Highly Regioselective Bromination of [3a*R*-(3aα,4*β*,7*β*,7aα)]-Hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2(3*H*)-one *via* Nonclassical Bornyl Cations

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Following our ongoing attempts to substitute [2*R*-(2α,-3aα,4*β*,7*β*,7aα)]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol[1] with switchable catalytic functions in close proximity to the acetal reaction center, we had to tackle the challenge of regioselective substitution of the monoterpene moiety. To this end, the well-aimed attack of bromine at specific regions (see Figure 1, left) of the precursor [3a*R*-(3aα,4*β*,7*β*,7aα)]-hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2(3*H*)-one **1**[2] appeared promising, in view of the arsenal of methods developed for the regioselective introduction of bromine into the corresponding methyl and methylene groups (Figure 1, right) of camphor **2** and its derivatives. In particular, elemental bromine in acetic acid is apt to replace either one or both hydrogens at C-3, in the α-position of the carbonyl group (route A in Figure 1, right).[3,4] Starting from 3,3-dibromocamphor**,** bromine in chlorosulfuric acid is preferentially introduced at C-8 (route B), and the subsequent removal of the two labile bromine substituents from C-3 with zinc dust yields 8-bromocamphor.[5] In contrast, the same reagent when applied to 3-bromocamphor leads to attack at C-9 (route C); again, the labile bromine is readily removed by reduction with zinc dust to give 9-bromocamphor.[6] The direct bromination of camphor **2** at C-10 (route D) is not feasible; instead, 10-bromocamphor is prepared *via* sulfonation of **2** at C-10, followed by thermolysis of the corresponding 10-camphorsulfonyl bromide.[7] Regarding the fairly unpredictable steric course of the majority of these reactions, on the other hand, it remained open as to what extent these empirical rules could be transferred to the lactone system **1**.

Results and Discussion

Syntheses. Our plan was to react **1** with bromine in acetic acid to yield a bromo lactone substituted at C-3 (route A in Figure 1, left) which in turn should be prepared for further attack of bromine in chlorosulfuric acid, at either one of the two 8-methyl groups (routes B and C, respectively). In fact, the former reagent, applied to **1** for 6 h at 80 °C, essentially afforded three compounds, as revealed by NMR spectroscopy of the crude reaction mixture. All major constituents could be identified after preparative liquid chromatography with dichloromethane (Scheme 1). Whereas ^{1}H NMR spectra of the main product (51%) **3** showed a characteristic AB system in addition to two intact methyl groups, ^{13}C NMR spectra reported the successful direct bromination of the 7-methyl group (route D). The structure of **3** was also confirmed by X-ray analysis (Figure 2).[8] By the same token, a second reaction product, isolated in a small amount (5%), was identified as the dibromo lactone **7**. Again, the assignment was corroborated by the X-ray structure, as depicted in Figure 3.[9] The third reaction product (21%) differed significantly from the previous ones; in particu-

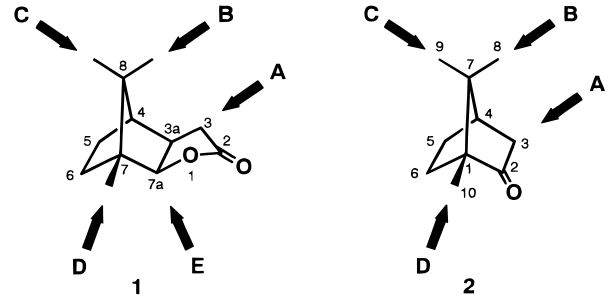
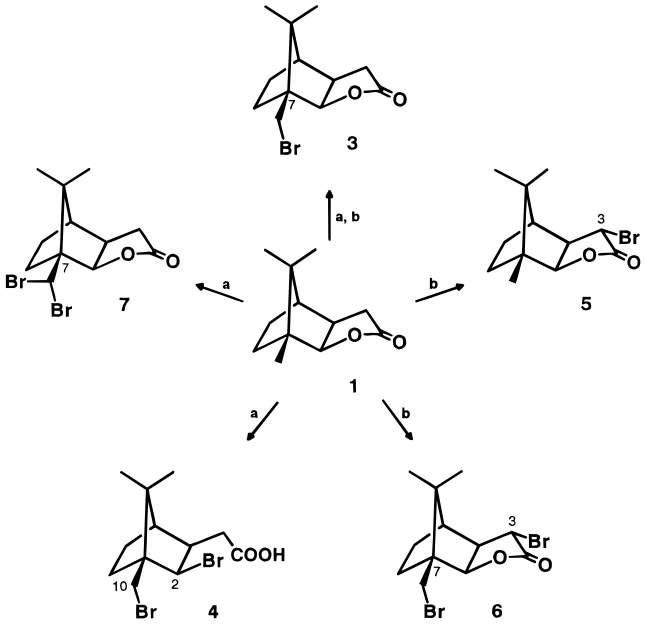


Figure 1. Potential routes for bromination of [3a*R*-(3aα,4*β*,7*β*,-7aα)]-hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2(3*H*)-one (**1**) and camphor **2**, respectively.

Scheme 1. Regioselectivity of the bromination of 1 under different reaction conditions: (a), Br_2 in MeCOOH, 6 h, 80 °C; (b) Br_2 and phosphorus, 3 h, 80 °C.



(1) Noe, C. R.; Knollmüller, M.; Ettmayer, P.; Gärtner, P; Letschnig, M. *Oesterr. Chem. Z.* **1990**, *91*, 36.
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(3) Stevens, R. V.; Gaeta, F. C. A.; Lawrence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713.
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(6) Vaillancourt, V.; Agharahimi, M. R.; Sundram, U. N.; Richou, O.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 378.
(7) Dallacker, F.; Ulrichs, K.; Lipp, M. *Liebigs Ann. Chem.* **1963**, *667*, 50.

(8) Crystal data for **3** ($C_{12}H_{17}BrO_2$): FW = 273.17, $P2_12_12_1$, a = 15.987(3) Å, b = 10.326(2) Å, c = 7.0980(10) Å, V = 1171.8(4) Å^3, Z = 4, D_{calc} = 1.548 g/mL, R = 0.035, Rw = 0.072.
(9) Crystal data for **7** ($C_{12}H_{16}Br_2O_2$): FW = 352.07, $P2_12_12_1$, a = 18.307(7) Å, b = 9.787(4) Å, c = 7.037(2) Å, V = 1260.8(8) Å^3, Z = 4, D_{calc} = 1.855 g/mL, R = 0.054, Rw = 0.116.

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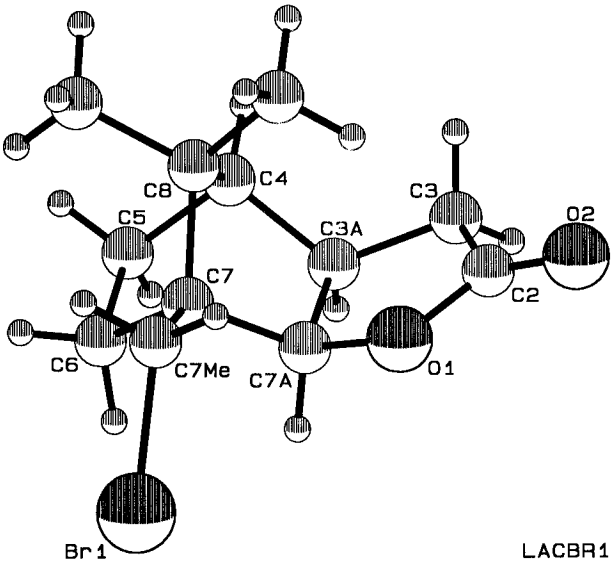

Figure 2. X-ray structure of **3**, PLUTO view.

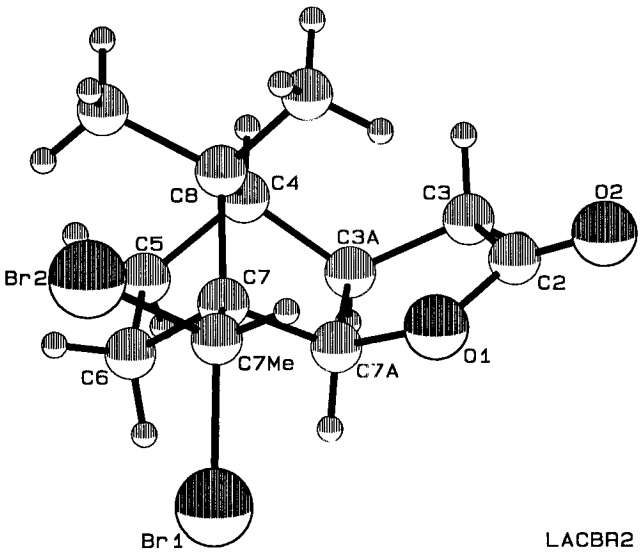

Figure 3. X-ray structure of **7**, PLUTO view.

lar, ^{13}C NMR spectra revealed an upfield shift for the C-7a signal, from 92.1 ppm for **1** to 63.5 ppm for **4**, thus pointing to acid-catalyzed ring opening of the lactone (route E). Both elemental analysis and the small R_f value in liquid and thin layer chromatography agree with a dibromo carboxylic acid. The *exo*-stereochemistry at C-2 follows from the coupling constant $^3J = 8.8$ Hz in ^1H-NMR spectroscopy that translates into a vanishing torsional angle H−(C-2)−(C-3)−H. In addition to spectroscopy, the volatile constituents were conveniently analyzed by capillary gas chromatography, taking advantage of its speed, sensitivity, and simplicity. To this end, the peptide chiral stationary phase[10] Chirasil-Val, due to specific recognition sites, showed a good ability to separate the regioisomers. Coupling to mass spectrometry allowed us to detect and identify even trace amounts of byproducts. Despite all these efforts, the desired α-substitution products (route A in Figure 1, left) could not be observed in the reaction mixture.

As a standard reagent for the α-bromination of carbonyl compounds, bromine and elemental phosphorus are well-known in the literature.[11] Nonetheless, treatment of **1** with 2 equiv of this reagent (at 80 °C for 3 h) afforded **3** (route D) as the only product that could be isolated. In order to force substitution in the α-position, the reaction of **1** was then performed with 4 equiv of bromine and phosphorus, yielding a mixture of the bromolactones **3** (route D), **5** (route A), and **6** (both routes, A and D). Compounds **3** and **6** were obtained in nearly equal amounts, whereas **5** was only present in a minute quantity.

Table 1. Regioselectivity of the Reaction of 1 with 1 Equiv of Bromine in Various Solvents, As Determined by Gas Chromatography (for Conditions See Experimental Section)

solvent	temp (°C)	reaction time (h)	conversion of **1** (%)	product distribution (%)		
				3	**7**	others
$PhNO_2$	20	24	87	80	6	14
	90	1	82	95	4	1
	90	5	93	93	6	1
MeCOOH	80	6	98	85	11	4
PhCl	90	3	90	75	6	19
CCl_4	75	1	43	86	9	5
	75	5	51	75	9	16
$(MeCO)_2O$	90	1	6	15	1	84
	90	3	6	37	2	61
$ClSO_3H$	20	1	decomposition			

In view of the apparent difference in the chemical behavior of **1** and **2**, it was decided at this point to abandon the original strategy as it was based on an analogy that did not hold. As the new reaction pathway D discovered for **1** held a promising access road to the desired substitution patterns, this reaction was screened in a systematic approach.

All experiments were performed with 1 equiv of bromine. The results are summarized in Table 1. The highest product selectivity was found in nitrobenzene as a solvent, the monobromo lactone **3** being the main product under all reaction conditions applied. Again, bromination at either one of the two 8-methyl groups was not detected, either by gas chromatography or by spectroscopy. In most solvents, the turnover of **1** proved sufficient for a preparative purpose, yielding the monobromo lactone **3** as the major reaction product, in addition to various amounts of **4** and **7**. Only in acetic anhydride was the course of the reaction completely different, as monitored by gas chromatography. In the early stage of the reaction, prior to the formation of brominated products, a new compound appeared that was subjected to GC/MS analysis. Although retention data and spectroscopy indicate a close relation to the reactant **1**, this reaction product could not yet be identified.

Chlorosulfuric acid, a reportedly successful medium for the bromination of camphor derivatives, showed even more discouraging results in this series (Table 1). A large number of peaks found in gas chromatography suggested the termination of the screening process at this point.

For the preparation of **3**, the reaction of **1** with 1 equiv of bromine in nitrobenzene for 5 h at 90 °C appeared most suitable. After the usual workup, complete removal of the solvent was not easily accomplished by applying reduced pressure; however, liquid chromatography with dichloromethane allowed the purification of all reaction products, the monobromo lactone **3** (68%), the acid **4** (13%), and the dibromo lactone **7** (5%). Recycling of the

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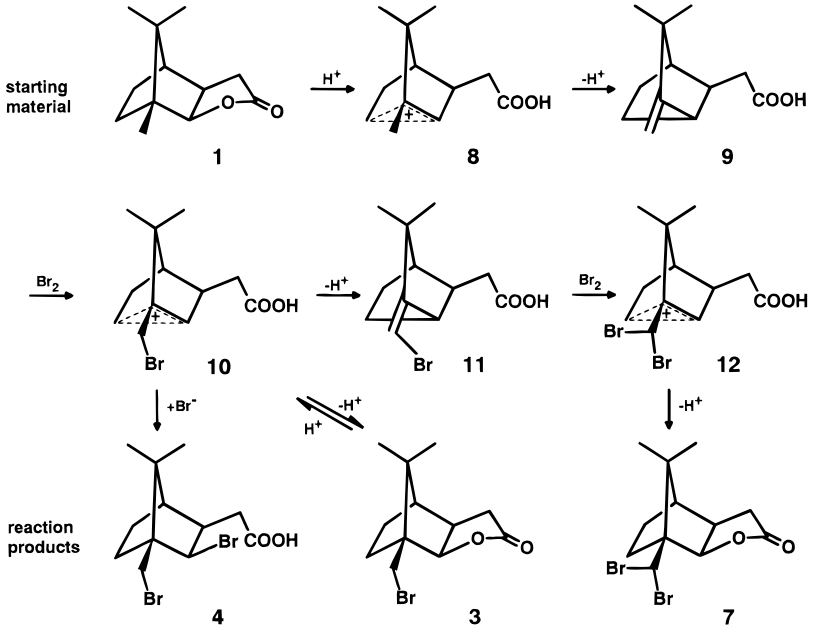
(11) Roedig, A. *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed.; Thieme Verlag: Stuttgart, Germany, 1960; Vol. V/4, p 206.

Scheme 2. Formation of 3, 4, and 7 by Bromination of 1 *via* the Postulated Nonclassical Bornyl Cations 8, 10, and 12, Respectively



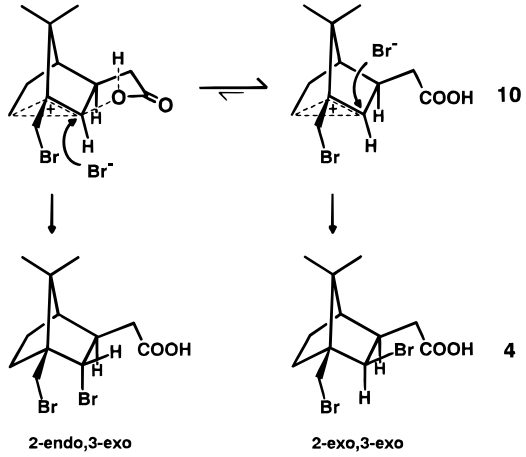
reactant **1** (7% acc. to gas chromatography analysis, see Table 1) although possible, is not worthwhile under these premises.

The dibromo lactone **7**, an aldehyde equivalent, is considered of particular value for further syntheses. The reaction of **1** with an excess of elemental bromine in nitrobenzene as the solvent was again monitored by gas chromatography. Even 3 equiv of bromine were not sufficient to drive the reaction to completion. After 6 h at 90 °C, there was still a substantial amount (25%) of the monobromo derivative **3** present, although bromine was totally consumed due to the formation of the side product **4**. Treatment of this mixture with one more equivalent of bromine for another 1 h, followed by the usual workup, gave a satisfactory yield (55%) of the dibromo derivative **7**. The multistep addition of the reagent was chosen to minimize side reactions.

All attempts to synthesize the tribromo analogue failed. It might be anticipated that the increasing stereoelectronic constraints at the C-7 methyl group favors ring opening at the expense of the substitution reaction. A more thoughtful attempt to interpret the reaction pattern observed, however, must bear in mind the peculiar behavior of the bornyl system.

Reaction Mechanism. More than 50 years ago,[12] Winstein proposed a nonclassical norbornyl cation as a reaction intermediate to account for the fact that *exo*-norbornyl acetate was formed exclusively by acetolysis of both *exo*- and *endo*-norbornyl *p*-bromobenzenesulfonate. This notion was subsequently supported by spectroscopic and kinetic evidence.[13] According to recent, high-level quantum mechanical ab initio calculations, only the nonclassical norbornyl cation, with a symmetrically bridged molecular structure, exists as a local minimum.[14] Along the same lines, the nonclassical (bridged) cations **8**, **10**, and **12**, respectively (see Scheme 2), are hypothesized to account for the formation of all reaction products

Scheme 3. Nonclassical Bornyl Cation *vs* Neighboring Group Participation of the Carboxylate Group



isolated from the bromination of the lactone system **1** with elemental bromine. Thus, protonation of **1** is supposed to give rise to a Wagner−Meerwein rearrangement *via* the cation **8** to the camphene derivative **9**, followed by electrophilic addition of bromine at the double bond of **9** to give the cation **10**. From here, several reaction paths are possible: (i) nucleophilic addition of a bromide anion results in the dibromo carboxylic acid **4**; (ii) nucleophilic attack of the carboxyl group, followed by deprotonation restores the lactone ring to give **3**; (iii) elimination of a proton may produce the vinyl bromide **11** that is prone to electrophilic addition of another bromine molecule *via* the cation **12**, followed by closure of the lactone ring to end up with the dibromo lactone **7**. This hypothesis is supported by the observation that the *exo* stereochemistry is strictly conserved in all reaction products **4**, **3**, and **7**, respectively. The stereochemical course of the formation of **4** is outlined in Scheme 3. Winstein et al.[15] reported the stabilization of simple carbocations by a neighboring carboxylate group. In our

(12) Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.
(13) Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P. v. R. *J. Org. Chem.* **1988**, *53*, 661.
(14) Schleyer, P. v. R.; Sieber, S. *Angew. Chem.* **1993**, *105*, 1676.
(15) Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 1581.

system, such an anchimeric effect should give rise to the 2-*endo*-3-*exo* stereoisomer of **4** (Scheme 3, left). In contrast to this prediction, the almost exclusive formation of the 2-*exo*-3-*exo* stereoisomer of **4** is observed. Apparently, the nonclassical bornyl cation depicted in Scheme 3 (right) does not require this type of anchimeric stabilization.

Conclusion

The highly regioselective bromination of lactone **1** bears a promising potential for the synthesis of derivatives of lactole[1] with interesting new properties. The course of the reaction, albeit quite unexpected from what is known for camphor, was confirmed by two X-ray structures. Product distribution and stereochemistry can be explained by intermediate nonclassical carbocations of the norbornyl type. In return, this rationale led us to try nitrobenzene as a nonprotic, strongly dipolar solvent. Indeed, a very smooth and fairly complete reaction was observed in this solvent.

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were run in $CDCl_3$; chemical shifts are quoted in ppm downfield from internal tetramethylsilane. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Infrared spectra were obtained as a KBr disk. TLC was performed on aluminum-backed silica plates. Liquid column chromatography was performed on Merck silica gel (40−63 μm particle size). GLC analyses were performed using a 25 m × 0.25 mm Duran glass capillary column coated with L-Chirasil-Val.[16]

[3a*S*-(3aα,4*β*,7*β*,7aα)]-7-(Bromomethyl)-8,8-dimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzofuran-2(3*H*)-one (3). Compound **1** (1.94 g, 10 mmol) was dissolved in nitrobenzene (2.5 mL), and bromine (0.55 mL, 10 mmol) was added. The reaction was stirred at 90 °C. After 5 h, the reaction mixture was cooled to room temperature. The organic layer was washed with an aqueous solution of $NaHSO_3$. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo as far as possible. Liquid chromatography on silica gel with dichloromethane furnished 1.85 g of **3** (68%), 0.45 g of **4** (13%), and 0.18 g of **7** (5%).

In a similar fashion, reaction of **1** (1.94 g, 10 mmol) with bromine (0.60 mL, 12 mmol) in acetic acid (4.4 mL) for 6 h at 80 °C, cooling and dripping in ice water, followed by extraction with diethyl ether gave 2.8 g of a brownish oil. Liquid chromatography on silica gel with dichloromethane provided 1.40 g of **3** (51%), 0.75 g of **4** (21%), and 0.18 g of **7** (5%), R_f = 0.55, 0.05, and 0.60, respectively.

3: white solid; mp 96 °C; GC purity >99.9%, k' = 9.9 (t_0 = 51 s, isothermal at 190 °C, 0.8 bar H_2); $[\alpha]^{20}_D$ −81.8° (*c* 0.68, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 4.63 (d, J = 7.7 Hz, 1H), 3.68/3.64/3.35/3.31 (AB system, 2H), 2.8−2.3 (m, 3H), 2.0−1.0 (m, 5H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 178.3, 88.1, 52.6, 51.1, 48.2, 42.3, 34.7, 32.7), 30.2, 28.1, 23.5, 20.6; IR (cm^{-1}, KBr) 2970, 1765, 1165, 1035; EI-MS *m*/*e* 275, 273, 194, 193, 175, 151, 147, 133, 107, 91, 81, 67. Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.80; H, 6.17; Br, 29.39. Single crystals of **3** were obtained by slow evaporation of a solution in dichloromethane.

4: colorless oil; $[\alpha]^{20}_D$ −30.5° (*c* 0.2, ethyl acetate); ^{1}H-NMR ($CDCl_3$) δ 4.57 (d, J = 8.8 Hz; 1H), 3.72/3.68/3.42/3.38 (AB system; 2H), 3.0−2.3 (m, 3H), 2.0−0.9 (m, 5H), 1.17 (s, 3H), 0.85 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 178.2, 63.5, 54.0, 53.0, 49.7, 44.3, 40.6, 37.0, 34.1, 28.7, 22.5, 21.7; IR (cm^{-1}, KBr) 3410, 2930, 1700, 1245, 1085; EI-MS *m*/*e* 355, 353, 351, 337, 273, 193, 151, 133, 105. Anal. Calcd for $C_{12}H_{18}Br_2O_2$ (354.08): C, 40.71; H, 5.12; Br, 45.13. Found: C, 40.80; H, 5.96; Br, 44.95.

7: white solid; GC purity >99.9%; k' = 24.3 (t_0 = 51 s, isothermal at 190 °C, 0.8 bar H_2); properties as described below.

[3aS-(3aα,4*β*,7*β*,7aα)]-7-Bis(Dibromomethyl)-8,8-dimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzofuran-2(3*H*)-one (7). Compound **1** (1.94 g, 10 mmol) was dissolved in nitrobenzene (2.5 mL), and bromine (1.65 mL, 30 mmol, 3 equiv) was added. The reaction was stirred at 90 °C. After 6 h, another portion of bromine (0.55 mL, 10 mmol) was added. After another 1 h, the reaction mixture was cooled to room temperature. After usual workup, 1.9 g of **7** (55%) and 0.40 g of **3** (15%) was obtained.

7: mp 95−96 °C; $[\alpha]^{20}_D$ −37.1° (*c* 1, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 6.05 (s, 1H), 4.74 (d, J = 8.0 Hz, 1H), 2.8−2.35 (m, 3H), 2.2−1.1 (m, 5H), 1.13 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 177.6, 90.7, 58.3, 52.8, 49.3, 45.7, 41.0, 34.3, 28.0, 26.8, 26.5, 20.6; IR (cm^{-1}, KBr) 2960, 1775, 1160, 1040; EI-MS *m*/*e* 355, 353, 351, 273, 271, 215, 213, 191, 163, 145, 131, 91, 79. Anal. Calcd for $C_{12}H_{16}Br_2O_2$: C, 40.94; H, 4.58; Br, 45.39. Found: C, 40.84; H 4.57; Br 45.42. Single crystals of **7** were obtained by slow evaporation of a solution in diethyl ether.

[3S-(3α,3aα,4*β*,7*β*,7aα)]-3-Bromo-7-(bromomethyl)-8,8-dimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzofuran-2(3*H*)-one (6). To a mixture of **1** (2.0 g, 10 mmol) and red phosphorus (0.30 g, 10 mmol) was added bromine (1.6 g, 10 mmol) dropwise under stirring and cooling. After the vigorous reaction had ceased, the reaction mixture was kept at 70 °C, and another portion of bromine (4.80 g, 31 mmol) was added. The reaction was stirred at 80 °C for 3 h. After cooling to room temperature and neutralization with saturated solution of $NaHCO_3$, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Liquid chromatography on silica gel with petrol ether/diethyl ether, applying a gradient from 10:1 to 1:1 (v/v), provided 0.07 g of **5** (3%), 0.43 g of **6** (12%), and 0.51 g of **3** (18%).

5: ^{1}H-NMR ($CDCl_3$) δ 4.97 (d, J = 7.3 Hz, 1H), 4.44 (d, J = 3.2 Hz, 1H), 2.92 (dd, J = 9.0, 4.5 Hz, 1H), 1.3−2.3 (m, 5H), 1.21 (s, 6H), 1.05 (s, 3H).

6: brownish crystals (petroleum ether/diethyl ether); mp 109−112 °C; $[\alpha]^{20}_D$ −61.0° (*c* 1.36, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 4.85 (d, J = 7.0 Hz, 1H), 4.43 (d, J = 3.0 Hz, 1H), 3.75/3.64/3.41/3.30 (AB system, 2H), 2.93 (dd, J = 8.0, 3.6 Hz, 1H), 1.0−2.3 (m, 5H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.4, 86.0, 53.9, 52.2, 50.9, 47.4, 41.3, 31.8, 29.4, 27.4, 22.6, 20.3. Anal. Calcd for $C_{12}H_{16}Br_2O_2$: C, 40.94; H, 4.58. Found: C, 40.75; H 4.55.

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