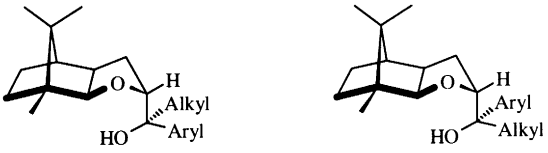
Fig. 1. *syn*- and *anti*-configuration of rearranged products **28**, **33–35**

As can be seen in Table 3 differences in coupling constants were significant and therefore, we deduced the relative configurations given. To our surprise in one case **34** the major isomer had a bigger coupling constant which would indicate that this is of the *syn*-form **34A**. For all other products this coupling constant was smaller and thus, the compound should have predominantly *anti*-configuration. However, since some of the rearranged products had no hydrogen at the newly formed asymmetric carbon, we proceeded to analyze the ^{13}C NMR data. In analogy to the former products the configuration of these compounds **29–31**, **37** was assigned with like (*R,R* or *S,S*) and unlike (*R,S* or *S,R*) as shown in Fig. 2. The chemical shift data for the carbons which should be influenced most by the relative configuration at the alcohol center due to the anticipated ɣ-effect are summarized in Table 4. Thus, the δ-values for C-3 of the methanobenzofuran system, C-1 of the aryl-ligand and the alkyl carbon which is directly connected with the alcohol center are listed and shift differences are calculated. To indicate the significance of the reported data the chemical shift for C-6 of the methanobenzofuran system is also given. This carbon has

Table 3
Coupling constants between the hydrogens at the former acetal carbon and the newly generated alcohol center

Compound		δ [ppm]	J [Hz]
28A	minor isomer	4.30	9.4
28B	major isomer	4.89	3.8
33A	minor isomer	4.51	7.3
33B	major isomer	4.77	4.8
34A	major isomer	4.84	9.3
34B	minor isomer	5.07	4.3
35A	minor isomer	4.17	9.4
35B	major isomer	4.78	3.5

its signal near to C-3 and therefore perhaps it may be exchanged for it. However, since this part of the molecules is very rigid only small shift differences for C-6 should be observed.



like
29A - 31A, 37A

unlike
29B - 31B, 37B

Fig. 2. Like- and unlike-configuration of rearranged products **29**–**31**

With the exception of **33** which bears a pyridine ring instead of a phenyl ring, C-1 of the aryl-ligand is shifted upfield (0.5–1.3 ppm) in all stereoisomers **A** compared with **B**. For compounds **28**, **33**–**35** which are secondary alcohols C-3 is more shielded in B than in A (0.9–1.7 ppm) whereas for the tertiary alcohols **29**–**32**, **37** the shift of C-3 in **B** is bigger than in **A** (0.5–0.9 ppm). For the latter a significant upfield shift of the first carbon of the aliphatic side chain is also observed for **A** in comparison to **B** (4.0–5.1 (5.2) ppm). These results are in good accordance with previous investigations[13a,14] on β-alkoxy alcohols in which it was observed that the carbons in question (C-3, C*-C_{aliph}) were more shielded in the isomer which has a higher probability for gauche orientations of the bulky ligands at the neighboring carbons.

From careful examination of the Newman projections shown in Fig. 3 it becomes quite clear that this should be the case for compounds **A** rather than for **B** if R is an alkyl group. First of all **A-1** should be highly favored over **A-2** due to strong steric repulsion of the big alkyl-ligand being placed under the furan ring. For conformation **B-2**, this holds true only to a limited extent because steric requirements of an aryl-ligand are far beyond those of an alkyl substituent. Thus, for **B** both conformations should be equally populated. For the rearranged products **28**, **33**–**35**, the interpretation of the ^{13}C NMR data is even more complicated because steric interactions should be far smaller with these molecules. Therefore, both conformations for **A** and **B** shown in Fig. 3 (R=H) should be considered as being represented in the equilibrium of rotamers. However, since the chemical shift of C-1 of the aryl substituent is shifted in

Table 4
^{13}C shifts and shift differences for C-3 and the *ipso*-C of the aryl substituent of the corresponding isomers

Compound		$\delta_{C\text{-}3}$ [ppm]	$\Delta\delta_{C\text{-}3}$ [ppm] (B - A)	$\delta_{C\text{-}6}$ [ppm]	$\delta_{C\text{-}1(Ar)}$ [ppm]	$\Delta\delta_{C\text{-}1(Ar)}$ [ppm] (B - A)	$\delta_{C(aliph)\text{-}C^*}$ [ppm]	$\Delta\delta_{C(aliph)\text{-}C^*}$ [ppm] (B - A)
28A	minor isomer	31.9		32.2	139.9		-	
28B	major isomer	31.0	- 0.9	32.3	141.1	+ 1.2	-	-
29A	minor isomer	31.9		32.0	143.9		22.3 (22.2)[a]	
29B	major isomer	32.6	+ 0.7	32.3	145.2	+ 1.3	27.4	+ 5.1 (+ 5.2)
30A	minor isomer	31.9		32.3	142.0		27.5	
30B	major isomer	32.8	+ 0.9	32.4	143.0	+ 1.0	31.9	+ 4.4
31A	minor isomer	31.9		32.3	142.5		35.0	
31B	major isomer	32.7	+ 0.8	32.4	143.4	+ 0.9	39.1	+4.1
33A	minor isomer	32.6		32.2	159.9		-	
33B	major isomer	31.7	- 0.9	32.2	158.8	- 1.1	-	-
34A	major isomer	32.5		32.3	128.8		-	
34B	minor isomer	31.2	- 1.3	32.4	129.3	+ 0.5	-	-
35A	minor isomer	32.8		32.2	135.9		-	
35B	major isomer	31.1	- 1.7	32.3	136.9	+ 1.0	-	-
37A	-	31.9		32.3	142.5		35.2	
37B	-	32.4	+ 0.5	32.2	143.4	+ 0.9	39.2	+ 4.0

[a] *Signals cannot be assigned unambiguously in this case.*

the same direction for these molecules as it was for the former products we assume that in general the conformations should be very similar. Since steric reasons cannot explain why **A-2** should be less stable we rationalized that **A-1** should be favored due to a general stereoelectronic interaction between the σ-orbital of a C–H bond and the σ*-orbital of a neighboring C–O bond. As a result of these considerations one would estimate from Fig. 3 that C-3 should be more shielded now in **B** than in **A** which corresponds exactly with the experimental data. The anomaly of C-1 of the pyridyl substituent in **33** with regard to the direction of shift differences may be attributed to the fact that this aryl-ligand has a nitrogen which can also be engaged in a hydrogen bond. Thus, it is likely that the distribution between possible conformations is different from the former products.

Eventually, we were able to confirm the structure of **28B** by X-ray crystallography. While alcohol **28** could not be separated by chromatography to give the pure diastereomers this operation was easily performed with acetals **38** and **39** which were obtained by acid-catalyzed reaction of **28** with anhydrolactol **1**. Treatment of **38** and **39** with methanol and *p*-toluenesulfonic acid yielded **28A** and crystalline **28B** (Scheme 3).

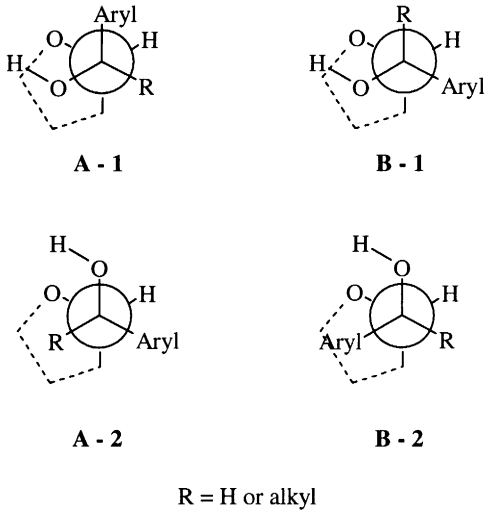
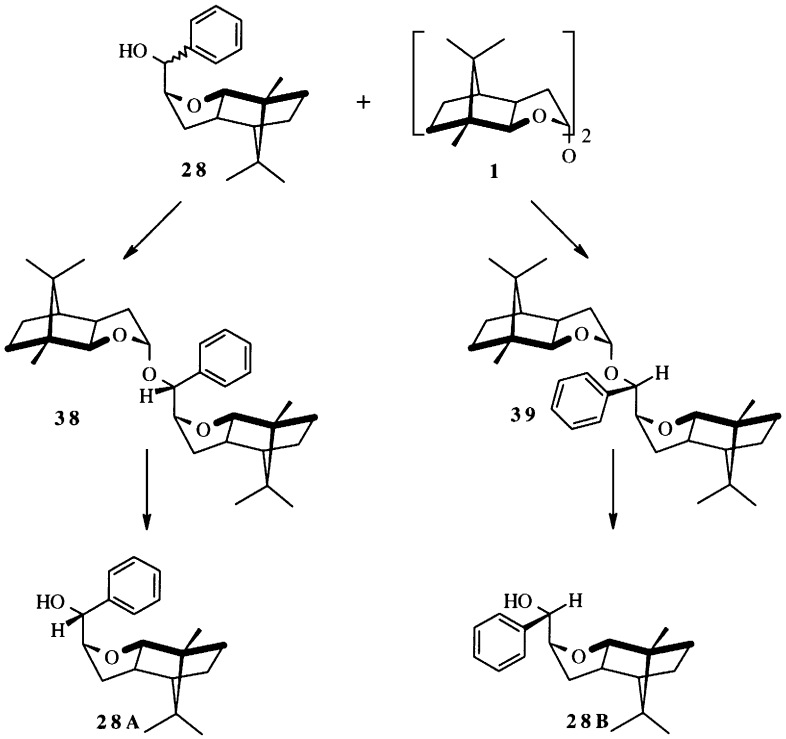


Fig. 3. Newman-projection of C* on C-2 for conformations of the rearranged products **28**–**35** in which a hydrogen bond can be established between the alcohol and the endocyclic oxygen



Scheme 3. Separation of alcohols **28A** and **28B** via acetals **38** and **39**

After crystallization from petroleum ether an X-ray structure determination of **28B** was carried out.[15] The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with two crystallographically independent molecules in the unit cell linked via O-H···O hydrogen bonds into chains parallel to the x-axis. Molecule 1 donates a hydrogen bond from its OH group to the OH oxygen of molecule 2 (O···O=2.79 Å), whereas molecule 2 donates a hydrogen bond to furyl oxygen O1 of

molecule 1 (O···O=2.77 Å). Both molecules are very similar in bond lengths and conformation, but differ somewhat in the orientations of their OH and phenyl groups: O1–C2–C12–O2=72.2(9)/67.9(9)°, O1–C2–C12–C13=−164.2(7)/−167.8(7)° for molecule 1/molecule 2; these values correspond to relative positional differences of 0.30 Å for C16 and C17 of both molecules if their camphor moieties are fitted to coincide.[16]

A view of the molecular structure of **28B** is shown in Fig. 4 which confirms the proposed configuration. Although no intramolecular hydrogen bond was found in the crystalline state the conformation fits well to **B-1** given in Fig. 3 for this compound. Thus, we conclude that the assignment of configuration based on NMR data is also correct for the other products **29**–**35**, **37**.

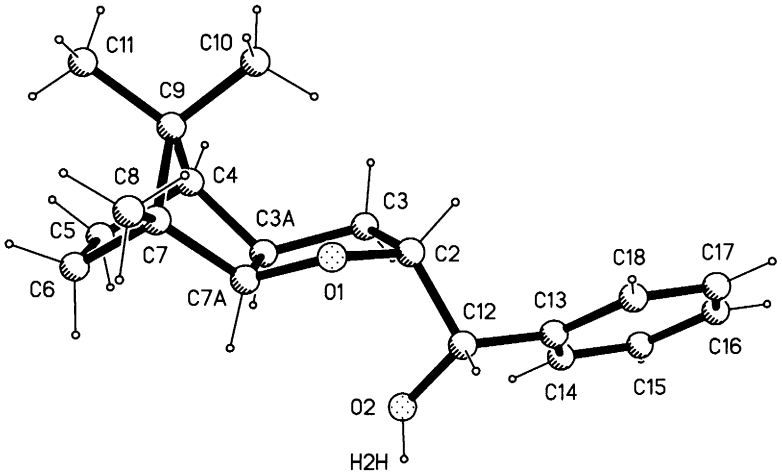
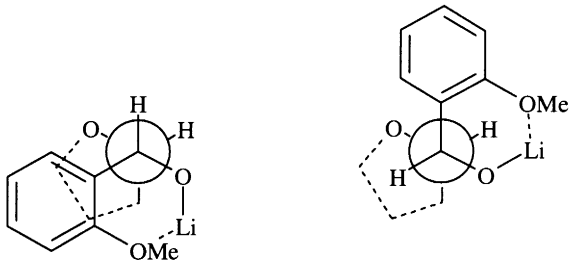


Fig. 4. Molecular structure of **28B** in crystalline state. Only one of the two independent molecules is shown. Selected geometric data [Å, °]: O1–C2=1.441(8), O1–C7A=1.425(8), C2–C12=1.517(9), C12–O2=1.420(8), O1–C2–C12–O2=72.2(9), O1–C2–C12–C13=−164.2(7), C2–C12–O2–H2H=−137

Having secured the configuration of the obtained alcohols we tried to rationalize the results with regard to the stereoselectivity in the formation of the new alcohol center. As noted previously[2d,3,7] the principle of 'inversion of configuration at the lithium bearing terminus' does not hold for the present [1,2]-Wittig variants which involve configurationally labile α-oxybenzyllithium and thus, so far, there are no rules for the prediction of the configuration at this center. Considering the proposed transition state models[2,3] wherein the two radical fragments are tightly held together through coordination with the lithium counterion we may take our conformations, shown in Fig. 3, as a first rough estimation for the recognition process. At this point it should be mentioned that this is only true for substrates which do not bear additional elements for coordination or at least they are not able to interact due to steric reasons.

As already outlined above in connection with the interpretation of the ^{13}C NMR data for alcohols **29**–**31** steric congestion should be more pronounced in diastereomer **A** than in **B**. Additionally, stereoelectronic stabilization due to interactions between the σ-orbital of the C–H bond and the σ^*-orbitals of the C–O bond or the C–aryl bond which are possible in **A-1**, **B-1** and **B-2** should be considered. Eventually, this has no influence, because both statements argue in the same direction, i.e. that the preferentially formed product should be the one with unlike-configuration. For the secondary alcohols **28**, **33**–**35** we argued that steric interactions should be less pronounced. In this case, if there is any influence at all the formation of **A** should be favored. However, in conformation **A-1** of these compounds there are two stereoelectronic interactions between a C–H-σ- and a C–O-σ*-orbital possible now. In **B-1** we still have one as we had already with alcohols **29**–**32**, but in **B-2**, in addition to the orbital interaction possible in **29**–**32**, a stabilization by overlapping of the C–H-σ-orbital with the C–O-σ^*-orbital should

be considered. Thus, from experimental data we must assume that stereoelectronic effects, which would preferentially yield the *anti*-isomer, override steric arguments. Compound **34** in which the lithium bearing radical can be coordinated by the 2-methoxy substituent of the phenyl ring to form a stable six-membered ring chelate violates the premise that coordination is only possible to the *endo*-oxygen of the former acetal. Thus, in addition to the transition states derived from the conformations **A-1**, **A-2**, **B-1**, **B-2**, further ones (**A-3**, **B-3**) in which no coordination to the other radical fragment is possible have to be considered (Fig. 5).



A - 3 **B - 3**

Fig. 5. Additional transition states **A-3** and **B-3** in which no coordination occurs to the endocyclic oxygen of the other radical fragment

While **B-3** exhibits less steric hindrance, which probably has not so much influence but cannot be stabilized stereoelectronically, **A-3** has the possibility of stereoelectronic stabilization. This may explain why the stereoselectivity is inverted for **24** as starting material.

3. Conclusion

In summary, we have shown that the above benzylacetals react in a [1,2]-Wittig rearrangement as long as the other ligands at the lithium bearing terminus are not too sterically demanding which results in low yields or prohibits the reaction. Electron donating groups on the aromatic ligand seem to be an advantageous influence with regard to yield whereas electron withdrawing groups are better with regard to stereoselectivity. Neither an O,S-benzylacetal nor 4-nitrobenzylacetal yields the anticipated products. The retention of configuration at the former acetal center was confirmed. In substrates where no additional coordination position is available the relative configuration at the formed alcohol center in the major diastereomer is of the *anti*- or unlike-configuration. A rationale for this observation was developed based on stereoelectronic effects. Further general investigations on this reaction type are in progress in our laboratories.

4. Experimental

4.1. General

Melting points are uncorrected. NMR: Bruker AC 200 (200 and 50 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H NMR $CHCl_3$ at δ_H 7.24 as internal standard; for ^{13}C NMR $CDCl_3$ at δ_C 77.0 as internal standard. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 10 cm cell. TLC was performed with Merck silica gel 60 F_{254}; with visualisation of the spots with molybdato phosphoric acid (5% in ethanol) and heating. Column chromatography and vacuum flash chromatography (VFC)

was carried out with Merck silica gel 60 (230–400 mesh). Abbreviations used: PE=petroleum ether. Gas chromatography was performed with a Carlo Erba HRGC 5300 Mega Series (Integration: Mega Series Integrator). The data was processed with Labnet 2 (Spectra Physics). Carbowax 57 CB capillary column (Chrompack) and helium (5.0) as carrier gas (preliminary pressure 50 kPa) were used. Detector: FID; sample concentration: 10–20 mg/ml (crude product). Temperatures: injection: 260°C; detection: 260°C; oven: 230°C/240°C (isotherm).

The content of *n*-butyllithium in *n*-hexane was determined by titration with *t*-butanol using 1,10-phenantroline as indicator.

For the synthesis of the compounds **16**, **20**, **24** and **34** see Ref. 10 and Ref. 8e, respectively.

*4.2. General procedure (**GP-1**) for the synthesis of the acetals **15**–**27***

A solution of (2*S*,2′*S*,-(2α,2′α,3aα,3a′α,4β,4′β,7β,7′β,7aα,7a′α))-2,2′-oxybis[octahydro-7,8,8-trimethyl-4,7-methanobenzofuran] ((MBE)$_2$O, **1**) (1 equiv.), the corresponding alcohol or thiol (**2**–**14**; 4 equiv.) and 4-methylbenzenesulfonic acid monohydrate (0.1 equiv.) in anhydrous dichloromethane was stirred for 30 min at room temperature. Sodium sulfate was added and the solution was stirred for a further 90 min. The reaction mixture was washed with a saturated sodium hydrogen carbonate solution. The aqueous phase was extracted twice with dichloromethane and the combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by VFC or SC.

*4.2.1. [2R-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-(phenylmethoxy)-4,7-methanobenzofuran **15***

Following **GP-1**, **15** was prepared from 8.23 g (23.8 mmol) of **1**, 10.3 g (92.2 mmol) of benzyl alcohol **2** and 0.4 g (2.1 mmol) of 4-methylbenzenesulfonic acid monohydrate in 100 ml of dichloromethane. The crude product was purified by VFC (300 g silica gel, PE:Et$_2$O, 10:1) and Kugelrohr distillation. Yield: 12.2 g (89%) of a colorless oil. Bp=90°C/0.01 torr (Kugelrohr), R_f (PE:Et$_2$O, 8:1)=0.5, $[\alpha]_D^{20}=-104$ (c 1.0, CH_2Cl_2); $C_{19}H_{26}O_2$ (286.42): calculated: C 79.68, H 9.15; found: C 79.63, H 9.43; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.8–2.45 (m, 17H, aliphatic-H, therein: 0.80, 0.98, and 1.01 (3s, 9H, 3CH$_3$)), 3.97 (d, 1H, J=6.6 Hz; 7a-H), 4.45 (d, 1H, Ph-CH$_2$), 4.72 (d, 1H, Ph-CH$_2$), 5.23 (dd, 1H, 2-H), 7.18–7.4 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.66/20.50/22.90 (3q, 3CH$_3$), 28.91 (t, C-5), 32.47 (t, C-6), 38.61 (t, C-3), 45.96 (d, C-3a), 47.0 (s, C-8), 47.61 (s, C-7), 48.44 (d, C-4), 68.28 (t, Ph-CH$_2$), 91.21 (d, C-7a), 104.32 (d, C-2), 127.35 (d, *para*-C), 127.77 (d, 2C, *ortho*-C), 128.28 (d, 2C, *meta*-C), 138.53 (s, *ipso*-C).

*4.2.2. [2R-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-(1-phenylpropoxy)-4,7-methanobenzofuran **17***

Following **GP-1**, **17** was prepared from 4 g (10.7 mmol) of **1**, 5.82 g (42.7 mmol) (±)-1-phenyl-1-propanol (**4**) and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 55 ml of dichloromethane. The crude product was purified by VFC (200 g silica gel, PE:Et$_2$O, 30:1) and Kugelrohr distillation. Yield: 6.1 g (91%, de=37% (S)) of a colorless oil. Bp=90°C/0.01 torr (Kugelrohr), R_f (PE:Et$_2$O, 4:1)=0.64; $C_{21}H_{30}O_2$ (314.47): calculated: C 80.21, H 9.62; found: C 80.15, H 9.51; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.72–2.46 (m, 44H, aliphatic-H (R,S)), 3.48 (d, 1H, 7a-H (R)), 3.97 (d, 1H, 7a-H (S)), 4.43 (dd, 1H, C*-H (R)), 4.54 (dd, 1H, C*-H (S)), 4.97 (d, 1H, 2-H (S)), 5.31 (d, 1H, 2-H (R)), 7.15–7.39 (m, 10H, aromatic-H (R,S)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=9.89/10.55 (2q, C*-CH$_2$-CH$_3$ (R,S)), 11.40/11.71/20.48/22.86/22.90 (6q, 6MBE-CH$_3$ (R,S)), 28.84 (t, C-5 (R)), 28.95 (t, C-5

(S)), 29.51 (t, C*-CH_2 (R)), 31.35 (t, C*-CH_2 (S)), 32.35 (t, C-6 (R)), 32.54 (t, C-6 (S)), 38.51 (t, C-3 (S)), 38.63 (t, C-3 (R)), 45.90 (d, C-3a (R)), 46.08 (d, C-3a (S)), 46.92 (2s, C-8 (R,S)), 47.29 (s, C-7 (R)), 47.56 (s, C-7 (S)), 48.43 (2d, C-4 (R,S)), 77.97 (d, C* (S)), 79.28 (d, C* (R)), 90.99 (d, C-7a (R)), 91.09 (d, C-7a (S)), 101.97 (d, C-2 (S)), 104.24 (d, C-2 (R)), 126.50 (2d, *ortho*-C (R)), 126.68 (d, *para*-C (R)), 126.93 (2d, *ortho*-C (S)), 127.11 (d, *para*-C (S)), 127.84 (2d, *meta*-C (R)), 128.12 (2d, *meta*-C (S)), 142.85 (s, *ipso*-C (S)), 143.70 (s, *ipso*-C (R)).

*4.2.3. [2*R*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-(1-phenylpentoxy)-4,7-methanobenzofuran **18***

Following **GP-1**, **18** was prepared from 4.23 g (11.3 mmol) of **1**, 8 g (48.7 mmol) of (±)-1-phenyl-1-pentanol **5** and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 55 ml of dichloromethane. The crude product was purified by VFC (220 g silica gel, PE:Et_2O, 100:1) and Kugelrohr distillation. Yield: 3.2 g (41%, de=67% (S)) of a colorless oil. Bp=90°C/0.01 torr (Kugelrohr), R_f (PE:Et_2O, 10:1)=0.53; $C_{23}H_{34}O_2$ (342.52): calculated: C 80.65, H 10.01; found: C 80.65, H 9.82; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.72–2.45 (m, 52H, aliphatic-H (R,S)), 3.46 (d, 1H, 7a-H (R)), 3.97 (d, 1H, 7a-H (S)), 4.45 (dd, 1H, C*-H (R)), 4.60 (dd, 1H, C*-H (S)), 4.93 (d, 1H, 2-H (S)), 5.29 (d, 1H, 2-H (R)), 7.16–7.43 (m, 10H, aromatic-H (R,S)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.43/11.71/20.48/22.92 (6q, 6CH_3 (R,S)), 14.03 (2q, butyl-CH_3 (R,S)), 22.43 (t, butyl-CH_2 (S)), 22.68 (t, butyl-CH_2 (R)), 27.76 (t, butyl-CH_2 (R)), 28.07 (t, butyl-CH_2 (S)), 28.81 (t, C-5 (R)), 28.97 (t, C-5 (S)), 32.43 (t, C-6 (R)), 32.59 (t, C-6 (S)), 38.20 (t, C*–CH_2 (R,S)), 38.51 (t, C-3 (S)), 38.66 (t, C-3 (R)), 45.91 (d, C-3a (R)), 46.08 (d, C-3a (S)), 46.94 (2s, C-8 (R,S)), 47.42 (s, C-7 (R)), 47.57 (s, C-7 (S)), 48.26 (2d, C-4 (R,S)), 76.50 (d, C* (S)), 78.32 (d, C* (R)), 91.00 (d, C-7a (R)), 91.14 (d, C-7a (S)), 101.97 (d, C-2 (S)), 104.40 (d, C-2 (R)), 126.47 (2d, *ortho*-C (R)), 126.68 (d, *para*-C (R)), 126.88 (2d, *ortho*-C (S)), 127.09 (d, *para*-C (S)), 127.87 (2d, *meta*-C (R)), 128.16 (2d, *meta*-C (S)), 143.21 (s, *ipso*-C (S)), 144.06 (s, *ipso*-C (R)).

*4.2.4. [2*S*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-(2-methyl-1-phenylpropoxy)-4,7-methanobenzofuran **19***

Following **GP-1**, **19** was prepared from 4.33 g (11.6 mmol) of **1**, 7.68 g (49.8 mmol) of (±)-2-methyl-1-phenyl-1-propanol **6** and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 55 ml of dichloromethane. The crude product was purified by VFC (220 g silica gel, PE:Et_2O, 100:1) and Kugelrohr distillation. Yield: 4.52 g (60%, de=67% (S)) of a colorless oil. Bp=90°C/0.01 torr (Kugelrohr), R_f (PE:Et_2O, 20:1)=0.60; $C_{22}H_{32}O_2$ (328.49): calculated: C 80.44, H 9.82; found: C 80.14, H 9.52; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.65–2.45 (m, 48H, aliphatic-H (R,S)), 3.32 (d, 1H, 7a-H (R)), 3.96 (d, 1H, 7a-H (S)), 4.08 (d, 1H, C*-H (R)), 4.27 (d, 1H, C*-H (S)), 4.89 (d, 1H, 2-H (S)), 5.23 (d, 1H, 2-H (R)), 7.15–7.40 (m, 10H, aromatic-H (R,S)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.33/11.73/20.50/22.92 (6q, 6MBE–CH_3 (R,S)), 18.84/18.93/19.24 (4q, C*-$(CH_3)_2$ (R,S)), 28.84 (t, C-5 (R)), 28.96 (t, C-5 (S)), 32.35 (t, C-6 (R)), 32.57 (t, C-6 (S)), 34.36 (d, C*-CH-$(CH_3)_2$ (R)), 34.65 (d, C*-CH-$(CH_3)_2$ (S)), 38.48 (t, C-3 (R,S)), 45.88 (d, C-3a (R)), 46.13 (d, C-3a (S)), 46.91 (2s, C-8 (R,S)), 47.20 (s, C-7 (R)), 47.56 (s, C-7 (S)), 48.43 (2d, C-4 (R,S)), 81.77 (d, C* (S)), 84.45 (d, C* (R)), 90.96 (d, C-7a(R)), 91.11 (d, C-7a (S)), 101.73 (d, C-2 (S)), 105.49 (d, C-2 (R)), 126.54 (d, *para*-C (R)), 127.06 (d, *para*-C (S)), 127.11/127.55 (2×2d, *ortho*-C (R), *meta*-C (S)), 127.77/127.87 (2×2d, *ortho*-C (S), *meta*-C (R)), 141.68 (s, *ipso*-C (S)), 143.44 (s, *ipso*-C (R)).

*4.2.5. [2*R*-(2α,3aα,4β,7β,7aα)]-2-(Diphenylmethoxy)-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran **21***

Following **GP-1**, **21** was prepared from 3.5 g (9.34 mmol) of **1**, 10.32 g (56.04 mmol) of diphenylmethanol **8** and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 50 ml of dichloromethane. The crude product was purified by VFC (200 g silica gel, PE:Et_2O, 30:1) and the resulting mixture of **21** and 1,1′-oxybis[diphenylmethane] was treated with PE:Et_2O, 100:1. The insoluble 1,1′-oxybis[diphenylmethane] was filtered off and the solvent was evaporated to furnish **21**. Yield: 4.68 g (69%) of a colorless oil. R_f (PE:Et_2O, 8:1)=0.54, $[\alpha]_D^{20}=-118$ (c 1.1, CH_2Cl_2); $C_{25}H_{30}O_2$ (362.51): calculated: C 82.83, H 8.34; found: C 82.93, H 8.27; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.48 (m, 17H, aliphatic-H, therein: 0.80, 0.93, and 1.00 (3s, 9H, $3CH_3$)), 3.93 (d, 1H, 7a-H), 5.17 (dd, 1H, 2-H), 5.78 (s, 1H, $(Ph)_2$-CH), 7.16-7.45 (m, 10H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.65/20.53/22.90 (3q, $3CH_3$), 28.91 (t, C-5), 32.45 (t, C-6), 38.58 (t, C-3), 46.01 (d, C-3a), 47.02 (s, C-8), 47.59 (s, C-7), 48.46 (d, C-4), 77.80 (d, Ph_2CH-), 91.28 (d, C-7a), 102.41 (d, C-2), 126.94/127.40 (2d, 2×*para*-C), 127.03/127.71/128.08/128.33 (4d, 2×2*ortho*-C, 2×2*meta*-C), 141.69/143.15 (2s, 2×*para*-C).

*4.2.6. [2*S*-(2α,3aα,4β,7β,7aα)]-1-[[2-[Octahydro-7,8,8-trimethyl-(4,7-methanobenzofuran-2-yl)-oxy]2-phenyl]ethyl]pyrrolidine **22***

Following **GP-1**, **22** was prepared from 2.4 g (6.4 mmol) of **1**, 2.1 g (12.97 mmol) of (±)-α-phenyl-1-pyrrolidineethanol **9** and 2.6 g (13.65 mmol) of 4-methylbenzenesulfonic acid monohydrate in 55 ml of dichloromethane. Sodium sulfate was added after 60 min and the reaction mixture was stirred for 3 h 30 min. The aqueous layer was extracted six times with dichloromethane and the crude product (4.4 g) was purified by VFC (100 g silica gel, gradient of PE:Et_2O, 1:1 to diethyl ether). Yield: 0.63g (13%, de=16% (R)) of a colorless oil. R_f (PE:Et_2O, 1:1)=0.11; $C_{24}H_{35}NO_2$ (314.47 g/mol): calculated: C 78.00, H 9.55, N 3.79; found: C 77.78, H 9.68, N 3.98; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.63–2.92 (m, 54H, aliphatic-H (R,S), therein: 0.72, 0.90, and 0.98 (3s, 9H, $3CH_3$ (S)), and 0.79, 0.88, and 0.98 (3s, 9H, $3CH_3$ (R))), 3.34 (d, 1H, 7a-H (S)), 4.01 (d, 1H, 7a-H (R)), 4.68 (dd, 1H, C*-H (S)), 4.87 (dd, 1H, C*-H (R)), 4.93 (d, 1H, 2-H (R)), 5.36 (d, 1H, 2-H (S)), 7.14–7.43 (m, 10H, aromatic-H (R,S)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.29/11.64/20.42/20.48/22.82/22.96 (6q, $6CH_3$ (R,S)), 23.49 (4t, 2×2N-CH_2-CH_2 (R,S)), 28.80 (t, C-5 (S)), 28.90 (t, C-5 (R)), 32.31 (t, C-6 (S)), 32.54 (t, C-6 (R)), 38.42 (t, C-3 (R)), 38.76 (t, C-3 (S)), 45.85 (d, C-3a (S)), 45.96 (d, C-3a (R)), 46.84 (s, C-8 (S)), 46.94 (s, C-8 (R)), 47.20 (s, C-7 (S)), 47.52 (s, C-7 (R)), 48.44 (2d, C-4 (R,S)), 54.42 (2t, 2×N-CH_2 (R)), 54.82 (2t, 2×N-CH_2 (R)), 62.97 (2t, C*-CH_2 (R,S)), 75.87 (d, C* (R)), 77.95 (d, C* (S)), 91.03 (d, C-7a (S)), 91.20 (d, C-7a (R)), 101.92 (d, C-2 (R)), 105.24 (d, C-2 (S)), 126.47 (2d, *ortho*-C (S)), 126.86 (d, *para*-C (S)), 127.09 (2d, *ortho*-C (R)), 127.38 (d, *para*-C (R)), 127.84 (2d, *meta*-C (S)), 128.18 (2d, *meta*-C (R)), 141.51 (s, *ipso*-C (R)), 143.05 (s, *ipso*-C (S)).

*4.2.7. [2*R*-(2α,3aα,4β,7β,7aα)]-2-[[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-methyl]pyridine **2***

Following **GP-1**, **23** was prepared from 4.12 g (11.84 mmol) of **1**, 2.58 g (23.68 mmol) of pyridine-2-methanol **10** and 4.76 g (25 mmol) of 4-methylbenzenesulfonic acid monohydrate in 30 ml of dichloromethane. In deviation of **GP-1** the solution was stirred for 5 h at room temperature, and the aqueous phase was extracted four times with dichloromethane. The crude product was purified by VFC (100 g silica gel, PE:Et_2O, 1:2). Compound **1** and the alcohol **10** were recovered, and the reaction was repeated with these substrates. The combined fractions containing the product (2.19 g) were again purified by column chromatography (80 g silica gel, gradient of PE:Et_2O, 2:1 to PE:Et_2O, 1:2) and after this by Kugelrohr distillation. Yield: 1.05 g (38%) of a colorless oil. Bp=90°C/0.005 torr (Kugelrohr), R_f

(Et_2O:PE, 2:1)=0.40, $[\alpha]_D^{20}=-99.4$ (c 1.0, CH_2Cl_2); $C_{18}H_{25}NO_2$ (287.4): calculated: C 75.22, H 8.77, N 4.87; found: C 75.29, H 8.82, N 4.83; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–2.45 (m, 17H, aliphatic-H, therein: 0.80, and 1.00 (2s, 9H, $3CH_3$)), 3.95 (d, 1H, 7a-H), 4.58 (d, 1H, O-CH_2), 4.81 (d, 1H, O-CH_2), 5.29 (dd, 1H, 2-H), 7.18 (dd, 1H, 5′-H), 7.40 (d, 1H, 3′-H), 7.68 (dd, 1H, 4′-H), 8.57 (d, 1H, 6′-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.18/20.08/22.47 (3q, $3CH_3$), 28.49 (t, C-5), 32.01 (t, C-6), 38.27 (t, C-3), 45.51 (d, C-3a), 46.60 (s, C-8), 47.23 (s, C-7), 48.06 (d, C-4), 68.87 (t, O-CH_2), 90.97 (d, C-7a), 104.53 (d, C-2), 121.20/121.78 (2d, C-3′/C-5′), 136.19 (d, C-4′), 148.56 (d, C-6′), 158.26 (s, C-2′).

*4.2.8. [2*R*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-[(3,4,5-trimethoxyphenyl)methoxy]-4,7-methanobenzofuran **2***

Following **GP-1**, **25** was prepared from 4.16 g (11.96 mmol) of **1**, 4.7 g (23.92 mmol) of 3,4,5-trimethoxybenzyl alcohol **12** and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 50 ml of dichloromethane. The crude product (8.64 g) was purified by VFC (160 g silica gel, PE:Et_2O, 1:1). Yield: 7.18 g (80%) of colorless crystals. Mp=75–77°C, R_f (Et_2O:PE, 2:1)=0.5, $[\alpha]_D^{20}=-70$ (c 1.0, CH_2Cl_2); $C_{22}H_{32}O_5$ (376.49): calculated: C 70.19, H 8.57; found: C 70.43, H 8.57; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–2.45 (m, 17H, aliphatic-H, therein: 0.81, 0.98, and 1.00 (3s, 9H, $3CH_3$)), 3.82 (s, 3H, *para*-O-CH_3), 3.87 (s, 6H, 2*meta*-O-CH_3), 3.97 (d, 1H, 7a-H), 4.37 (d, 1H, O-CH_2), 4.61 (d, 1H, O-CH_2), 5.23 (dd, 1H, 2-H), 6.57 (s; 2H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.66/20.48/22.88 (3q, $3CH_3$), 28.90 (t, C-5), 32.47 (t, C-6), 38.63 (t, C-3), 45.97 (d, C-3a), 47.01 (s, C-8), 47.64 (s, C-7), 48.46 (d, C-4), 56.07 (2q, *meta*-O-CH_3), 60.78 (q, *para*-O-CH_3), 68.70 (t, O-CH_2), 91.33 (d, C-7a), 104.48 (d, C-2), 104.96 (2d, *ortho*-C), 134.12/137.2 (2s, *para*-C/*ipso*-C), 153.19 (2s, *meta*-C).

*4.2.9. [2*R*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-[(4-nitrophenyl)methoxy]-4,7-methanobenzofuran **26***

Following **GP-1**, **26** was prepared from 6.12 g (16.3 mmol) of **1**, 10 g (65.3 mmol) of 4-nitrobenzyl alcohol (**13**) and 0.5 g (2.6 mmol) of 4-methylbenzenesulfonic acid monohydrate in 75 ml of dichloromethane. The crude product (12.5 g) was purified by VFC (240 g silica gel, gradient of PE:Et_2O, 20:1 to 5:1). Yield: 8.82 g (82%) of slightly yellow crystals. Mp=56–57°C, R_f (PE:Et_2O, 10:1)=0.31; $C_{19}H_{25}NO_4$ (331.41): calculated: C 68.86, H 7.60, N 4.23; found: C 69.02, H 7.68, N 4.24; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.45 (m, 17H, aliphatic-H; therein: 0.81, 0.97, and 0.99 (3s, 9H, $3CH_3$)), 3.92 (d, 1H, 7a-H), 4.53 (d, 1H, O-CH_2), 4.78 (d, 1H, O-CH_2), 5.22 (dd, 1H, 2-H), 7.48 (d, 2H, aromatic-H (*meta*)), 8.18 (d, 2H, aromatic-H (*ortho*)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.53/20.39/22.81 (3q, $3CH_3$), 28.80 (t, C-5), 32.33 (t, C-6), 38.60 (t, C-3), 45.81 (d, C-3a), 46.94 (s, C-8), 47.61 (s, C-7), 48.38 (d, C-4), 67.03 (t, O-CH_2), 91.47 (d, C-7a), 104.73 (d, C-2), 123.44 (2d, *ortho*-C), 127.74 (2d, *meta*-C), 146.30/147.14 (2s, *para*-C/*ipso*-C).

*4.2.10. [2*S*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-2-[(phenylmethyl)thio]-4,7-methanobenzofuran **27***

Following **GP-1**, **27** was prepared from 3 g (8.0 mmol) of **1**, 4.02 g (32.4 mmol) of benzyl thiol **14** and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 55 ml of dichloromethane. In deviation to **GP-1** the solution was stirred for 20 h at room temperature, 2N sodium hydroxide solution was added to the reaction mixture and the crude product (5.5 g) was purified by VFC (130 g silica gel, PE:Et_2O, 40:1). The combined fractions containing the product (3 g of 4.8 g) were further purified by column chromatography (200 g silica gel, PE:Et_2O, 40:1). Yield: 2.35 g (78% based on 3 g of purified product) of a colorless oil. R_f (PE:Et_2O, 30:1)=0.33, $[\alpha]_D^{20}=-365$ (c 1.06, $CHCl_3$); $C_{19}H_{26}OS$ (302.48): calculated: C 75.45, H 8.66; found: C 75.30, H 8.63; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–2.42 (m,

17H, aliphatic-H, therein: 0.83, 0.99, and 1.03 (3s, 9H, $3CH_3$)), 3.72 (d, 1H, S-CH_2), 3.88 (d, 1H, S-CH_2), 4.02 (d, 1H, 7a-H), 5.42 (dd, 1H, 2-H), 7.17–7.41 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.59/20.65/22.80 (3q, $3CH_3$), 28.79 (t, C-5), 32.27 (t, C-6), 34.61 (t, S-CH_2), 38.52 (t, C-3), 46.95 (d, C-3a), 47.09 (s, C-8), 47.53 (s, C-7), 48.40 (d, C-4), 84.16 (d, C-7a), 90.66 (d, C-2), 126.58 (d, *para*-C), 128.32/128.87 (2×2d, *meta*-C/*ortho*-C), 138.98 (s, *ipso*-C).

*4.3. General procedure (**GP-2**) for the rearrangements of the acetals **15**–**27***

The acetals **15**–**27** were dissolved in anhydrous THF under a nitrogen atmosphere. *n*-Butyllithium in *n*-hexane was added dropwise to this solution at room temperature. The reaction mixture was stirred for 3 h at this temperature and then quenched with water. The mixture was concentrated and diethyl ether was added. The aqueous phase was extracted twice with diethyl ether. The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The crude products were purified by VFC or column chromatography.

*4.3.1. Rearrangement of **15***

Following **GP-2**, 2.2 ml (5.24 mmol) of *n*-butyllithium was added to a solution of 0.5 g (1.75 mmol) of **15** in 6.3 ml of anhydrous THF. The crude product was purified by VFC (10 g silica gel, gradient of PE:Et_2O, 30:1 to 4:1). Yield: 0.277 g (55%) of a slightly yellow oil (diastereomeric mixture, **28A**:**28B**, 1:1.63 (GC)). The diastereomers were separated by formation of the two acetals **38** and **39** and subsequent column chromatography.

*4.3.1.1. [2*R*-[2α(*R**,(2*S**,3a*R**,4*R**,7*S**,7a*R**)),3aα,4β,7β,7aα]]-Octahydro-2-[[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]phenylmethyl]-7,8,8-trimethyl-4,7-methanobenzofuran **38**, and [2*R*-[2α(*S**,(2*S**,3a*R**,4*R**,7*S**7a*R**)),3aα,4β,7β,7aα]]-octahydro-2-[[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]phenylmethyl]-7,8,8-trimethyl-4,7-methanobenzofuran **39***. Following **GP-1**, **38** and **39** were prepared from 5.408 g (15.4 mmol) of **1**, 4.408 g (15.4 mmol) of a mixture of **28A** and **28B** and 0.3 g (1.575 mmol) of 4-methylbenzenesulfonic acid monohydrate in 50 ml of dichloromethane. The crude product (9.47 g) was purified by MPLC (1000 g silica gel, PE:Et_2O, 30:1). Compound **38**: yield: 1.622 g (23%) of a colorless rigid foam. R_f (PE:Et_2O, 8:1)=0.44, $[\alpha]_D^{20}$=−143 (c 1, CH_2Cl_2); $C_{31}H_{44}O_3$ (464.69): calculated: C 80.13, H 9.54; found: C 80.25, H 9.28; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.5 (m, 34H, aliphatic-H, therein: 0.78, 0.80, 0.92, 0.98, 1.00, and 1.02 (6s, 18H, $6CH_3$)), 3.98 (d, 1H, 7a-H (1)), 4.12 (d, 1H, 7a-H (2)), 4.15–4.27 (m, 1H, 2-H (1)), 4.45 (d, 1H, C*-H), 4.95 (d, 1H, 2-H (2)), 7.18–7.38 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.48/11.54/20.06/20.28/22.42/22.48 (6q, $6CH_3$) 28.53 (2t, C-5 (1), C-5 (2)), 32.03/32.19/32.70/37.94 (4t, C-3 (1), C-3 (2), C-6 (1), C-6 (2)), 46.44/46.70/47.05/47.57 (4s, C-7 (1), C-7 (2), C-8 (1), C-8 (2)), 45.44/47.32/48.10/48.36 (4d, C-4 (1), C-4 (2), C-3a (1), C-3a (2)), 77.31 (d, C*), 82.10 (d, C-2 (1)), 90.41/90.91 (2d, C-7a (1), C-7a (2)), 101.85 (d, C-2 (2)), 127.19 (d, *para*-C), 127.70 (2d, *ortho*-C), 127.89 (2d, *meta*-C), 139.62 (s, *ipso*-C). Compound **39**: yield: 2.06 g (29%) of a colorless rigid foam. R_f (PE:Et_2O, 8:1)=0.33, $[\alpha]_D^{20}$=−37.6 (c 1.25, CH_2Cl_2); $C_{31}H_{44}O_3$ (464.69): calculated: C 80.13, H 9.54; found: C 80.36, H 9.61; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.73–2.4 (m, 34H, aliphatic-H, therein: 0.76, 0.78, 0.79, 0.92, 0.94, and 0.98 (6s, 18H, $6CH_3$)), 3.88 (d, 1H, 7a-H (1)), 4.12 (d, 1H, 7a-H (2)), 4.17–4.28 (m, 1H, 2-H (1)), 4.65 (d, 1H, C*-H), 5.29 (d, 1H, 2-H (2)), 7.14–7.34 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.41/11.68/20.25/20.48/22.77/22.87 (6q, $6CH_3$) 28.81/28.91 (2t, C-5 (1), C-5 (2)), 31.39/32.40/32.48/38.90 (4t, C-3 (1), C-3 (2), C-6 (1), C-6 (2)), 46.49/46.88/47.43/48.26 (4s, C-7 (1), C-7 (2), C-8 (1), C-8 (2)), 46.09/48.51/48.92/49.07 (4d, C-4

(1), C-4 (2), C-3a (1), C-3a (2)), 81.74 (d, C*), 84.59 (d, C-2 (1)), 91.40/93.78 (2d, C-7a (1), C-7a (2)), 106.10 (d, C-2 (2)), 126.33 (2d, *ortho*-C), 126.68 (d, *para*-C), 127.83 (2d, *meta*-C), 140.95 (s, *ipso*-C).

*4.3.1.2. [2*R*-(2α(R*),3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol **28A***. Compound **38** (1.622 g, 3.49 mmol) was dissolved in 35 ml of methanol and 10 ml of dichloromethane and 4-methylbenzenesulfonic acid monohydrate was added. This mixture was stirred for 3 h at room temperature. Sodium hydrogen carbonate was added and the mixture was stirred again for 10 min. After extraction with water the aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by VFC (40 g silica gel, PE:Et_2O, 10:1). Yield: 0.952 g (95%) of a slightly yellow oil. R_f (PE:Et_2O, 1:1)=0.47, $[\alpha]_D^{20}=-34.1$ (c 1, CH_2Cl_2); $C_{19}H_{26}O_2$ (286.42): calculated: C 79.68, H 9.15; found: C 79.97, H 9.33; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–1.9 (m, 16H, aliphatic-H, therein: 0.80, 0.99, and 1.03 (3s, 9H, CH_3)), 2.16–2.38 (m, 1H, 3a-H), 3.26 (s, 1H, OH), 3.94 (d, 1H, 7a-H), 4.03–4.16 (m, 1H, 2-H), 4.30 (d, 1H, C*-H), 7.23–7.42 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.21/20.00/22.32 (3q, 3CH_3), 28.37 (t, C-5), 31.85 (t, C-3), 32.20 (t, C-6), 46.36/47.86 (2s, C-7, C-8), 47.25/48.51 (2d, C-4, C-3a), 74.90 (d, C*), 84.24 (d, C-2), 90.82 (d, C-7a), 127.16 (2d, *ortho*-C), 127.61 (d, *para*-C), 127.97 (2d, *meta*-C), 139.89 (s, *ipso*-C).

*4.3.1.3. [2*R*-(2α(S*),3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol **28B***. Following the above procedure (Section 4.3.1.2), 2.058 g (4.44 mmol) of **39** was dissolved in 35 ml of methanol and 10 ml of dichloromethane and 4-methylbenzenesulfonic acid monohydrate was added. The crude product was purified by VFC (40 g silica gel, PE:Et_2O, 10:1). Yield: 0.954 g (75%) of colorless crystals. Mp=119–123°C, R_f (PE:Et_2O, 1:1)=0.47, $[\alpha]_D^{20}=-7.8$ (c 1, CH_2Cl_2); $C_{19}H_{26}O_2$ (286.42): calculated: C 79.68, H 9.15; found: C 79.98, H 9.01; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–2.28 (m, 17H, aliphatic-H, therein: 0.80, 0.96, and 0.99 (3s, 9H, CH_3)), 3.97 (d, 1H, 7a-H), 4.29–4.40 (m, 1H, 2-H), 4.89 (d, 1H, C*-H), 7.15–7.40 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.63/20.11/22.70 (3q, 3CH_3), 28.66 (t, C-5), 31.02 (t, C-3), 32.30 (t, C-6), 46.41/48.51 (2s, C-7, C-8), 48.57/49.24 (2d, C-4, C-3a), 77.05 (d, C*), 84.72 (d, C-2), 94.20 (d, C-7a), 126.01 (2d, *ortho*-C), 127.27 (d, *para*-C), 128.22 (2d, *meta*-C), 141.06 (s, *ipso*-C).

*4.3.2. Rearrangement of **16***

Following **GP-2**, 2.1 ml (4.99 mmol) of *n*-butyllithium was added to a solution of 0.5 g (1.66 mmol) of **16** in 6.3 ml of anhydrous THF. The crude product was purified by VFC (10 g silica gel, gradient of PE:Et_2O, 30:1 to 4:1). Yield: 0.13 g (26%) of a colorless oil (diastereomeric mixture, **29A**:**29B**, 1:3 (GC)). The diastereomers **29A** and **29B** were separated by column chromatography (10 g silica gel, PE:Et_2O, 5:1).

*4.3.2.1. [2*R*-(2α(R*),3aα,4β,7β,7aα)]-Octahydro-α,7,8,8-trimethyl-α-phenyl-4,7-methanobenzo-furan2-methanol **29A***. R_f (PE:Et_2O, 3:1)=0.35, $[\alpha]_D^{20}=-39.1$ (c 1.12, CH_2Cl_2); $C_{20}H_{28}O_2$ (300.44): calculated: C 79.96, H 9.39; found: C 79.86, H 9.48; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.35 (m, 20H, aliphatic-H, therein: 0.78, 0.92, and 0.99 (3s, 9H, CH_3) and 1.51 (s, 3H, C*-CH_3)), 2.90 (s, 1H, OH), 3.94 (d, 1H, 7a-H), 4.19 (dd, 1H, 2-H), 7.18–7.55 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.17/19.46/22.20/22.27 (4q, 3CH_3, and C*-CH_3), 28.12 (t, C-5), 31.87/31.99 (2t, C-3, C-6), 45.91/48.33 (2s, C-7, C-8), 48.08/48.96 (2d, C-4, C-3a), 76.70 (s, C*), 88.21 (d, C-2), 94.05 (d, C-7a), 125.92 (2d, *ortho*-C), 126.67 (d, *para*-C), 127.61 (2d, *meta*-C), 143.90 (s, *ipso*-C).

*4.3.2.2. [2*R*-(2α(*S**),3aα,4β,7β,7aα)]-Octahydro-α,7,8,8-tetramethyl-α-phenyl-4,7-methanobenzofuran2-methanol* ***29B***. R_f (PE:Et_2O, 3:1)=0.45, $[\alpha]_D^{20}=-18.7$ (c 1, CH_2Cl_2); $C_{20}H_{28}O_2$ (300.44): calculated: C 79.96, H 9.39; found: C 79.83, H 9.26; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.15 (m, 20H, aliphatic-H, therein: 0.78, 0.97, and 0.99 (3s, 9H, CH_3) and 1.59 (s, 3H, C*-CH_3)), 2.62 (s, 1H, OH), 3.85 (d, 1H, 7a-H), 4.29 (dd, 1H, 2-H), 7.18–7.60 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.65/20.03/22.70 (3q, 3CH_3), 27.43 (q, C*-CH_3), 28.59 (t, C-5), 32.32 (t, C-6), 32.62 (t, C-3), 46.28/48.61 (2s, C-7, C-8), 48.61/49.26 (2d, C-4, C-3a), 77.64 (s, C*), 87.50 (d, C-2), 94.65 (d, C-7a), 125.41 (2d, *ortho*-C), 126.53 (d, *para*-C), 128.00 (2d, *meta*-C), 145.23 (s, *ipso*-C).

4.3.3. Rearrangement of ***17***

Following **GP-2**, 3.7 ml (9.54 mmol) of *n*-butyllithium was added to a solution of 1 g (3.18 mmol) of **17** in 13 ml of anhydrous THF. The crude product was purified by SC (100 g silica gel, PE:Et_2O, 10:1).

*4.3.3.1. [2*R*-(2α(*R**),3aα,4β,7β,7aα)]-α-Ethyl-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol* ***30A***. Yield: 0.027 g (2.7%) of a colorless oil. R_f (PE:Et_2O, 4:1)=0.30, $[\alpha]_D^{20}=-21.3$ (c 0.54, $CHCl_3$); $C_{21}H_{30}O_2$ (314.47): calculated: C 80.21, H 9.62; found: C 80.13, H 9.84; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.64–2.20 (m, 22H, aliphatic-H, therein: 0.78, 0.93, and 0.97 (3s, 9H, CH_3) and 0.83 (s, 3H, C*-CH_2-CH_3)), 2.55 (s, 1H, OH), 3.84 (d, 1H, 7a-H), 4.14 (dd, 1H, 2-H), 7.18–7.52 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=7.52 (q, 3H, C*-CH_2-CH_3), 11.54/19.84/22.68 (3q, 3CH_3), 27.46 (t, C*-CH_2), 28.57 (t, C-5), 31.87 (t, C-3), 32.29 (t, C-6), 46.26/48.70 (2s, C-7, C-8), 48.44/49.35 (2d, C-4, C-3a), 79.70 (s, C*), 88.67 (d, C-2), 94.52 (d, C-7a), 126.71 (d, *para*-C), 126.93 (2d, *ortho*-C), 127.93 (2d, *meta*-C), 142.00 (s, *ipso*-C).

*4.3.3.2. [2*R*-(2α(*S**),3aα,4β,7β,7aα)]-α-Ethyl-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol* ***30B***. Yield: 0.034 g (3.4%) of a colorless oil. R_f (PE:Et_2O, 4:1)=0.43, $[\alpha]_D^{20}=-9.56$ (c 0.68, $CHCl_3$); $C_{21}H_{30}O_2$ (314.47): calculated: C 80.21, H 9.62; found: C 80.36, H 9.80; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.64–2.20 (m, 22H, aliphatic-H, therein: 0.78, 0.95, and 0.98 (3s, 9H, CH_3) and 0.71 (s, 3H, C*-CH_2-CH_3)), 3.84 (d, 1H, 7a-H), 4.32 (dd, 1H, 2-H), 7.15–7.40 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=7.47 (q, 3H, C*-CH_2-CH_3), 11.66/20.04/22.71 (3q, 3CH_3), 28.63 (t, C-5), 31.89/32.35 (2t, C*-CH_2, C-6), 32.83 (t, C-3), 46.25/48.66 (2s, C-7, C-8), 48.66/49.31 (2d, C-4, C-3a), 80.66 (s, C*), 87.43 (d, C-2), 94.74 (d, C-7a), 125.92 (2d, *ortho*-C), 126.34 (d, *para*-C), 127.96 (2d, *meta*-C), 143.03 (s, *ipso*-C).

4.3.4. Rearrangement of ***18***

Following **GP-2**, 3.38 ml (8.76 mmol) of *n*-butyllithium was added to a solution of 1 g (2.92 mmol) of **18** in 13 ml of anhydrous THF. The crude product was purified by SC (100 g silica gel, PE:Et_2O, 10:1).

*4.3.4.1. [2*R*-(2α(*R**),3aα,4β,7β,7aα)]-α-Butyl-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol* ***31A***. Yield: 0.015 g (1.5%) of a colorless oil. R_f (PE:Et_2O, 4:1)=0.35, $[\alpha]_D^{20}=-20.7$ (c 1.5, $CHCl_3$); $C_{23}H_{34}O_2$ (342.52): calculated: C 80.65, H 10.01; found: C 80.93, H 9.81; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.30 (m, 26H, aliphatic-H, therein: 0.77, 0.92, and 0.96 (3s, 9H, CH_3)), 2.55 (s, 1H, OH), 3.83 (d, 1H, 7a-H), 4.13 (dd, 1H, 2-H), 7.16–7.53 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.57/14.11/19.84/22.69 (4q, 4CH_3), 23.43/25.49 (2t, C*-CH_2-*C*H_2-*C*H_2), 28.56 (t, C-5), 31.90 (t, C-3), 32.29 (t, C-6), 34.98 (t, C*-CH_2), 46.24/48.73 (2s, C-7, C-8), 48.44/49.39

(2d, C-4, C-3a), 79.48 (s, C*), 88.80 (d, C-2), 94.54 (d, C-7a), 126.68 (d, *para*-C), 126.83 (2d, *ortho*-C), 127.90 (2d, *meta*-C), 142.49 (s, *ipso*-C).

*4.3.4.2. [2*R*-(2α(*S**),3aα,4β,7β,7aα)]-α-Butyl-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol **31B**.* Yield: 0.022 g (2.2%) of a colorless oil. R_f (PE:Et_2O, 4:1)=0.50, $[\alpha]_D^{20}=-13.3$ (c 2.2, $CHCl_3$); $C_{23}H_{34}O_2$ (342.52): calculated: C 80.65, H 10.01; found: C 80.43, H 10.30; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.72–2.20 (m, 26H, aliphatic-H, therein: 0.77, 0.93, and 0.97 (3s, 9H, CH_3)), 3.84 (d, 1H, 7a-H), 4.28 (dd, 1H, 2-H), 7.11–7.41 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.67/14.04/20.03/22.70 (4q, 4CH_3), 23.09/25.39 (2t, C*-CH_2-*C*H_2-*C*H_2), 28.62 (t, C-5), 32.35 (t, C-6), 32.74 (t, C-3), 39.06 (t, C*-CH_2), 46.26/48.64 (2s, C-7, C-8), 48.64/49.30 (2d, C-4, C-3a), 80.41 (s, C*), 87.65 (d, C-2), 94.75 (d, C-7a), 125.80 (2d, *ortho*-C), 126.30 (d, *para*-C), 127.96 (2d, *meta*-C), 143.43 (s, *ipso*-C).

*4.3.5. Rearrangement of **21***

Following **GP-2**, 0.46 ml (1.18 mmol) of *n*-butyllithium was added to a solution of 0.14 g (0.46 mmol) of **21** in 2 ml of anhydrous THF. The crude product was purified by VFC (5 g silica gel, PE:Et_2O, 30:1).

*4.3.5.1. [2*R*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α,α-diphenyl-4,7-methanobenzofuran-2-methanol **32**.* Yield: 0.068 g (41%) of a colorless oil. R_f (PE:Et_2O, 8:1)=0.21, $[\alpha]_D^{20}$=+36.5 (c 1.2, $CHCl_3$); $C_{25}H_{30}O_2$ (362.51): calculated: C 82.83, H 8.34; found: C 82.56, H 8.25; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.23 (m, 17H, aliphatic-H, therein: 0.81, 0.97, and 1.07 (3s, 9H, CH_3)), 2.62 (s, 1H, OH), 3.90 (d, 1H, 7a-H), 5.15 (dd, 1H, 2-H), 7.13–7.54 (m, 10H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.51/19.96/22.73 (3q, 3CH_3), 28.59 (t, C-5), 32.20 (t, C-6), 33.33 (t, C-3), 46.03/48.84 (2s, C-7, C-8), 48.73/49.43 (2d, C-4, C-3a), 81.40 (s, C-OH), 85.07 (d, C-2), 95.04 (d, C-7a), 126.49/126.87 (2d, 2×*para*-C), 126.21/127.59/127.90 (8d, 4×*ortho*-C, 4×*meta*-C), 144.95/146.04 (2s, 2×*ipso*-C).

*4.3.6. Rearrangement of **22***

Following **GP-2**, 0.84 ml (2.17 mmol) of *n*-butyllithium was added to a solution of 0.267 g (0.72 mmol) of **22** in 3.5 ml of anhydrous THF. The crude product (complex mixture) was purified by SC (27 g silica gel, gradient of PE:Et_2O, 30:1 to Et_2O to Et_2O:MeOH, 8:1 to MeOH). Compounds **37A** and **37B** were isolated instead of the expected products.

*4.3.6.1. [2*R*-(2α(*R**),3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α-pentyl-α-phenyl-4,7-methanobenzofuran-2-methanol **37A**.* Yield: 0.026 g (10%) of a slightly yellow oil. R_f (PE:Et_2O, 10:1)=0.29, $[\alpha]_D^{20}=-12.3$ (c 1.22, $CHCl_3$); $C_{24}H_{36}O_2$ (356.55): calculated: C 80.85, H 10.18; found: C 80.79, H 10.37; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.72–2.24 (m, 28H, aliphatic-H, therein: 0.76, 0.90, and 0.96 (3s, 9H, CH_3)), 3.83 (d, 1H, 7a-H), 4.12 (dd, 1H, 2-H), 7.13–7.52 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.57/14.07/19.84/22.69 (4q, 4CH_3), 22.65/22.98 (2t, C*-CH_2-CH_2-*C*H_2-*C*H_2), 28.56 (t, C-5), 31.90 (t, C-3), 32.29 (t, C-6), 32.64 (t, C*-CH_2-*C*H_2), 35.15 (t, C*-CH_2), 46.25/48.73 (2s, C-7, C-8), 48.39/49.39 (2d, C-4, C-3a), 79.51 (s, C*), 88.83 (d, C-2), 94.54 (d, C-7a), 126.68 (d, *para*-C), 126.83 (2d, *ortho*-C), 127.91 (2d, *meta*-C), 142.48 (s, *ipso*-C).

*4.3.6.2. [2*R*-(2α(*S**),3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α-pentyl-α-phenyl-4,7-methanobenzofuran-2-methanol **37B**.* Yield: 0.026 g (10%) of a slightly yellow oil. R_f (PE:Et_2O, 10:1)=0.44, $[\alpha]_D^{20}=-8.57$ (c 0.98, $CHCl_3$); $C_{24}H_{36}O_2$ (356.55): calculated: C 80.85, H 10.18; found: C 80.57, H

10.28; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.30 (m, 28H, aliphatic-H, therein: 0.76, 0.93, and 0.97 (3s, 9H, CH_3)), 3.83 (d, 1H, 7a-H), 4.29 (dd, 1H, 2-H), 7.12–7.40 (m, 5H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.67/14.01/20.02/22.70 (4q, 4CH_3), 22.54/22.84 (2t, C*-CH_2-CH_2-*C*H_2-*C*H_2), 28.61 (t, C-5), 32.23 (t, C-6), 32.35 (t, C-3), 32.73 (t, C*-CH_2-*C*H_2), 39.24 (t, C*-CH_2), 46.25/48.64 (2s, C-7, C-8), 48.64/49.30 (2d, C-4, C-3a), 80.43 (s, C*), 87.65 (d, C-2), 94.73 (d, C-7a), 125.79 (2d, *ortho*-C), 126.30 (d, *para*-C), 127.95 (2d, *meta*-C), 143.42 (s, *ipso*-C).

*4.3.7. Rearrangement of **23***

Following **GP-2**, 1.76 ml (3.13 mmol) of *n*-butyllithium was added to a solution of 0.3 g (1.04 mmol) of **23** in 3.8 ml of anhydrous THF. The crude product was purified by SC (80 g silica gel, gradient of PE:Et_2O, 2:1 to Et_2O to MeOH).

*4.3.7.1. [2*R*-(2α,3aα,4β,7β,7aα)]-α-(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)-pyridin-2-methanol **33A**, **33B**.* Yield: 0.035 g (12%) of colorless crystals (diastereomeric mixture, **33A**:**33B**, 1:4.71 (^{1}H NMR)). R_f (Et_2O:PE, 2:1)=0.23; $C_{18}H_{25}NO_2 \cdot 0.25\ H_2O$ (291.91): calculated: C 74.06, H 8.81, N 4.80; found: C 74.07, H 8.83, N 4.64; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.78–2.40 (m, 34H, aliphatic-H, therein: 0.80, 0.96, and 0.98 (6s, 18H, CH_3)), 3.85 (d, 1H, 7a-H (A)), 4.07 (d, 1H, 7a-H (B)), 4.14–4.29 (m, 2H, 2-H (A,B)), 4.51 (d, 1H, C*–H (A)), 4.77 (d, 1H, C*–H (B)), 7.20 (2dd, 2H, 5′-H (A,B)), 7.27 (d, 1H, 3′-H (B)), 7.42 (d, 1H, 3′-H (A)), 7.66 (2dd, 2H, 4′-H (A,B)), 8.53 (2d, 2H, 6′-H (A,B)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.57/20.28/22.67 (6q, 6CH_3), 28.63 (2t, C-5 (A,B)), 31.66 (t, C-3 (B)), 32.21 (2t, C-6 (A,B)), 32.63 (t, C-3(A)), 46.58/48.24 (4s, C-7, C-8 (A,B)), 47.73/48.90 (2d, C-4, C-3a (A)), 48.38/49.03 (2d, C-4, C-3a (B)), 74.87 (d, C* (B)), 75.67 (d, C* (A)), 83.85 (d, C-2 (A)), 84.04 (d, C-2 (B)), 92.16 (d, C-7a (A)), 93.29 (d, C-7a (B)), 121.61/122.40 (2d, C-3′/C-5′ (B)), 121.68/122.54 (2d, C-3′/C-5′ (A)), 136.44 (d, C-4′ (B)), 136.57 (d, C-4′ (A)), 147.79 (d, C-6′ (B)), 148.23 (d, C-6′ (A)), 158.79 (s, C-2′ (B)), 159.92 (s, C-2′ (A)).

*4.3.8. Rearrangement of **25***

Following **GP-2**, 2.24 ml (3.98 mmol) of *n*-butyllithium was added to a solution of 0.5 g (1.33 mmol) of **25** in 6.3 ml of anhydrous THF. The crude product was purified by SC (50 g silica gel, gradient of PE:Et_2O, 1:1 to MeOH).

*4.3.8.1. [2*R*-(2α,3aα,4β,7β,7aα)]-Octahydro-7,8,8-trimethyl-α-(3,4,5-trimethoxyphenyl)-4,7-methanobenzofuran-2-methanol **35A**, **35B**.* Yield: 0.210 g (42%) of a colorless oil (diastereomeric mixture, **35A**:**35B**, 1:1.78 (^{1}H NMR)). R_f (Et_2O:PE, 2:1)=0.28; $C_{22}H_{32}O_5$ (376.49): calculated: C 70.19, H 8.57; found: C 70.42, H 8.58; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.70–2.36 (m, 34H, aliphatic-H (A,B)), 3.65–4.32 (m, 23H, C*-H (A), 2-H (A,B), 7a-H (A,B)), 4.78 (d, 1H, C*-H (B)), 6.54 (s, 4H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.55/20.36/22.54 (3q, 3CH_3 (A)), 11.61/20.10/22.66 (3q, 3CH_3 (B)), 28.63 (t, C-5 (B)), 28.71 (t, C-5 (A)), 31.09/32.29 (2t, C-3, C-6 (B)), 32.18/32.78 (2t, C-6, C-3 (A)), 46.70/48.22 (2s, C-7, C-8 (A)), 46.39/48.43 (2s, C-7, C-8 (B)), 47.58/48.86 (2d, C-3a, C-4 (A)), 48.57/49.18 (2d, C-4, C-3a (B)), 56.03 (4q, O-CH_3 (A,B)), 60.74 (2q, O-CH_3 (A,B)), 75.46 (d, C*-OH (A)), 76.93 (d, C*-OH (B)), 84.50 (d, C-2 (A)), 84.72 (d, C-2 (B)), 91.19 (d, C-7a (A)), 94.06 (d, C-7a (B)), 102.81 (2d, *ortho*-C (B)), 104.39 (2d, *ortho*-C (A)), 135.88/136.92/137.67 (4s, *para*-C, *ipso*-C (A,B)), 153.14/153.06 (4s, *meta*-C (A,B)).

References

1. Wittig, G.; Löhman, L. *Liebigs Ann. Chem.* **1942**, *550*, 260.
2. (a) Schöllkopf, U. *Angew. Chem.* **1970**, *82*, 795; *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763. (b) Schöllkopf, U. In *Methoden der Organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Thieme: Stuttgart, 1970; Vol. 13/1, 228. (c) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 3, 975. (d) Tomooka, K.; Nakai, T. *J. Synth. Org. Chem., Jpn.* **1996**, *54*, 1000.
3. Yamamoto, H.; Tomooka, K.; Nakai, T. *Liebigs Ann.* **1997**, 1275.
4. (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.
5. (a) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043. (b) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (c) Grindley, T. B.; Wickramage, C. *J. Carbohydr. Chem.* **1988**, *7*, 661. (d) Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.
6. (a) Lansbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78. (b) Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* **1968**, 2809. (c) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375. (d) Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1957. (e) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1993**, *34*, 8139. (f) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927. (g) Maleczka Jr., R. E.; Geng, F. *J. Am. Chem. Soc.* **1998**, *120*, 8551.
7. Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317.
8. (a) Letschnig, M. F. Diploma Thesis, Inst. of Org. Chem., Vienna University of Technology, 1995. (b) Knollmüller, M.; Gärtner, P.; Letschnig, M. F. 11th International Conference on Organic Synthesis, Amsterdam, The Netherlands, June 30–July 4 1996; Abstract p. 479. (c) Knollmüller, M.; Gärtner, P.; Letschnig, M. F. 6th Blue Danube Symposium on Heterocyclic Chemistry, Brno, Czech Republic, September 1–4, 1996; Abstract p. 88. (d) Knollmüller, M.; Gärtner, P.; Letschnig, M. F. 7th Blue Danube Symposium on Heterocyclic Chemistry, Eger, Hungary, June 7–10, 1998; Abstract PO86. (e) Knollmüller, M.; Gärtner, P.; Letschnig, M. F. *Monatsh. Chem.* **1998**, *129*, 953.
9. Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917.
10. Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231.
11. Noe, C. R.; Knollmüller, M.; Wagner, E.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 1733.
12. (a) Noe, C. R.; Knollmüller, M.; Oberhauser, B.; Steinbauer, G.; Wagner, E. *Chem. Ber.* **1986**, *119*, 729. (b) Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231. (c) Noe, C. R.; Knollmüller, M.; Göstl, G.; Oberhauser, B.; Völlenkle, H. *Angew. Chem.* **1987**, *99*, 467; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 442.
13. (a) *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E.; Eds.; Thieme: Stuttgart, 1996; Vol. E21, p. 335. (b) Mousset, G. *Bull. Soc. Chim. Fr.* **1971**, 4097.
14. Banfi, L.; Potenza, D.; Severini Ricca, G. *Org. Magn. Reson.* **1984**, 224.
15. Crystal data: $C_{18}H_{26}O_2$; M=286.40, orthorhombic, space group $P2_12_12_1$, a=7.090(2), b=20.182(6), c=23.354(8) Å, $\alpha=\beta=\gamma$=90°, U=3342(2) Å^3, Z=8, D_c 1.139 Mg/m^3, T=297(2) K, μ=0.072 mm^{-1}, F(000)=1248, colorless prism (0.07×0.07×0.56 mm). Data were collected on a Philips PW1100 four-circle diffractometer (sealed X-ray tube, graphite monochromator, Mo-Kα radiation, λ=0.71073 Å, ω-scans). Structure solution by direct methods, refinement by full-matrix least squares on F^2 (Sheldrick, G. M.; *SHELX-97, A System of Computer Programs for Crystal Structure Determination*; University of Göttingen, 1997.) Data/restraints/parameters=2366/69/382; final $R1$=0.073 (observed data), $wR2$=0.147 (all data).
16. Further details on the crystal structure determination have been deposited with the Cambridge Structural Database.