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[1,2]-Wittig rearrangement of acetals. Part 2: The influence of reaction conditions[1]

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Abstract

Acetals of seven alcohols with (+)-camphor derived enantiomerically pure 7,8,8-trimethyl-4,7-methanobenzofuran-2-ol were subjected to different reaction conditions favorable for a [1,2]-Wittig rearrangement. Results with regard to conversion, yield and stereochemical course depending on the reaction conditions are discussed.

1. Introduction

The [1,2]-Wittig rearrangement of acetals has gained much interest as a new method for the synthesis of *C*-glycosides which cannot be obtained easily by other methods.[2] In our own efforts towards a better understanding of this reaction we have recently described results with regard to substrate dependence of conversion, yield and stereochemical course.[1] To exclude the possibility that observed differences with regard to the investigated parameters were due only to the different structure of the substrates we carried out all the reactions under a standardized protocol. Since the observed yields and stereoselectivities were only satisfactory to a limited degree we wanted to investigate whether some improvement could be achieved by running the reaction under other conditions, i.e. varying solvent, temperature, reaction time, equivalents of base and base activating additives.

2. Results and discussion

The acetals **1**–**10**[1] were treated with butyl lithium under conditions which were systematically changed for each experiment (Scheme 1).

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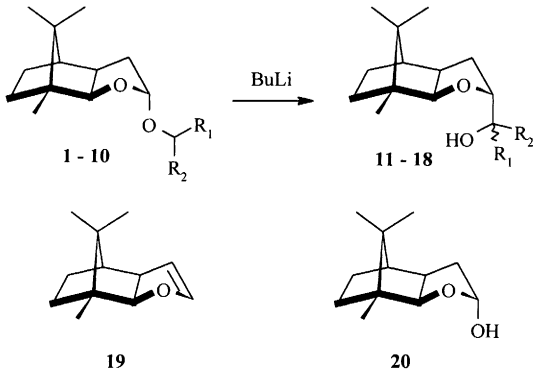


	R_1	R_2
1, 11	Ph	H
2, 12	Ph	Me
3, 13	Ph	Et
4, 14	Ph	*n*-Bu
5, 15	Ph	Ph
6, 16	2-Pyridyl	H
7, 17	2-MeOPh	H
8, 18	3,4,5-$(MeO)_3$Ph	H
9	Ph	*i*-Pr
10	Ph	*t*-Bu

Scheme 1. [1,2]-Wittig rearrangement of the acetals **1**–**10**

Details for experimental parameters and results with regard to conversion, yield and stereoselectivity as well as for by-product formation in each series are given in Tables 1–10.

Most of the substrates yielded only the rearranged alcohols **11**–**18** besides unreacted starting material **1**–**10** and product **19** which can be formed under these conditions by β-elimination from the acetals. The relative amount of **19** was usually higher under more basic conditions (**1**–**7**, **1**–**12**, **5**–**5**). All reactions proceeded with complete retention with regard to the former acetal center. The assignment of configuration for this center as well as for the newly formed alcohol center which is given in Tables 1–10 was based on characteristic shift differences observed in the ^{1}H and ^{13}C NMR spectra, as described earlier.[1] Only in the rearrangement of **6** was a further by-product **20** formed each time: it is the product of water addition to **19** and it seems as if the pyridine ring present in the aglycon-part of **6** has a significant influence on the formation of **20**.

Depending on the scale of the reaction and the rate of addition of the base a rise in temperature was usually observed. Since the temperature seems to be a crucial factor with regard to yield (compare **1**–**6** with **1**–**4**, **6**–**2** with **6**–**1**, **7**–**7** with **7**–**5**) and selectivity (compare **1**–**6** with **1**–**4**, **7**–**7** with **7**–**5**) it was important to observe and control it very carefully for reasons of comparison. In general we always tried to compare experiments in which the only parameter under question was changed. In the large scale experiment **1**–**3** the rise in temperature was already high at the beginning of the addition of the base so we had to cool the mixture before more base was added. In contrast to other experiments conducted at lower temperature in this case the stereoselectivity dropped.

Reactions in Et_2O for most of the acetals gave better selectivities but lower yields (**1**–**4**, **2**–**2**, **7**–**4**, **8**–**2**) even if the configuration of the major product was switched (**7**–**4**). However, in two experiments yields are better in this solvent (**5**–**2**, **6**–**4**) but selectivities are worse (**6**–**4**) compared with experiments performed in THF under standard temperature conditions. If the reaction was carried out in the apolar solvents *n*-hexane or toluene the yield was usually very low (**1**–**9**, **1**–**10**, **2**–**3**, **2**–**4**, **5**–**3**, **5**–**4**) and sometimes the stereoselectivity was inverted (**1**–**9**, **1**–**10**, **7**–**5**, **7**–**8**, **8**–**3**, **8**–**4**) compared to the results in THF. For acetals **6**–**8** which bear additional moieties capable of complex formation with butyl lithium no such influence on the yield was observed. For the other acetals yields in apolar solvents could be improved if more equivalents of base at higher temperature (**1**–**11**) or additives such as TMEDA (**1**–**12**, **2**–**5**, **5**–**5**) or (−)-sparteine (**7**–**9**) were used. But this again resulted in a switch of the configuration of the major isomer (**1**–**11**, **1**–**12**, **2**–**5**, **7**–**9**). This change in stereoselectivity was also observed when these additives were used in more polar solvents (**3**–**2**), but this time not necessarily improving the yield. One experiment (**3**–**3**) in which HMPA was used as an additive in THF even showed no conversion at all. So did another one in which a polar coordinating solvent was used (**4**–**3**).

Table 1
Summary of the [1,2]-Wittig rearrangement of acetal **1**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 1 [%]	Yield of 19 [%]	Yield of 11 [%]	De [%] of 11
1-1	THF	3	3	28→39→28[a]	-	21	55	24 (S)
1-2	THF	1	15	22	29	11	36	14 (S)
1-3	THF	3	3	22→40→-5→22[b]	-	27	53	8 (S)
1-4	Et_2O	3	3	24→25→24[a]	35	19	35	38 (S)
1-5[c]	Et_2O	3	3	20→33.5[d]	12	34	49	20 (S)
1-6	Et_2O	3	3	34→39→36[a]	8	27	59	18 (S)
1-7	Et_2O	6[e]	3.5	-60→22[f]	20	42	17	24 (S)
1-8	Et_2O	12[g]	18	-10→22[h]	6	24	42	48 (S)
1-9	Toluene	3	3	22→29→22[a]	85	-	4	12 (R)
1-10	*n*-hexane	3	3	22→26→22[a]	90	5	4	26 (R)
1-11	*n*-hexane	12[g]	48	22→50[i]	39	21	28	24 (S)
1-12	*n*-hexane	3[j]	3	22→33→22[a]	-	42	30	12 (S)

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] Rise in temp. was so high already at the beginning in this large scale experiment that mixture was cooled to -5°C before the remaining amount of base was added. When add. was complete the cooling bath was removed. [c] React. was irradiated with a wide-band lamp. [d] Rise in temp. occurred during add. of base, but temp. did not drop afterwards due to heat produced by irradiation lamp. [e] *t*-BuLi was used instead of *n*-BuLi. [f] React. was cooled, base was added, and cooling bath was removed. [g] 3 equiv. was added at the beginning and further 9 equiv. 3h before the react. was stopped. [h] React. was cooled and kept at this temp. for 2h before it was allowed to reach RT. [i] React. was kept at RT for 24h and then heated. [j] 3 equiv. of TMEDA was added to BuLi.

If less than 3 equiv. of base were used yields in most of the experiments were lower (**1**–**2**, **7**–**2**) even if the reaction was allowed to proceed longer (**1**–**2**) or at higher temperature (**7**–**2**). Addition of further base at a later stage also did not improve the yield significantly (**7**–**3**). For acetal **6** with the pyridine-moiety the yield was not influenced at all, but unexpectedly the stereoselectivity was higher when less base for a shorter reaction time was used (**6**–**3**). It was also the other diastereomer which was formed in excess under these conditions.

Bearing in mind the proposed radical mechanism[2b,c,3] for the [1,2]-Wittig-rearrangement we carried out one experiment (**1**–**5**) in which we irradiated the reaction mixture with a wide-band lamp. As expected the yield could be improved, but the selectivity dropped to half of the value obtained without irradiation. However, as was shown by another experiment at elevated temperature without irradiation (**1**–**6**), this was due only to the rise in temperature caused by the irradiation lamp.

The use of *t*-BuLi at lower temperatures instead of *n*-BuLi resulted for acetal **1** in a low yield (**1**–**7**) and a slight drop in stereoselectivity whereas no significant changes were observed with acetal **4**. The addition of base in two portions did not influence either the yield or the selectivity (**7**–**6**), but if a large excess of

Table 2
Summary of the [1,2]-Wittig rearrangement of acetal **2**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 2 [%]	Yield of 19 [%]	Yield of 12 [%]	De [%] of 12
2-1	THF	3	3	23→30→23[a]	64	3	26	50 (S)
2-2	Et_2O	3	3	25→27→25[a]	88	-	4.4	72 (S)
2-3	toluene	3	3	22	100	-	-	-
2-4	*n*-hexane	3	3	22	>99	-	<1	38 (S)
2-5	*n*-hexane	3[b]	3	23→27→23[a]	63	6	23	13 (R)

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] 3 equiv. of TMEDA was added to BuLi.

Table 3
Summary of the [1,2]-Wittig rearrangement of acetal **3**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 3 [%]	Yield of 13 [%]	De [%] of 13
3-1	THF	3	3	20→30→20[a]	88	6	12 (S)
3-2	THF	3[b]	3	20→30→20[a]	97	1.2	67 (R)
3-3	THF	3[c]	3	20→35→20[a]	n.d.[d]	-	-

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] 3.3 equiv. of TMEDA was added to BuLi. [c] 9 equiv. of HMPA was added to BuLi. [d] Not determined, but no conversion was seen on TLC.

Table 4
Summary of the [1,2]-Wittig rearrangement of acetal **4**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 4 [%]	Yield of 14 [%]	De [%] of 14
4-1	THF	3	3	24→35→24[a]	95	4	20 (S)
4-2	THF	6[b]	3	-10→-6→-10[a]	96	3	25 (S)
4-3	Et_3N	3	4	22→27→22[a]	100	-	-

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] *t*-BuLi was used instead of *n*-BuLi.

Table 5
Summary of the [1,2]-Wittig rearrangement of acetal **5**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 5 [%]	Yield of 19 [%]	Yield of 15 [%]
5-1	THF	3	3	19→26→19[a]	-	-	41
5-2	Et_2O	3	3	22→26→22[a]	31	-	68
5-3	toluene	3	3	22→24→22[a]	74	-	1
5-4	*n*-hexane	3	3	18→20→18[a]	98	-	-
5-5	*n*-hexane	3[b]	3	23→27→23[a]	-	27	40

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base.
[b] 3 equiv. of TMEDA was added to BuLi.

Table 6
Summary of the [1,2]-Wittig rearrangement of acetal **6**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 6 [%]	Yield of 19 [%]	Yield of 20 [%]	Yield of 16 [%]	De [%] of 16
6-1	THF	3	3	23→39→23[a]	-	14	18	12	65 (S)
6-2	THF	3	2.5	-60 to -75	72	-	8	-	-
6-3	Et_2O	1	1.3	23→34→23[a]	15	-	8	29	27 (S)
6-4	Et_2O	3	3	24→35→24[a]	-	12	21	28	4 (R)
6-5	toluene	3	3	23→40→23[a]	-	20	18	15	62 (S)
6-6	*n*-hexane	3	3	20→30→20[a]	-	22	16	18	58 (S)

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base.

base was used the yield and selectivity could be raised to acceptable values even at low temperature (**1**–**8**).

The highly hindered acetals **8** and **9** which could not be rearranged under our standard reaction conditions were also resistant in several experiments in which stronger bases, irradiation and a higher temperature were applied.

In one experiment with acetal **5** as the substrate in ether, which was carried out for 72 h to see whether the yield could be further improved, only 37% of **15** was isolated instead of 68%. However, besides **15**, 33% of **21** was obtained. This phenol must have been formed by *ortho*-lithiation of **15** followed by air-oxidation (Scheme 2), which is not unprecedented.[4] Obviously, due to the long reaction time some air must have passed into the reaction flask yielding **21**. Anyway, the combined yield of **15** and **21** was not higher than in the short term experiment.

It is noteworthy that **21** was formed as a single diastereomer, the configuration of which was established by X-ray analysis of the *m*-nosylate **22** (Fig. 1).[5] This was obtained by treatment of **21** with 3-

Table 7
Summary of the [1,2]-Wittig rearrangement of acetal **7**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 7 [%]	Yield of 19 [%]	Yield of 17 [%]	De [%] of 17
7-1	THF	3	3	25→43→25[a]	2	22	67	34 (R)
7-2	THF	1	48	7→23→50[b]	n.d.	n.d.	26	n.d.
7-3	THF	4[c]	72	7→23[d]	n.d.	n.d.	33	n.d.
7-4	Et_2O	3	3	22→26→22[a]	9	33	52	64 (S)
7-5	toluene	3	3	27→36→27[a]	16	24	44	54 (S)
7-6	toluene	3[e]	3	25→30 (28)→25[f]	18	19	41	58 (S)
7-7	toluene	3	3	-70 to –80	93	-	3	68 (S)
7-8	*n*-hexane	3	3	23→30→23[a]	13	25	35	46 (S)
7-9	toluene	2.22[g]	2	-60 to -70	n.d.	n.d.	~10	>90 (R)

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] React. was cooled and kept at this temp. for 3h before it was allowed to reach RT and was then heated for 24h. [c] 1 equiv. of base was added at the beginning and further 3 equiv. after 24h. [d] React. was cooled and kept at this temp. for 3h before it was allowed to reach final temp. [e] 1.5 equiv. of base was added at the beginning and further 1.5 equiv. after 1.5h. [f] Rise in temp. after 2nd add. of base is given in brackets. [g] 2.14 equiv. of (-)-sparteine was added to BuLi.

Table 8
Summary of the [1,2]-Wittig rearrangement of acetal **8**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 8 [%]	Yield of 19 [%]	Yield of 18 [%]	De [%] of 18
8-1	THF	3	3	22→35→22[a]	13	25	42	28 (S)
8-2	Et_2O	3	3	22→28→22[a]	40	16	19	40 (S)
8-3	toluene	3	3	22→30→22[a]	52	27	16	6 (R)
8-4	*n*-hexane	3	3	24→29→24[a]	36	26	20	16 (R)

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base.

nitrobenzenesulfonic acid in the presence of triethylamine. The compound crystallizes in the chiral orthorhombic space group $P2_12_12_1$ with four equivalent molecules in the unit cell linked in chains parallel to **b** via hydrogen bonds O(2)–H(2o)···O(5) with O(2)···O(5)=2.91 Å. The absolute structure could be determined via the anomalous dispersion effect of sulfur and was consistent with the known configuration of the (+)-camphor moiety. The configuration at the carbinol carbon atom C13 was found to be *S*, as shown in Fig. 1.[6]

A further interesting observation was made when acetal **8** was rearranged in *n*-hexane. Unexpectedly

Table 9
Summary of the [1,2]-Wittig rearrangement of acetal **9**

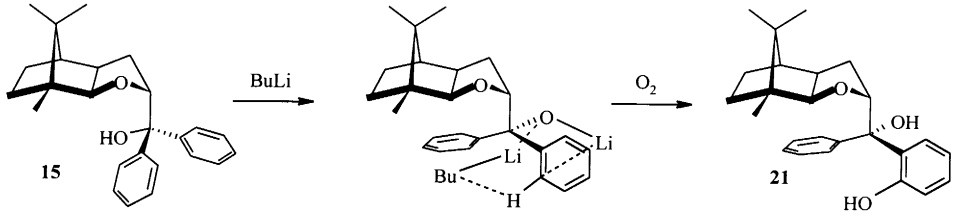
React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 9 [%]
9-1	THF	3	3	22→31→22[a]	97
9-2	THF	6[b]	2.5	22→-15 to -8[c]	n.d.[d]
9-3[e]	THF	3	3	22	n.d.[d]
9-4	*n*-hexane	3	144	69	n.d.[d]

[a] Temp. before add. → rise in temp. caused by add. → temp. after add. of base. [b] *t*-BuLi was used instead of *n*-BuLi. 3 equiv. was added at the beginning and further 3 equiv. after 0.5h. [c] After 0.5h at RT react. was cooled before the second portion of base was added. [d] Not determined, but no significant conversion was seen on TLC. [e] React. was irradiated with a wide-band lamp.

Table 10
Summary of the [1,2]-Wittig rearrangement of acetal **10**

React. No.	Solvent	Equiv. of BuLi.	React. time [h]	React. temp. [°C]	Rec. 10 [%]
10-1	THF	3	24	22	n.d.[a]
10-2	toluene	5[b]	24	23→33→23[c]	>99

[a] Not determined, but no significant conversion was seen on TLC. [b] *s*-BuLi was used instead of *n*-BuLi. 1.6 equiv. of (-)-sparteine was added to BuLi. [c] Temp. before add. → rise in temp. caused by add. → temp. after add. of base.



Scheme 2. Stereoselective hydroxylation of **15**

one of the phenolic methyl ethers was cleaved selectively during this reaction, giving rise to compound **23** (Fig. 2). Since a separation of the diastereomeric alcohols **18** was not possible and we had already been successful via formation of acetals,[1] product **24** (Fig. 2) was synthesized from **18** by a standard procedure.[7] Unfortunately, in this case even the acetals **24** could not be separated.

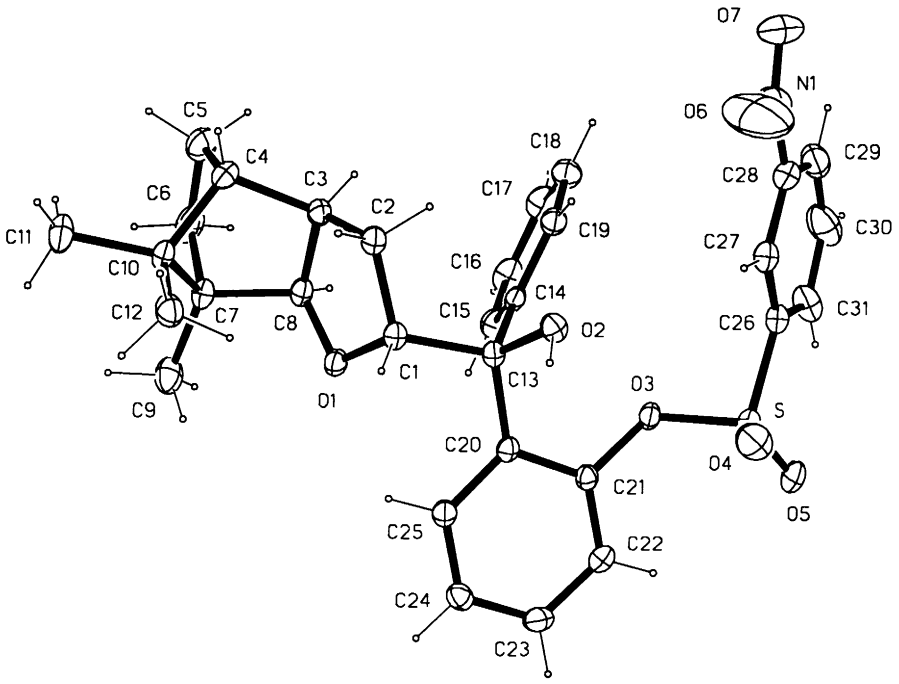


Fig. 1. Molecular structure of **22** in crystalline state (20% ellipsoids) with crystallographic atom numbering. Selected geometric data [Å, °]: O1–C1=1.429(3), O1–C8=1.438(3), C1–C13=1.559(3), C13–O2=1.437(3), C21–O3=1.415(3), O(3)–S=1.582(3), O1–C1–C13–O2=−177.8(2), C1–C13–O2–H2o=70.7

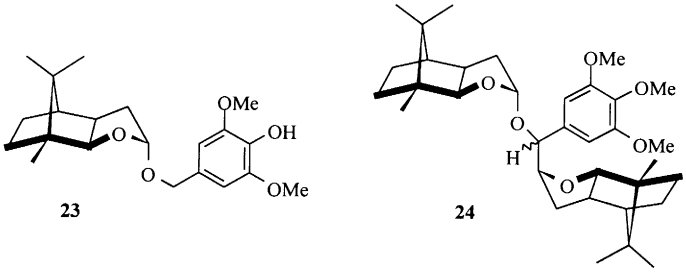


Fig. 2. By-product **23** derived from **8** by selective ether-cleavage and acetal **24**

3. Conclusion

From the obtained data it must be concluded that the yield as well as the selectivity, and this not only with regard to the absolute value but also the configuration of the newly formed alcohol carbon for the major isomer, in the [1,2]-Wittig rearrangement of acetals can be heavily influenced by solvent, additives, temperature and amount of base. Although some general dependencies could be elaborated it is difficult to predict, for a single experiment under different reaction conditions, what will be the result. However, one point on which we could shed light is the fact that the earlier proposed mechanism[2b–c,3b–d] in which the two radical fragments are tightly held together through coordination with the lithium counter-ion cannot be operative, or at least not in this simple manner; otherwise the selectivity should be higher in solvents which are not able to coordinate, and more convincingly the configuration of the major isomer should not be changed. Since the opposite is observed we have to assume that in the presence of coordinating agents these are involved in the transition state and have a high impact on the stereoselectivity. Only in

cases where coordination within the radical fragment itself is possible is no such dependence observed. A further consideration which might be of general interest, but which must be secured by some further experiments, is a possible reaction time or conversion dependence of the stereoselectivity. Experiments with regard to this aspect will be published in the near future.

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}; visualization of the spots with molybdato phosphoric acid (5% in ethanol) and heating. Column chromatography and vacuum flash chromatography (VFC) were carried out with Merck silica gel 60 (230–400 mesh). Abbreviation used: PE=petroleum ether. The concentration of *n*-butyl lithium in *n*-hexane was determined by titration with *t*-butanol using 1,10-phenanthroline as indicator. For a general procedure for the rearrangements of acetals **1**–**10** see Ref. 1.

4.2. [2R-(2α(S*),3aα,4β,7β,7aα)]-Octahydro-α-(2-hydroxyphenyl)-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanol **21**

n-Butyl lithium (0.49 ml, 1.26 mmol) in *n*-hexane was added dropwise to a solution of **5** (0.150 g, 0.41 mmol) in anhydrous diethyl ether (2.5 ml) at room temperature. The reaction mixture was stirred for 72 h, quenched with water, and 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 product was purified by VFC (10 g silica gel, gradient of PE:Et_2O=30:1 to 10:1). Yield: 0.055 g (37%) of **15**[1]and 0.049 g (33%) of **21**. Colorless crystals, mp=154–155°C (*n*-hexane:CH_2Cl_2), R_f (PE:Et_2O=8:1)=0.13, $[\alpha]_D^{20}$=+22.0 (c 0.60, $CHCl_3$); $C_{25}H_{30}O_3$ (378.51): calculated: C 79.33, H 7.99; found: C 79.37, H 8.23; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.75–2.45 (m, 17H, aliphatic-H, therein: 0.81, 0.97 and 1.06 (3s, 9H, CH_3)), 3.20 (s, 1H, OH), 3.94 (d, 1H, 7a-H), 5.07 (dd, 1H, 2-H), 6.65–7.60 (m, 9H, aromatic-H), 9.22 (s, 1H, Ph-OH); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.46/19.93/22.72 (3q, 3 CH_3), 28.58 (t, C-5), 32.21 (t, C-6), 33.47 (t, C-3), 46.01/48.97 (2s, C-7, C-8), 48.76/49.47 (2d, C-4, C-3a), 85.45 (d, C-2), 86.01 (s, C*), 95.38 (d, C-7a), 117.83/119.25 (2d, 2**meta*-C), 127.13 (s, *ipso*-C), 127.66/128.09 (2d, 2**ortho*-C′, 2**meta*-C′), 127.52/128.59/128.73 (3d, *para*-C, *ortho*-C, *para*-C′), 145.03 (s, *ipso*-C′), 155.88 (s, *ortho*-C-OH).

4.3. [2R-(2α(S*),3aα,4β,7β,7aα)]-2-[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)-hydroxyphenylmethyl]phenyl 3-nitrobenzenesulfonate **22**

m-Nitrobenzenesulfonic acid (0.891 g, 0.402 mmol) and anhydrous NEt_3 (0.11 ml, 0.654 mmol) were added dropwise to a solution of **21** (0.10 g, 0.264 mmol) in anhydrous dichloromethane (5 ml) at 0°C. The cooling bath was removed, the reaction mixture was stirred for 17 h at room temperature and then quenched with water. The aqueous phase was extracted twice with dichloromethane and the combined organic layers were dried with sodium sulfate and filtered. The solvent was evaporated and the crude product was purified by VFC (10 g silica gel, PE:Et_2O=4:1). Yield: 0.131 g (88%)

of colorless crystals. Mp=203–206°C (*n*-hexane:$CHCl_3$), R_f (PE:Et_2O=1:1)=0.42, $[\alpha]_D^{20}$=+29.8 (c 0.62, CH_2Cl_2); $C_{31}H_{33}NO_7S$ (563.67): calculated: C 66.06, H 5.90, N 2.48; found: C 66.21, H 6.11, N 2.39; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.65–2.20 (m, 17H, aliphatic-H, therein: 0.79, 0.92 and 1.04 (3s, 9H, CH_3)), 2.75 (s, 1H, OH), 3.68 (d, 1H, 7a-H), 5.14 (dd, 1H, 2-H), 7.00–7.45 (m, 8H, aromatic-H), 7.55–7.80 (m, 2H, aromatic-H), 8.00–8.08 (m, 1H, aromatic-H), 8.45 (dd, 1H, aromatic-H), 8.48 (d, 1H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.48/19.82/22.73 (3q, 3 CH_3), 28.54 (t, C-5), 32.12 (t, C-6), 33.28 (t, C-3), 45.97/48.73 (2s, C-7, C-8), 48.59/49.38 (2d, C-4, C-3a), 79.87 (s, C*), 83.52 (d, C-2), 94.97 (d, C-7a), 120.05/123.26 (2d, 2*aromatic -C), 127.47/127.54 (2d, 4*aromatic-C), 126.43/126.90/128.33/128.94/129.34/130.42/133.30 (7d, 7*aromatic-C), 136.55/137.87/144.03/146.85/148.02 (5s, 5*aromatic-C).

*4.4. [2*R*-(2α,3aα,4β,7β,7aα)]-4-[[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-methyl]-2,6-dimethoxyphenol* ***23***

n-Butyl lithium (2.24 ml, 3.98 mmol) in *n*-hexane was added dropwise to a solution of **8** (0.5 g, 1.33 mmol) in anhydrous *n*-hexane (10 ml) under nitrogen at room temperature. The mixture was stirred for 3 h at room temperature and then quenched with water. The aqueous phase was extracted twice with diethyl ether and the combined organic layers were dried with sodium sulfate and filtered. The solvent was evaporated and the crude product was purified by column chromatography (50 g silica gel, gradient of PE:Et_2O=1:1 to Et_2O). Yield: 0.099 g (20%) of **18**[1] and 0.039 g (3%) of **23**. Colorless oil, R_f (Et_2O:PE=2:1)=0.37, $[\alpha]_D^{20}$=−63.2 (c 0.94, $CHCl_3$); $C_{21}H_{30}O_5$ (362.47): calculated: C 69.59, H 8.34; found: C 69.54, H 8.34; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.73–2.42 (m, 17H, aliphatic-H, therein: 0.79, 0.97 and 1.00 (3s, 9H, CH_3)), 3.86 (s, 6H, 2*O-CH_3), 3.94 (d, 1H, 7a-H), 4.35 (d, 1H, Ph-CH_2), 4.58 (d, 1H, Ph-CH_2), 5.19 (d, 1H, 2-H), 5.52 (s, 1H, Ph-OH), 6.57 (s, 2H, aromatic-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.64/20.44/22.85 (3q, 3 CH_3), 28.85 (t, C-5), 32.43 (t, C-6), 38.57 (t, C-3), 45.93 (d, C-3a), 46.97 (s, C-8), 47.60 (s, C-7), 48.41 (d, C-4), 56.22 (q, 2*O-CH_3), 68.79 (t, Ph-CH_2-O), 91.26 (d, C-7a), 104.26 (d, C-2), 104.97 (d, 2**ortho*-C), 129.38 (s, *ipso*-C), 134.11 (s, *para*-C), 146.90 (s, 2**meta*-C).

*4.5. [2*R*-[2α(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](3,4,5-trimethoxyphenyl)methyl]-7,8,8-trimethyl-4,7-methanobenzofuran* ***24***

A solution of $(MBE)_2O$ (0.876 g, 2.34 mmol), **8** (0.44 g, 1.17 mmol) and 4-methylbenzenesulfonic acid monohydrate (0.038 g, 0.2 mmol) in anhydrous dichloromethane (7 ml) was stirred for 30 min at room temperature. Sodium sulfate was added and stirring was continued 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 and filtered. The solvent was evaporated and the crude product was purified by column chromatography (80 g silica gel, PE:Et_2O=3:1). Yield: 0.287 g (44%) of **24**. Colorless rigid foam. R_f (PE:Et_2O=2:1)=0.27; $C_{34}H_{50}O_6$ (554.77): calculated: C 73.61, H 9.08; found: C 74.02, H 9.27; ^{1}H NMR (200 MHz; $CDCl_3$): δ_H=0.70–2.50 (m, 68H, aliphatic-H (A,B)), 3.75–3.88 (m, 18H, 6*O-CH_3), 3.73/3.87 (2d, 2*1H, 7a-H, 7a′-H (A)), 3.89/4.10 (2d, 2*1H, 7a-H, 7a′-H (B)), 4.10-4.25 (m, 2H, 2*2′-H (A,B)), 4.35 (d, 1H, C*-H (B)), 4.56 (d, 1H, C*-H (A)), 4.97 (dd, 1H, 2-H (B)), 5.27 (dd, 1H, 2-H (A)), 6.56 (s, 2*2H, aromatic-H (A,B)); ^{13}C NMR (50 MHz; $CDCl_3$): δ_C=11.41/11.83/11.91/20.25/20.44/20.62/22.78/22.84 (8q, 12 CH_3 (A,B)), 28.91/31.30/32.39/32.55/33.31/38.34/38.92 (7t, C-3 (A,B), C-3′(A,B), C-6 (A,B), C-6′(A,B), C-5 (A,B), C-5′(A,B)), 46.80/47.06/47.40/47.92 (4s, C-7 (B), C-7′(B), C-8 (B), C-8′(B)),

48.20/47.06/46.80/46.48 (4s, C-7 (A), C-7′(A), C-8 (A), C-8′(A)), 48.78/48.45/47.76/45.82 (4d, C-4 (B), C-4′(B), C-3a (B), C-3a′(B)), 49.2/49.01/48.45/46.17 (4d, C-4 (A), C-4′(A), C-3a (A), C-3a′(A)), 56.01 (s, 2*_meta_-OCH_3 (B), 2*_meta_-OCH_3 (A)), 60.71 (s, _para_-OCH_3 (B), _para_-OCH_3 (A)), 78.07(d, C* (B)), 81.99 (d, C* (A)), 82.37 (d, C-2′ (B)), 84.51 (d, C-2′ (A)), 91.38/90.83 (2d, C-7a (B), C-7a′ (B)), 93.72/91.55 (2d, C-7a (A), C-7a′ (A)), 102.28 (d, C-2 (B)), 103.26 (d, C-2 (A)), 105.07 (d, 2*_ortho_-C (B)), 106.31 (d, 2*_ortho_-C (A)), 137.31/136.64/135.67 (3s, _para_-C (B), _para_-C (A), _ipso_-C (B), _ipso_-C (A)), 152.74 (s, 2*_meta_-C (A)), 152.92 (s, 2*_meta_-C (B)).

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5. Crystal data of **22** (*m*-nosylate of **21**): $C_{31}H_{33}NO_7S$, M=563.64, orthorhombic, space group $P2_12_12_1$, a=10.176(3), b=12.377(4), c=22.164(8) Å, $\alpha=\beta=\gamma=90°$, U=2791.5(16) Å^3, Z=4, D_c=1.341 Mg/m^3, T=296(2) K, μ=0.166 mm^{-1}, F(000)=1192, colorless plate (0.03×0.25×0.30 mm) from ethanol. Diffraction data were collected with a Siemens/Bruker SMART CCD area detector 3-circle diffractometer (sealed X-ray tube, graphite monochromator, Mo-Kα radiation, λ=0.71073 Å, 0.3° ω-scans, 8×606 frames covering the entire reciprocal space with θ_{max}=25°). 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=4925/3/377; final $R1$=0.0468 (observed data), $R1$=0.0588 (all data), $wR2$=0.0947 (all data).
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