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Synthesis of 1,2-annulated adamantane heterocycles: structural determination studies of a bioactive cyclic sulfite

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ABSTRACT

The novel heterocycle 3-oxatetracyclo[5.3.1.1^{5,9}.0^{2,5}]dodecane **4** is prepared by a simple and effective method, involving synthesis of the corresponding 2-hydroxy-1-adamantanomethanol followed by its intramolecular cyclization with thionyl chloride, along with 4-oxo-adamantane-3,5,4-dioxathiane **5** in yields depending on the reaction temperature. Dioxathiane **5** was markedly active against vesicular stomatitis virus, its potency being 2.5-fold higher than that of (*S*)-9-(2,3-dihydroxypropyl)adenine. NMR data and theoretical calculations on sulfite **5** and the corresponding dioxane **6** suggest that S=O is oriented equatorially.

Adamantane derivatives constitute a significant class of pharmacologically important agents that exhibit a variety of therapeutic activities such as antiviral, antibacterial, trypanocidal, anticancer and anti-Parkinson's.[1,2]

In the course of our research efforts to obtain new antiviral agents, several adamantane derivatives have been synthesized, mainly spiro,[1a–d,f] exocyclic[1e] and 1,2-annulated heterocycles and carbocycles.[1g] The subsequent structure–activity analysis showed that the most potent analogues usually bear a five- or a six-membered heterocyclic ring. In this respect, introduction of a pharmacologically active cyclic sulfite ring is considered as an attractive modification. The 2-oxo-1,2,3-dioxathiane ring is present in several biologically active compounds. Among 2-oxo-1,2,3-dioxathiane structures, the cyclic sulfite analogues of topiramate have proven to be promising anticonvulsant agents,[1h] whereas a cyclosulfite podophyllotoxin analogue was shown to be a potent antitumor agent.[1i] Moreover, the conformation of 2-oxo-1,3,2-dioxathianes has been studied intensively by means of dipole moments,[3] infrared spectroscopy,[4,5] electron diffraction,[6] chemical equilibration,[7] ultrasonic absorption,[8] ^{1}H and ^{13}C NMR spectroscopy,[4,5,9–11] X-ray diffraction,[12] and mass spectroscopy.[13] It has been shown that an equilibrium exists in this type of rings with the exocyclic oxygen in the axial or equatorial orientation depending on the substituents of the six-membered ring.[11]

We present here the synthesis, structural analysis, and biological evaluation of the novel 1,2-annulated adamantane dioxathiane **5**. To explore the conformational equilibrium, ^{1}H and ^{13}C NMR spectral data as well as theoretical calculations were used and compared with the corresponding data for dioxane **6** which was specifically synthesized to assist the complete structural characterization of **5**. It is noteworthy that compound **5** exhibited remarkable antiviral activity against vesicular stomatitis virus. To the best of our knowledge, this is the first time that such activity is reported for a cyclic sulfite derivative.

The syntheses of cyclic sulfite **5** and dioxane **6** are depicted in Scheme 1. Interestingly, the 1,2-annulated adamantane oxetane **4** was formed along with the desired cyclic sulfite **5** (Scheme 1). Oxetane **4**, is a key intermediate for the preparation of 1,2-disubstituted adamantanes as well as heterocyclic adamantane derivatives. Oxetanes are known to be useful intermediates in organic synthesis undergoing bimolecular ring opening with a variety of good nucleophiles.[14,15] To fully explore this synthetic pathway, the ring opening of oxetane **4** was carried out yielding dibromo derivative **7** and bromoalcohol **8**, which constitute useful precursors for the synthesis of bioactive adamantane derivatives.

For the synthesis of the oxetane **4**, cyclic sulfite **5,** and dioxane **6**, protoadamantanone **1** was used as starting material (Scheme 1).[16] This was converted to oxirane **2**,[17] which was obtained as

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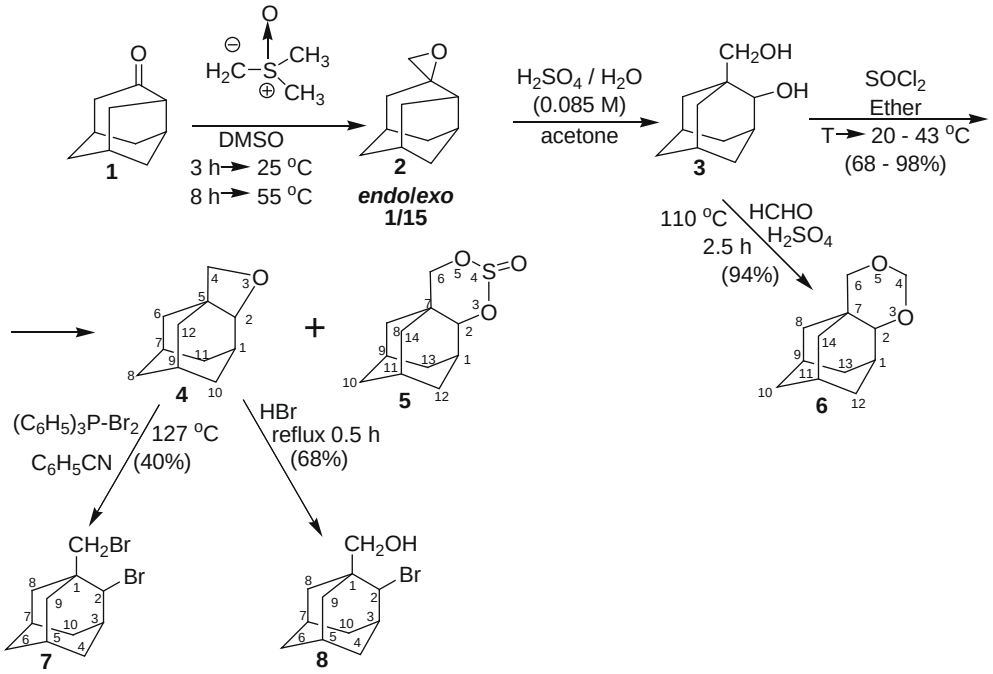

Scheme 1. Synthetic route to 1,2-annulated adamantane oxetane **4**, cyclic sulfite **5,** and dioxane **6**.

an inseparable mixture of epimers (*endo*/*exo*, 1:15), as was evident from the ^{1}H NMR spectral data, upon treatment with dimethylsulfonium methylide. Ring opening of **2** with a solution of H_2SO_4 (0.085 M) in acetone afforded diol **3**. Reaction of diol **3** with $SOCl_2$[18] in dry ether resulted in the formation of a mixture consisting of two different products: oxetane **4**[19] and cyclic sulfite **5**.[20] A possible mechanism for the formation of the two products involves reaction of $SOCl_2$ with the less hindered hydroxy group of the diol **3** to form the intermediate chlorosulfonyl ester, which was not isolated. Intramolecular nucleophilic attack of the *sec*-hydroxy group on the chlorosulfonyl ester can follow two different reaction pathways. According to the first pathway, formation of oxetane **4** results from nucleophilic attack on the methylene group and subsequent elimination of SO_2 and HCl, while the second pathway furnished the cyclic sulfite **5** and HCl through nucleophilic attack on the sulfur atom.

To explore the full scope and versatility of this method, the effect of temperature on the reaction yield was investigated. The results are highlighted in Table 1. The temperature seems to be of critical importance in the conversion of diol **3** into oxetane **4** with the best yield (98%) obtained at 43 °C, and at which negligible cyclic sulfite **5** formation (2%) was observed. A plausible explanation may involve the higher activation barrier for formation of the four-membered oxetane ring.

The susceptibility of oxetane **4** to nucleophilic attack and ring opening was investigated. Treatment of **4** with bromine, triphenylphosphine in benzonitrile provided the dibromo derivative **7**[21] in 40% yield. Additionally, reaction of **4** with hydrobromic acid under reflux for 0.5 h gave bromoalcohol **8**[22] in 68% yield. Both 2-bromo-1-(bromomethyl)tricyclo[3.3.1.1^{3,7}]decane **7** and (2-bromotricyclo[3.3.1.1^{3,7}]dec-1-yl)methanol **8** are intermediates of broad utility in the preparation of 1,2-disubstituted adamantanes and heterocyclic adamantane derivatives.[23]

Finally, dioxane **6**[24] was synthesized in 94% yield from diol **3** by heating with HCHO in H_2SO_4 (33%).

Compound **5** was found to be active against vesicular stomatitis virus with an EC_{50} of 20 μM, being 2.5-fold more potent than (*S*)-DHPA and comparable with Ribavirin (6 μM) (Table 2). No activity was noted for several unrelated viruses, for example, the RNA viruses: Coxsackie B4 virus; Sindbis virus; Punta Toro virus; Reovirus-1; Parainfluenza-3 virus, influenza virus, and respiratory syncytial virus; and the DNA viruses: HSV (type 1 or 2) and vaccinia virus.

The activity demonstrated by **5** as well as the general interest in studying the conformational preferences of the S=O bond in cyclic sulfites has prompted us to perform a conformational analysis of **5** and **6** on the basis of NMR data and theoretical calculations.

Conformational analysis requires the detailed assignment of compounds **5** and **6** which is challenging due to overlapping of the adamantane signals (Fig. 1). It should be noted that both **5** and **6** exist as a mixture of enantiomers (see Fig. S1, Supplementary data, for annotation of both enantiomers). A combination of homonuclear (COSY and NOESY at mixing times of 1 and 3.5 s) and het-

Table 1
Effect of temperature on the yield of **4** and **5**

T (°C)	Oxetane **4** (%)	Cyclic sulfite **5** (%)
20	68	32
25	79	21
32	89	11
43	98	1–2

Table 2
Antiviral activity and cytotoxicity of 1,2-annulated adamantane cyclic sulfite **5**

Compound	Minimum cytotoxic concentration[a] (μM)	EC_{50}[b] (μM)
5	>250	20
(*S*)-DHPA[c]	>250	50
Ribavirin	>250	6

[a] Concentration required to cause a microscopically detectable alteration of normal cell morphology.
[b] Concentration affording a 50% reduction in virus-induced cytopathic effect (CPE), as determined in a microscopical CPE reduction assay on human epithelial HeLa cells.
[c] (*S*)-DHPA = (*S*)-9-(2,3-dihydroxypropyl)adenine.

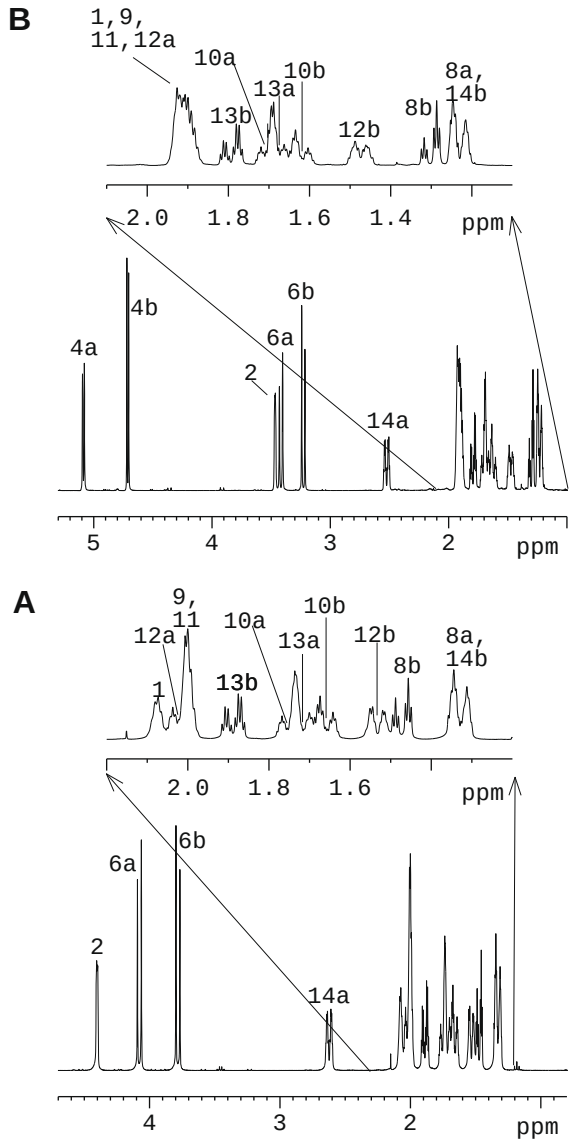

Figure 1. 1D ^{1}H NMR (400 MHz) spectra of **5** (A) and **6** (B) in $CDCl_3$.

Table 3
Experimental (exp) ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) chemical shifts (ppm) along with calculated ^{13}C (cal) shifts for compounds **5** and **6** in $CDCl_3$

Position	**5**		**5**-*ax*	**5**-*eq*	**6**		
	exp		cal	cal	exp		cal
	δ ^{1}H	δ ^{13}C	δ ^{13}C	δ ^{13}C	δ ^{1}H	δ ^{13}C	δ ^{13}C
1	2.07	31.8	28.4	29.2	1.92	32.3	29.1
2	4.39	82.7	63.7	70.4	3.47	83.41	71.2
4					5.09(a)	94.15	80.9
					4.71(b)		
6	4.07(a)	76.0	60.2	66.2	3.42(a)	76.96	66.7
	3.78(b)				3.23(b)		
7		33.0	29.2	28.2		33.5	28.1
8	1.32(a)	37.0	32.8	32.2	1.23(a)	37.9	31.0
	1.47(b)				1.30(b)		
9	2.00	27.3	24.1	23.9	1.89	28.0	24.1
10	1.75(a)	36.5	32.3	32.2	1.71(a)	37.0	32.7
	1.65(b)				1.62(b)		
11	2.00	27.0	23.8	23.6	1.92	27.6	24.4
12	2.02(a)	29.6	26.9	26.5	1.92(a)	30.13	27.2
	1.53(b)				1.48(b)		
13	1.71(a)	36.1	31.3	31.1	1.68(a)	36.6	32.1
	1.89(b)				1.79(b)		
14	2.63(a)	33.7	30.7	30.3	2.52(a)	34.86	31.6
	1.32(b)				1.23(b)		

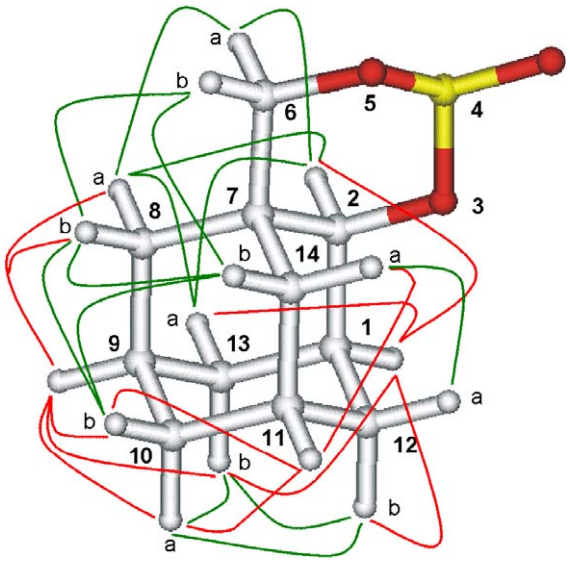

Figure 2. Graphical representation of the NOE correlations (green) and scalar couplings (red) of **5** as observed experimentally in the NOESY spectrum with a mixing time of 3.5 s.

eronuclear (HSQC, HMBC) 2D experiments was used for the complete assignment of these two compounds. ^{1}H and ^{13}C chemical shifts for both compounds are summarized in Table 3, while important COSY and NOESY correlations are depicted in Figure 2.

The ^{1}H NMR spectrum of **5** (Fig. 1A) is characterized by the relatively crowded upfield region due to the adamantane moiety and a well-resolved downfield region showing a singlet at 4.39 ppm (1H) and two doublets at 4.07 ppm (1H) and 3.78 ppm (1H), ascribed to H-2 and H-6, respectively. The observation of a weak NOE cross-peak between H-2 and H-6 at 4.07 ppm is indicative of their homoaxial orientation (hereafter referred to as H-6a). The H-2 $^{3}J_{H,H}$ correlation (Fig. S2, Supplementary data) and NOE cross-peak (Fig. S3, Supplementary data) with the singlet at 2.07 ppm (1H) allowed us to attribute this resonance to H-1.

Proton H-1 shows $^{3}J_{H,H}$ correlations as well as NOE cross-peaks with the proton at 1.53 ppm and methylene protons (defined from the HSQC spectrum, Fig. S4, Supplementary data) at 1.89 and 1.71 ppm. The latter exhibits an NOE with H-2, suggesting their homoaxial orientation and is thus attributed to H-13a. Accordingly, the proton at 1.89 ppm corresponds to geminal H-13b, while the signal at 1.53 ppm and its geminal partner at 2.02 ppm, as defined by HSQC and COSY spectra, are assigned to H-12. The NOE correlation observed between H-13b and the proton at 1.53 ppm suggests their homoaxial orientation in the 13-1-12-11-10-9 cyclohexane ring and is attributed to H-12b.

The observation of NOE cross-peaks between the H-2, H-6a, and H-13a protons and the signal at 1.32 ppm led unambiguously to its assignment to H-8a and consequently its geminal partner at 1.47 ppm to H-8b. The NOE correlation between H-8b and H-6b further confirms their homoaxial orientation. Accordingly, the signal at 1.32 ppm showing NOEs with both H-6b and H-8b can only be attributed to H-14b. The resonance at 2.63 ppm is attributed to geminal H-14a. Proton H-14a shows an NOE cross-peak with H-12a at 2.02 ppm as was expected, and with the intense peak at 2.00 ppm ascribed to H-11. Proton H-8a shows through space connectivity with the other 2.00 ppm resonance suggesting that H-9 also resonates at this frequency. The H-10 methylene protons were

defined at 1.75 ppm and 1.65 ppm due to their correlations with H-9 and H-11. Proton H-10b was identified at 1.65 ppm through the NOE peaks observed with both H-14b and H-8b. The assignment of H-10a at 1.75 ppm was also confirmed by its NOE correlations with H-12b and H-13b.

The NMR spectra of compound **6** (Fig. 1B) show a number of similarities with those of **5** as was expected, and the conformational assignment was accomplished in an analogous way. The ^{1}H and ^{13}C chemical shifts of **6** are summarized in Table 3. Only weak differences in chemical shifts between compounds **5** and **6** were observed. A downfield shift of 0.7 ppm for C-2 and 1.0 ppm for C-6 of compound **6** was apparent. The corresponding protons experience an upfield shift of 0.82 ppm for H-2 and an average of 0.60 ppm for the H-6 methylene protons. Additionally, C-8 shows a 0.9 ppm downfield shift although the H-8 methylene protons seem to be less affected with an average upfield shift of 0.13 ppm (Table 3).

Theoretical calculations were performed to rationalize the observed NMR differences and elucidate the orientation of the thiocarbonyl group of **5**. Ab initio single point calculations were performed on AM1 preoptimized geometries at the restricted HF level of theory using the 6-31(d,p) basis set for compounds **5-eq** (with S=O in equatorial orientation), **5-ax** (with S=O in axial orientation), and **6**. All C and H chemical shifts were determined within the GIAO approach as implemented in the GAUSSIAN98 program[25] and are summarized in Table 3. Large deviations were noticed for C-2 (6.7 ppm), and C-6 (6.0 ppm) between the two conformations of **5**, which demonstrate the influence of the thiocarbonyl orientation on the chemical shift, while for all the other carbons the difference varied from −1.0 to 0.8 ppm. Moreover the C-2 and C-6 calculated chemical shifts of **5-eq** are nearly identical with the corresponding values of dioxane **6**. More specifically, in the case of conformer **5-eq**, carbons C-2 and C-6 are shifted upfield by only 0.8 and 0.5 ppm being close to the overall average difference. In contrast, in the case of conformer **5-ax**, the calculated chemical shifts of C-2 and C-6 are 7.5 and 6.5 ppm upfield with respect to the corresponding carbons of dioxane **6**, while all the other carbons differ by 0.4 ppm on average. These calculated chemical shift differences between **5-ax** and **6** as well as the calculated and experimentally observed similarities of the corresponding values between **5-eq** and **6**, suggest that the thiocarbonyl moiety adopts an equatorial orientation.

The proposed configuration is in agreement with Virtanen et al.,[11] who have described that 2-oxo-1,3,2 dioxathianes, when substituted with large alkyl groups such as isopropyl and *tert*-butyl, exist preferentially in the chair conformation with an equatorial S=O group. Moreover, our findings are in accordance with NMR data reported recently by Garcia-Granados et al.,[26] for two cyclic sulfite derivatives of the eudesmane natural product. These two compounds differing only in the S=O orientation were structurally characterized by X-ray crystallography and NMR spectroscopy. Carbon chemical shift differences were only observed for the atoms in γ positions relative to the exocyclic oxygen atom. The chemical shifts of carbons C-2 and C-6 of compound **5** are in complete agreement with the corresponding carbons in eudesmane cyclic sulfite (84.2 and 72.5 ppm, respectively) with the S=O in the equatorial position. In the axial isomer, the corresponding atoms were shielded as rationalized by the γ-*gauche* effect and predicted by our calculations in the case of the **5-ax** conformer.

In conclusion, 1,2-annulated adamantane dioxathiane was synthesized, structurally characterized, and examined for its antiviral activity. NMR data suggest that the cyclic sulfite moiety exists in a chair conformation with the S=O group equatorially oriented. The antiviral properties of **5** should trigger future research on cyclic sulfite derivatives and possibly the discovery of new antiviral drugs. Furthermore, we describe a facile and effective synthesis of the 1,2-annulated oxetane **4**, which is a useful intermediate for the preparation of bioactive adamantane derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.132.

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19. Oxetane **4** (viscous oil) ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.35–1.38 (m, 2H, H-6b, H-12b), 1.48 (m, 1H, H-6a), 1.57 (m, 1H, H-10b), 1.70 (m, 1H, H-8b), 1.79 (m, 2H, H-8a, H-11a), 1.85–1.93 (m, 2H, H-1, H-11b), 1.93–2.01 (m, 2H, 7-H, H-10a), 2.04 (m, 1H, H-9), 2.60 (m, 1H, H-12a), 3.25 (d, *J* = 11.2 Hz, 1H, H-4b), 4.55 (d, *J* = 11.0 Hz, 1H, H-4a), 5.00 (br s, 1H, H-2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 27.0 (C-9), 27.5 (C-7), 30.0 (C-10), 31.3 (C-1), 34.1 (C-12), 34.3 (C-5), 38.1 (C-6), 36.9 (C-11), 36.9 (C-8), 67.3 (C-4), 73.6 (C-2) ppm. HRMS (ESI, *m/z*) calcd for $C_{11}H_{16}O$ [M^+] 164.2468, found 164.2484.
20. Dioxathiane **5**, mp 83 °C (ether-*n*-pentane); HRMS (ESI, *m/z*) calcd for $C_{11}H_{16}O_3S$ [M^+] 228.3116, found 228.3193.
21. *2-Bromo-1-tricyclo[3.3.1.1^{3,7}]decanemethyl bromide (7)*: A solution of triphenyldibromophosphorane was prepared by the dropwise addition of Br_2 (2.78 g, 17.4 mmol) in benzonitrile (12 mL) to a solution of triphenylphosphine (4.57 g, 17.4 mmol) in benzonitrile (15 mL) and the resulting solution was stirred at 122 °C under an argon atmosphere. To this solution, was added in one portion, the oxetane derivative **4** (2.26 g, 13.7 mmol) and the mixture was heated at 127 °C for 4 h. The mixture was cooled to room temperature, *n*-pentane was added, and the precipitate formed was removed by filtration and washed with *n*-pentane. The washings were combined and the upper layer was

removed and evaporated under vacuum to give a viscous oil. The remaining benzonitrile was removed by fractional distillation in vacuo (0.01 mmHg 50–60 °C) and the residue was purified by flash column chromatography on silica gel eluted with cyclohexane to give the dibromide **7** (1.68 g, 40%) as a white solid; mp 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.35 (dd, 1H, J = 10.0, 2.0 Hz, 9e-H), 1.53–1.88 (complex m, 6H, 4e, 6a, 8, 10-H), 1.94–2.00 (m, 4H, 5, 6e, 7, 9a-H), 2.24 (m, 2H, 3, 4a-H), 3.10 (d, 1H, J = 10.1 Hz, CH_A-H), 3.46 (d, 1H, J = 10.1 Hz, CH_B-H), 4.55 (s, 1H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 26.9 (5-C), 27.7 (7-C), 31.3 (4-C), 35.6 (9-C), 37.0 (3, 8-C), 37.9 (1, 10-C), 40.8 (6-C), 46.2 (CH_2), 65.7 (2-C) ppm. Anal. Calcd for $C_{11}H_{16}Br_2$: C, 42.89; H, 5.23. Found: C, 42.77; H, 5.01.

22. *2-Bromo-1-tricyclo[3.3.1.1^{3,7}]decanemethanol (8)*: A solution of oxetane **4** (170 mg, 1.03 mmol) in HBr 47% (5 mL) was refluxed for 0.5 h. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel, using *n*-pentane–Et_2O (2:1) as eluent, to give the solid bromide **8** (176 mg, 68%); mp 122 °C. IR (mull) ν 3238 cm^{-1} (OH); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.23 (d, 1H, J = 12.5 Hz, 9e-H), 1.55–1.98 (complex m, 10H, 4e, 5, 6, 7, 9a, 8, 10-H), 2.26 (m, 2H, 3, 4a-H), 3.16 (d, 1H, J = 11.3 Hz, CH_A-H), 3.50 (d, 1H, J = 11.7 Hz, CH_B-H), 4.62 (s, 1H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 27.3 (5-C), 27.9 (7-C), 31.7 (4-C), 33.1 (9-C), 37.2 (3-C), 37.4 (8-C), 38.3 (10-C), 39.2 (1-C), 40.2 (6-C), 66.1 (2-C), 71.5 (CH_2) ppm. Anal. Calcd for $C_{11}H_{17}BrO$: C, 53.89; H, 6.99. Found: C, 54.11; H, 7.32.
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