New one-pot synthesis of a benzonorcaradiene derivative by reduction of naphthalic anhydride with $LiAlH_4$

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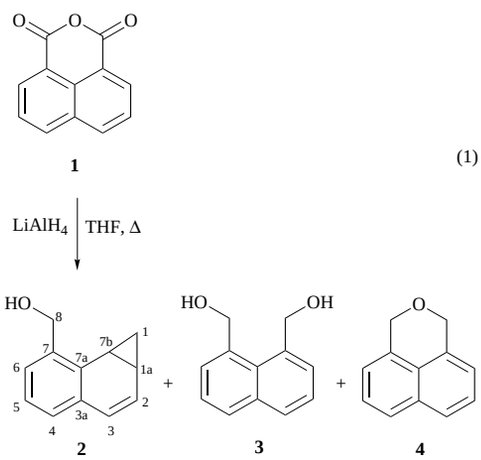
Reaction of naphthalic anhydride (naphthalene-1,8-dicarboxylic anhydride) (1) or of 1,8-bis(hydroxymethyl)naphthalene (3) with $LiAlH_4$ in refluxing THF yields the benzonorcaradiene derivatives 2 in yields of up to 50%. It is proposed that in the formation of this (strained) product an *anti*-hydroalumination reaction is involved, which is facilitated by the assistance of a neighbouring alkoxide function.

Results

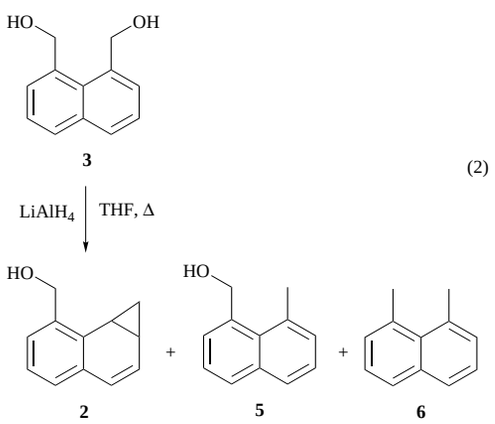
In our efforts to synthesize strained derivatives of [5]metacyclophanes,[1] we were interested in using 1,8-disubstituted naphthalene systems as bridging groups. As the starting material, we used the readily available naphthalic anhydride (systematic name: naphthalene-1,8-dicarboxylic anhydride) (**1**). However, in the reduction reaction of **1** with $LiAlH_4$, we encountered an unexpected product which was identified as the benzonorcaradiene derivative **2** (systematic name: 1a,7b-dihydro-7-hydroxymethyl-1*H*-cyclopropa[*a*]naphthalene) [reaction (1)].



(1)

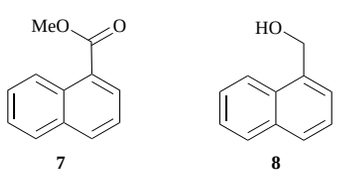
The reduction of **1** has been reported, but besides the expected diol **3**, only the cyclic ether 2-oxaperinaphthane (**4**) (systematic name 2-oxa-2,3-dihydrophenalene) was mentioned as a byproduct; apparently the formation of **2** has not been observed.[2] The unexpected occurrence of **2** in our experiments tempted us to investigate this reaction in more detail.

First of all, the formation of **2** turned out to be strongly dependent on the quality of the $LiAlH_4$ used; yields varied from traces to 16%. Sometimes 1-hydroxymethyl-8-methylnaphthalene [**5**, reaction (2)] was also observed as a product. Purification of **2** was achieved as follows: after crystallization of most of the diol **3**, an oily residue remained which was separated by careful column chromatography or preferably by TLC. An analytical sample of **2** was obtained by preparative GLC (mp = 111 °C). Identification was achieved by NMR spectroscopy; essential features of its spectrum were almost identical with those reported in the literature for analogous compounds.[3,4] Very characteristic are the signals (*i*) of the aromatic ring [δ 7.21 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz), 7.12 (t, ^3J = 7.5 Hz) and 7.04 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz)] indicating a trisubstituted benzene ring; (*ii*) of the (conjugated) olefin [AB-system at δ 6.26, δA = 6.27 (dd, $^3J_{cis}$ = 9.4 Hz, ^3J = 4.7 Hz), δB = 6.24 (d, $^3J_{cis}$ = 9.4 Hz)]; (*iii*) of the prochiral hydroxymethyl group [δ 4.83 (AB-system: δA = 4.85, δB = 4.81, $^2J_{AB}$ = 12.4 Hz)]; and (*iv*) of the multiplets at δ 2.55 (benzylic), 1.96 (allylic), 1.59 and −0.21. The latter two high-field signals are attached to one carbon (CH-COSY), with a geminal coupling of 3.5 Hz, which is characteristic for a cyclopropane CH_2-group. Also, the CH-couplings of the three cyclopropane carbons fall in the expected range of 160–170 Hz.



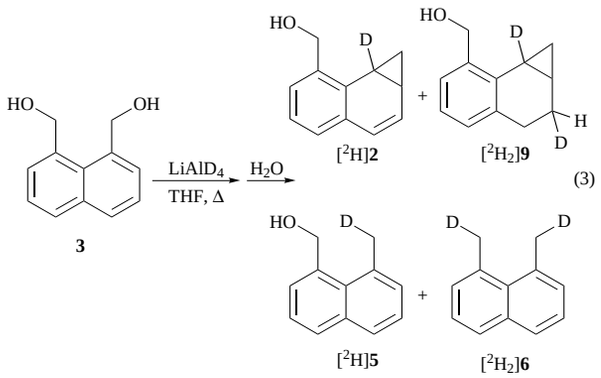
(2)

It was found that the direct precursor of **2** was the diol **3**. When **3** was allowed to react with $LiAlH_4$ in tetrahydrofuran (THF) for 140 h at reflux temperature, 50% of unreacted diol **3** was recovered after work-up; about 30% of the consumed diol was converted to **2**, 20% to **5**, and about 3% to 1,8-dimethylnaphthalene (**6**) [reaction (2)]. The analogously performed reduction reaction of **4** (see reaction 1), of methyl 1-naphthoate (**7**) or of 1-hydroxymethylnaphthalene (**8**)



yielded no benzonorcaradiene derivatives; only starting material was recovered, in addition to a small amount of 1-methylnaphthalene (from **7** to **8**). It follows that both hydroxymethyl groups are required for the formation of **2**.

The reaction was also performed with **3** and $LiAlD_4$ which gave, after hydrolysis, [^{2}H]**2**, mono-deuterated at position 7b (^{1}H NMR: the signal at δ 2.55 was missing; ^{2}H NMR: one signal at $\delta = 2.57$), together with [^{2}H]**5**, [$^2H_2$]**6** and [$^2H_2$]**9**, a dideuterated hydrogenation product of [^{2}H]**2** [reaction (3)]. The

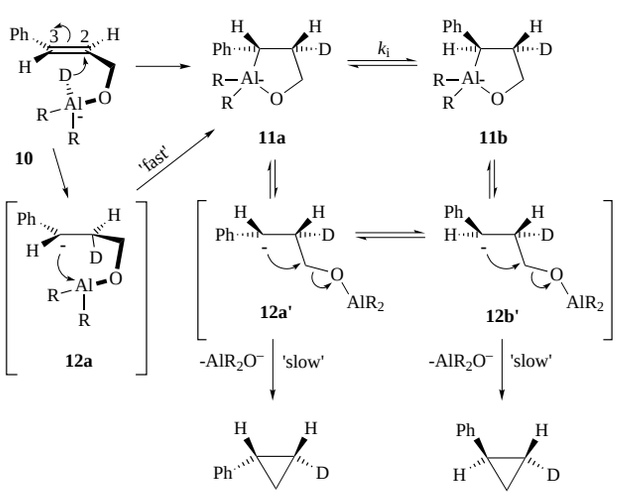


formation of the last presumably occurs by reduction of the styrene type double bond of [^{2}H]**2**.[5] This reduction and also the high yield of [^{2}H]**2** (about 50% isolated yield) is possibly due to the 'good quality' and high activity of the $LiAlD_4$. We cannot exclude the alternative explanation suggested by a referee that H/D isotope effects are involved. However, a systematic investigation of this aspect has not been performed.

Discussion

Formation of a cyclopropane ring during the reduction of an allylic alcohol with $LiAlH_4$ has precedents. In the mid 1960s, Jorgenson and Friend reported the formation of a cyclopropane derivative in the reduction of cinnamyl alcohol.[6] Independently, Uyeda and Cram discovered the formation of a cyclopropane system in the reduction of a cinnamic acid derivative.[7] Another example was found in the reduction of substituted 3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactones to yield substituted tetrahydro-1*H*-cyclopropa[*a*]naphthalenes.[8]

The mechanism postulated for the (aluminium) hydride reduction of cinnamyl alcohol involves a *syn*-hydroalumination of the double bond as outlined in Scheme 1. In the first step, the



Scheme 1

aluminium species is complexed to the alkoxide group to give **10**. It has been suggested that the following transformation proceeds *via* a hydride transfer from the complexed aluminium species in **10** to C2, with simultaneous formation of a (benzylic) carbanion at C3 (**12a**). This is, in a fast step, transformed to the five-membered aluminium cycle **11a**, which is believed to be an intermediate in the reaction.[9,10] As the last step, ring opening was proposed to give the conformer **12a**′ which, with subsequent intramolecular nucleophilic substitution of the complexed alkoxide function by the carbanion equivalents, leads to the formation of the cyclopropane ring (Scheme 1).[6,11]

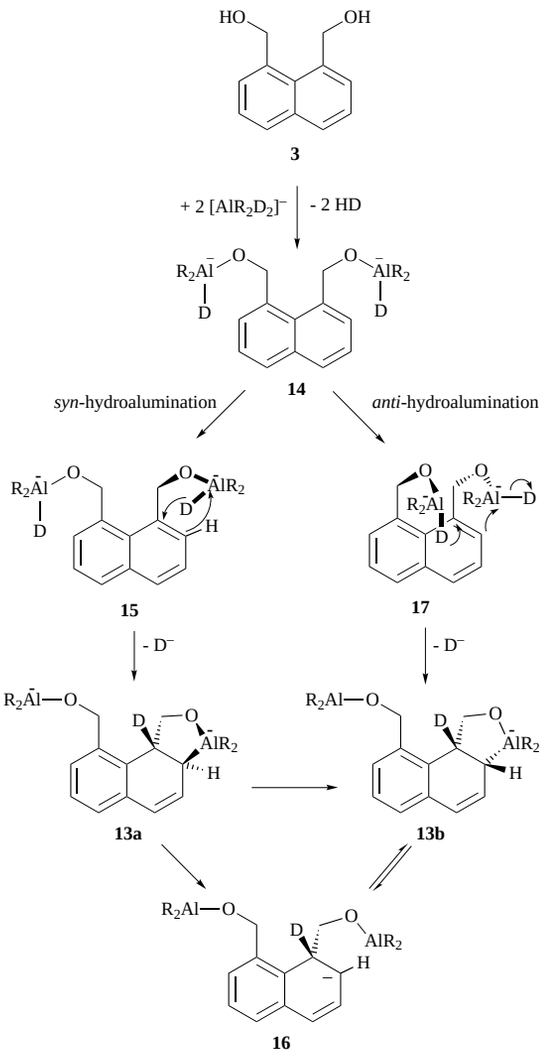
Mechanistic studies have been performed in order to determine the stereochemistry of the reduction and of the cyclopropane ring formation. These studies indicate that the reaction occurs with loss of stereochemical integrity. Thus, both (*Z*)- and (*E*)-*α*,*β*-dimethylcinnamyl alcohol yielded only *cis*-1,2-dimethylphenylcyclopropane,[11] and reduction of methyl cinnamate with $LiAlD_4$ followed by deuterolysis yielded equal amounts of *erythro*- and *threo*-PhCHD–CHD–CD_2OH.[5a] There are several mechanisms which would explain this lack of specificity. Snyder favoured a rapid equilibrium of the initially formed intermediate **11a** with its diastereomer **11b** by Al–C bond fission (k_i in Scheme 1). This should occur *via* the carbanions **12a** and **12b** (or their conformers **12a**′ or **12b**′).[5a] Other mechanisms [such as equilibration of the initially formed carbanion (**12a** to **12b**) prior to formation of **11**, or non-stereospecific solvolysis of the aluminium–carbon bond] cannot be excluded, but seem less plausible. As only derivatives of cinnamyl alcohol undergo this remarkable reaction, it seems[6] that the phenyl substituent at C3 is necessary, obviously for the benzylic stabilization of the carbanion (*cf.* **12**). Whether **12** is best described as a 'free' carbanion or as a carbanion having a partially negatively charged carbon atom in close contact to aluminium in the five-membered cycle remains unclear, although the latter seems more logical.[10]

In our specific case, however, the situation is more complex. Here the double bond is part of a naphthalene ring which has steric consequences, and, more importantly, the initial attack of a hydride at C1 must be accompanied by loss of the resonance energy of one of the two rings of naphthalene! First we discuss the two possible reaction pathways which will lead to the five-membered oxa–alumina cycles **13a** and **13b**, which, in analogy to **11**,[10] are believed to be intermediates in the reaction (Scheme 2).

Starting from the diol **3**, the bisaluminate **14** is a logical primary product. In the normal *syn*-hydroalumination, **14** would be transformed to **13a** *via* the transition state **15**. However, this *syn*-hydroalumination is unlikely for several reasons. In the first place, the initially formed intermediate **13a** is relatively strained. As the dihydronaphthalene has a fairly rigid structure, the *trans*-five-membered ring in **13a** is more strained than the *cis*-five-membered ring in **13b**; this follows convincingly from the inspection of models. Furthermore, if the sequence **14**→**15**→**13a** really is the reaction pathway, it would be difficult to understand why the monofunctional derivatives **4**, **7** and **8** do not follow the same course, which in reality is not the case: neither reduction of the double bond nor cyclopropane formation was observed.

The two cyclic intermediates **13a** and **13b** differ in the position of the five-membered ring; they can interconvert by Al–C bond fission in which the (planar?) allylic carbanion **16** is an intermediate. However, in contrast to Scheme 1 where a 'simple' rotation of the benzylic C–C bonds in **12** interconverts both stereoisomers, this kind of rearrangement requires a more complex conformational movement to transfer the aluminium from one side of the ring to the other; it would occur with more extensive, unfavourable separation of carbanionic charge and aluminium center. Hence, the transformation of **13a** to **13b** is thermodynamically favourable, but might be kinetically more difficult than in rotationally 'free' systems like **12**.

The intermediates **13a** and **13b** are formal products of a *syn*- and *anti*-hydroalumination, respectively (Scheme 2). The normal *syn*-addition, resulting in **13a**, is highly unlikely for the reasons discussed above. The alternative *anti*-addition to yield **13b** directly normally does not occur as it would require approach of the hydride and of the aluminium of the Al–H bond to take place from opposite sides of the ring.

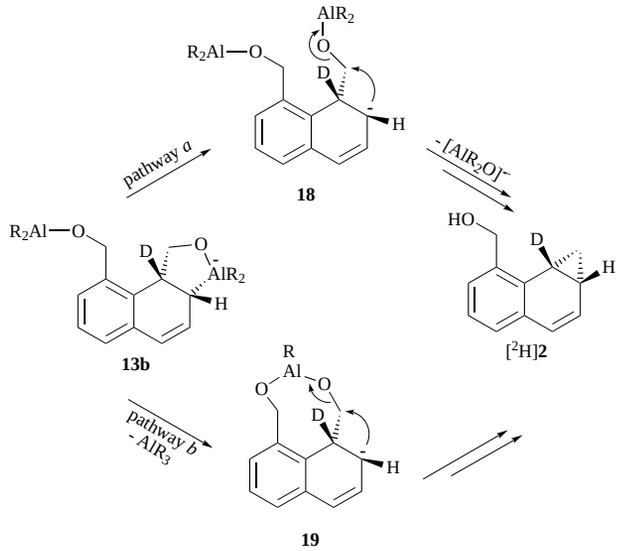


Scheme 2

However, in this specific case, an *anti*-hydroalumination by a different mechanism is feasible: attack of a hydride of one aluminate group may occur on the *ipso*-carbon of the neighbouring group from the top as shown in **17**. The double bond is simultaneously activated by electrophilic attack by the other aluminate function from underneath during formation of the five-membered ring intermediate **13b**. In this *anti*-hydroalumination, both aluminate functions are necessary, in contrast to the *syn*-hydroalumination of cinnamyl alcohol. Examination of models suggests that the neighbouring group participation is favoured by the formation of a relatively strain-free transition state. This neighbouring group participation also explains the non-reactivity of monofunctional derivatives such as **4**, **7** and **8**.

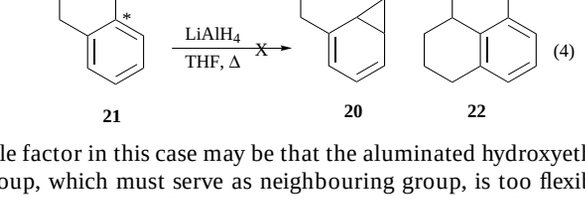
After formation of the cyclic intermediate **13b**, the reaction may proceed as postulated for the cinnamyl reductions. Ring opening of **13b** with subsequent nucleophilic displacement of the aluminate group yields the cyclopropane ring product [^{2}H]**2** (Scheme 3). This may occur either *via* the 'normal' ring opening in which the same aluminate is the leaving group (pathway *a*, transition state **18**) or, again, neighbouring group assistance may occur; the 'free' aluminium replaces that in the five-membered ring (pathway *b*, transition state **19**) followed by substitution of the aluminium alkoxide function through attack by the (quasi) carbanion. Both reaction pathways yield the same product by an analogous S_N2-type process. Finally, work up and decomplexation yield [^{2}H]**2**.

The most surprising aspect of the formation of the cyclopropane ring in **2** is that in this process, the aromaticity of one ring of the naphthalene system is broken to form a strained



Scheme 3

three-membered ring. This is an important difference compared with the previous cases which involve attack of the double bond of an allylic alcohol.[6–8] Due to the relative ease of the reaction (refluxing THF), we were encouraged to investigate whether, aided by a similarly favourable substitution pattern, a monocyclic benzene ring would also be cyclopropanated. The thermodynamic odds were against us, because they are clearly less favourable for benzene [$\Delta\Delta_fH°$(benzene − 1,3-cyclohexadiene) = +1.4 kcal mol^{-1}] than for naphthalene [$\Delta\Delta_fH°$(naphthalene − 1,2-dihydronaphthalene) = −6.2 kcal mol^{-1}].[12] Nevertheless we tried to synthesize norcaradiene **20** from diol **21**, but without success [reaction (4)]. An additional unfavourable factor in this case may be that the aluminated hydroxyethyl group, which must serve as neighbouring group, is too flexible and points away from the *ipso*-carbon atom (marked by a star *) which has to be attacked by the hydride ion. Therefore, a more rigid structure (such as **22**) might prove to be a better candidate for this interesting reaction.



Experimental

General

The ^{1}H NMR, ^{2}H NMR and ^{13}C NMR spectra were recorded on a Bruker MSL-400 spectrometer operating at 400, 61.42 and 100.6 MHz respectively. The ^{2}H NMR samples were measured in $CHCl_3$, the other samples in $CDCl_3$, with $CHCl_3$ as internal standard (δ = 7.27). Chemical shifts are given in ppm; *J* values in Hz.

HRMS spectra were measured at a Finnigan Mat-90 spectrometer operating at an ionization potential of 70 eV. GLC was performed on an Intersmat P120 apparatus using a glass column (1.5 m × $\frac{1}{4}$″; 15% SE-30 on Chromosorb WAW 60–80) with H_2 as carrier gas.

$LiAlH_4$ was purchased from Baker and Aldrich, $LiAlD_4$ was purchased from Janssen Chimica. Tetrahydrofuran was freshly distilled from $LiAlH_4$.

1a,7b-Dihydro-7-hydroxymethyl-1*H*-cyclopropa[*a*]naphthalene (2)

To a suspension of $LiAlH_4$ (27.4 mmol, 1.04 g) in THF (75 ml), diol **3** (7.17 mmol, 1.35 g) was added in small portions. The

reaction mixture was stirred for 6 days under reflux. Then the reaction mixture was cooled and the excess hydride carefully quenched with water. The mixture was poured into a cold 5% HCl aqueous solution and extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated and unreacted **3** was crystallized from the solution. Removal of **3** (0.5 g) and concentration of the mother liquor yielded a yellow oil (0.47 g). Purification by column chromatography (silica/pentane–diethyl ether) or by TLC yielded **2**, contaminated with small amounts of **4**. Further purification was easily achieved by preparative GLC, yielding **2** as a crystalline material, mp 111 °C (Found: C, 83.64; H, 7.05. Calc. for $C_{12}H_{12}O$: C, 83.67; H, 7.02%); [HRMS ($C_{12}H_{12}O$) calc. 172.0888. Found 172.0884]; *m*/*z* 172 ($M^{\cdot+}$), 154 ($M^{\cdot+} - H_2O$, 100%), 153 (66), 141 (52), 128 (40), 115 (30); δ_H(400 MHz; $CDCl_3$) 7.21 [1 H, dd, *J* 7.5 and 1.2, C(6)H], 7.12 [1 H, t, *J* 7.5, C(5)H], 7.04 [1 H, dd, *J* 7.5 and 1.2, C(4)H], 6.27 [1 H, dd, *J* 9.4 and 4.7, C(2)H], 6.24 [1 H, d, $J_{2,3}$ 9.4, C(3)H], 4.85 [1 H, d, J_{AB} 12.4, C(8)H], 4.81 [1 H, d, J_{AB} 12.4, C(8)H], 2.55 [1 H, ddd, *J* 9.1, 7.7 and 5.1, C(7b)H], 1.99 (1 H, br s, OH), 1.96 [1 H, dddd, *J* 8.9, 7.7, 5.1 and 4.7, C(1a)H], 1.59 [1 H, ddd, *J* 9.1, 8.9 and 3.5, $C(1)H_{exo}$], −0.21 [1 H, ddd, *J* 5.1, 5.1 and 3.5, $C(1)H_{endo}$]; δ_C(100.6 MHz; $CDCl_3$) 8.1 [t, *J* 165, C(1)], 16.1 [d, *J* 164, C(1a)], 17.4 [d, *J* 166, C(7b)], 63.4 [t, *J* 143, C(8)], 123.6 [d, *J* 160, C(3)], 125.4 [d, *J* 161, C(5)], 127.0 [d, *J* 156, C(6)], 127.6 [d, *J* 158, C(4)], 128.7 [d, *J* 162, C(2)], 130.8 [s, C(7a)], 133.5 [s, C(3a)], 138.7 [s, C(7)].

[7b-^{2}H]-1a,7b-Dihydro-7-hydroxymethyl-1*H*-cyclopropa[*a*]-naphthalene ([^{2}H]2)

To a suspension of $LiAlD_4$ (7.78 mmol, 0.35 g) in dry THF (20 ml), diol **3** (2.1 mmol, 0.40 g) was added in small portions. The reaction mixture was stirred for 6 days at reflux temperature. Then the mixture was cooled to 0 °C and the excess hydride was carefully quenched with water. The mixture was poured into a cold 5% HCl aqueous solution and extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After filtration and concentration at reduced pressure, a yellow oil (0.33 g) remained, consisting mainly of [^{2}H]**2** (1 mmol, 48%) and [$^2H_2$]**9** (0.5 mmol, 24%). Purification for analytical purposes by preparative GLC resulted in a mixture of [^{2}H]**2** and [$^2H_2$]**9** (3:1).

[^{2}H]2. δ_H(400 MHz; $CDCl_3$) 7.23 [1 H, dd, *J* 7.5 and 1.0, C(6)H], 7.14 [1 H, t, *J* 7.5, C(5)H] 7.06 [1 H, dd, *J* 7.5 and 1.0, C(4)H], 6.29 [1 H, dd, *J* 9.6 and 4.7, C(2)H], 6.25 [1 H, d, $J_{2,3}$ 9.6, C(3)H], 4.87 [1 H, d, J_{AB} 12.4, C(8)H], 4.83 [1 H, d, J_{AB} 12.4, C(8)H], 1.99 (1 H, br s, OH), 1.97 [1 H, ddd, *J* 8.8, 4.7 and 4.6, C(1a)H], 1.61 [1 H, dd, *J* 8.8 and 3.5, $C(1)H_{exo}$], −0.21 [1 H, dd, *J* 4.6 and 3.5, $C(1)H_{endo}$]; δ_D(61.42 MHz; $CHCl_3$) 2.57; δ_C(100.6 MHz; $CDCl_3$) 8.0 [t, *J* 166, C(1)], 17.3 [d, *J* 164, C(1a)], 18.8 [t, *J* 19, C(7b)], 63.5 [t, *J* 143, C(8)], 123.5 [d, *J* 160, C(3)], 125.5 [d, *J* 161, C(5)], 126.9 [d, *J* 159, C(6)], 127.6 [d, *J* 158, C(4)], 128.6 [d, *J* 161, C(2)], 130.8 [s, C(7a)], 133.5 [s, C(3a)], 138.0 [s, C(7)]; *m*/*z* 173 ($M^{\cdot+}$), 155 ($M^{\cdot+} - H_2O$, 100%), 154 (95), 142 (58), 129 (41), 116 (30).

[2,7b-$^2H_2$]-1a,2,3,7b-Tetrahydro-7-hydroxymethyl-1*H*-cyclopropa[*a*]naphthalene. [$^2H_2$]**9**: δ_H(400 MHz; $CDCl_3$) 7.19 [1 H, dd, *J* 7.5 and unresolved, C(6)H], 7.06 [1 H, t, *J* 7.5, C(5)H], 6.99 [1 H, dd, *J* 7.56 and unresolved, C(4)H], 4.81 [2 H, s, $C(8)H_2$], 2.64 [1 H, dd, *J* 15.8 and 2.4, $C(3)H_AH_B$], 2.47 [1 H, dd, *J* 15.8 and 5.8, $C(3)H_AH_B$], 2.06 [1 H, m, C(2)H], 1.99 (1 H, br s, OH), 1.58 [1 H, m, C(1a)H], 0.96 [1 H, dd, *J* 8.2 and 4.8, $C(1)H_{exo}$], −0.21 [1 H, dd, *J* 5.6 and 4.8, $C(1)H_{endo}$]; δ_D(61.42 MHz; $CHCl_3$) 2.10 [1 D, s, C(7b)D], 1.78 [1 D, s, C(2)D]; δ_C(100.6 MHz; $CDCl_3$) 8.6 [t, *J* 161, C(1)], 13.9 [d, *J* 160, C(1a)], 16.0 [m, C(2)], 18.9 [t, *J* 20, C(7b)], 25.7 [t, *J* 129, C(3)], 63.7 [t, *J* 143, C(8)], 124.4 [d, *J* 159, C(5)], 126.1 [d, *J* 160, C(6)], 128.4 [d, *J* 163, C(4)], 132.5 [s, C(7a)], 134.6 [s, C(3a)], 138.0 [s, C(7)]; *m*/*z* 176 ($M^{\cdot+}$), 158 ($M^{\cdot+} - H_2O$, 100%), 157 (78), 143 (34), 142 (34), 130 (39), 129 (37), 116 (25).

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