Oxyfunctionalization of Non-Natural Targets by Dioxiranes. 4.[1] Efficient Oxidation of Binor S Using Methyl(trifluoromethyl)dioxirane

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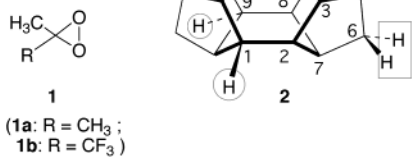
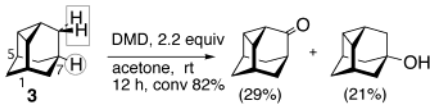
The direct oxyfunctionalization of hydrocarbons under mild conditions is an active area that continues to present challenging goals. A number of oxidizing systems, stoichiometric as well as catalytic, have been reported.[2,3]

Dioxiranes (**1**)[3] have been proven to be outstanding reagents for the selective oxidation of a variety of alkanes, including polycyclic saturated hydrocarbons.[3,4] It was shown that dioxiranes are capable of easy O-insertion into unactivated C−H bonds by an oxenoid-type mechanism;[3,4] tertiary C−H bonds are considerably more prone to oxidation than their secondary and primary counterparts. Thus, it was suggested that some aspects of the chemistry of dioxiranes resemble the behavior of certain monooxygenase enzymes,[5] and dioxiranes also are known to oxidize even more readily secondary alcohols to ketones.[3,4a,6]



Binor S (**2**) is a saturated heptacyclic hydrocarbon synthesized by dimerization of norbornadiene with transition metal catalysts;[7] it presents two symmetric methylene groups and 12 tertiary carbons ordered in four different geometries. The ratio of tertiary to secondary carbons and the different reactivity toward oxidation for each type of C−H bond in Binor S (**2**) render it attractive as a probe for the study of regioselectivity of saturated hydrocarbon functionalization.

Scheme 1



Eaton et al. showed that the oxidation of Binor S with dimethyldioxirane (DMD) (**1a**) in acetone solution results in the hydroxylation at the tertiary carbons, selectively affording the 1-ol in practically quantitative yield (98%); further oxidation of the latter with DMD gives the symmetrical 1,9-diol (**4**) as the major product (75% yield).[8] Under the given conditions, the reaction of **2** with DMD does not lead to oxidation at the C-6 methylene positions α to the cyclopropyl groups.

In this respect, it is worthy of noting that the direct oxyfunctionalization on the C-6 methano group of Binor S has not been achieved in reasonable yield, and it is indeed still a challenge. In fact, treatment of Binor S (**2**) under standard GoAgg^{III} conditions[9] was found to proceed with only 10% conversion to give the corresponding 6-one in only 8% yield;[10] however, this reaction suggests that the methylene positions in **2** could become activated. Indeed, Murray et al. have reported that the DMD oxidation of a related strained tetracyclic hydrocarbon such as 2,4-didehydroadamantane (**3**) gives didehydroadamantan-2-one along with the 7-hydroxy derivative (Scheme 1).[4e]

The efficient oxyfunctionalization of "unactivated" C−H bonds of alkanes under extremely mild conditions undoubtedly counts to date among the highlights of the

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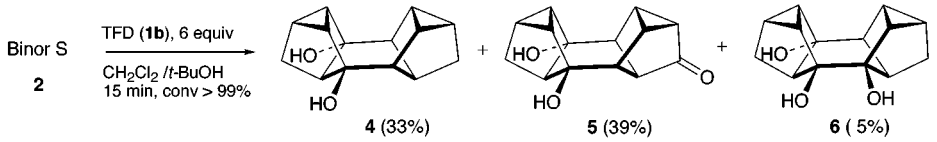
Scheme 2



chemistry of dioxiranes.[3] We have shown that in these reactions, methyl(trifluoromethyl)dioxirane (TFD) (**1b**)[11] appears better suited than DMD (**1a**),[3] leading to higher yields, much faster conversions, and no loss of selectivity. In these alkane oxyfunctionalizations, high tertiary vs secondary selectivities (R_s^t from 15 to >250) are customarily observed (with the norbornane case as a notable exception).[4b] Valuable is the selective bridgehead hydroxylation of adamantane by TFD (**1b**) to afford adamantan-1,3,5,7-tetraol along with the 1,3,5-triol in 73 and 24% yields, respectively.[4c] In this reaction, kinetic data showed that **1b** is more reactive than DMD (**1a**) by a factor of >700. Despite this, the high selectivity for tertiary bridgehead C−H hydroxylation remained unchanged.[4c]

In this work, we report on the application of the powerful dioxirane **1b** to the regiospecific oxidation of Binor S.

Results and Discussion

Methyl(trifluoromethyl)dioxirane (**1b**) solutions [0.7−0.8 M in 1,1,1-trifluoropropanone (TFP), its parent ketone] were prepared as already reported in detail.[4b,c] To Binor S (**2**),[8] dissolved in CH_2Cl_2/*t*-BuOH (ca. 50:50 v/v) and kept at 0 °C was added excess dioxirane **1b** in one portion. The reactions were carried out at the conditions given by the equation in Scheme 2 on a 30−50 mL scale and monitored by GC and GC/MS. Removal of the solvent in vacuo and column chromatography (silicagel) afforded products **4**−**6**; the given product yields refer to isolated materials and are average values from triplicate runs agreeing within 2%.

The 1,9-diol **4** presented physical constants, MS data, and ^{1}H and ^{13}C NMR spectra in full agreement with literature.[8] The novel Binor S 1,9-diol-6-one (**5**) became fully characterized by HRMS and by NMR.[12] The high-resolution mass spectrum (EI) gave a formula of $C_{14}H_{14}O_3$ (*m*/*z* 230.0945, calcd 230.0943). The IR spectrum showed a strong carbonyl signal at 1736 cm^{-1} and broad O−H stretching absorptions centered at 3360 cm^{-1}. ^{1}H and ^{13}C NMR spectroscopy substantiated that the compound contains one CH_2 group, ten CH groups, and one carbonyl moiety. In the ^{1}H NMR spectra, two complex multiplets at δ 2.34 and 1.80 (integral 2:1) could be attributed to the C^2-*H*, C^8-*H*, and to the C^7-*H* methine proton, respectively. In the high-field region of the ^{13}C NMR spectrum, four well-resolved methine carbon signals (δ 19.5, 25.3, 25.8, 26.6) are assigned to unfunctionalized cyclopropane carbons reflecting the C_s symmetry of **5**, while the C=O group gives a resonance at δ 214.9.[12] Other finer details of the structure and rigorous resonance assignments could be gained from COSY and 1D-TOCSY as well as NOESY NMR experiments (cf. Supporting Information).

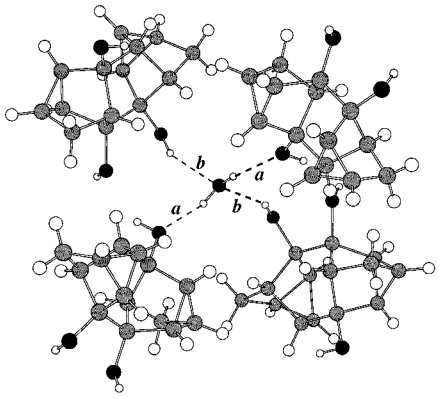


Figure 1. Ball-and-stick view of the three-dimensional crystal network assembling four molecules of triol **6** around one water molecule. Hydrogen-bonding parameters for the four independent molecules that exist in the solid state are a = 1.93 and b = 2.07 Å.

Along with the main products above, the 1,2,8-triol (**6**)[13] could also be isolated as small colorless crystals, albeit in low yield (Scheme 2); ^{1}H and ^{13}C NMR spectroscopy established that this compound is not symmetrical, yielding, for instance, three distinct tertiary *C*-OH resonances at δ 81.3, 81.5, and 83.5.[13] Its structure could be established unambiguously as **6** by X-ray analysis. The carbon skeleton of the molecule has an approximate mirror plane through carbon atoms numbered 1, 4, 7, 8, 11, and 14 in the ORTEP diagram reported in Supporting Information (Figure 6, S-8); distances of corresponding atoms from this plane differ by less than 0.05 Å. Only the O(3) hydroxyl oxygen has no corresponding atom, thereby making the molecule chiral. The space group is centrosymmetric, so both enantiomers are present in equal numbers.

An interesting feature of the crystal structure is that a water molecule appears, located on a 2-fold rotation axis, so the molecular formula is $C_{10}H_{16}O_3 \cdot 0.5H_2O$. One water molecule bridges to four triol units as displayed in Figure 1; two hydrogen atoms on bridgehead C−OH participate in hydrogen bonds to H_2O to produce the three-dimensional network shown.

The results of the application of TFD (**1b**) to the selective oxyfunctionalization of **2** are quite telling. In fact, the cyclopropyl moieties in **2** should have a significant activating influence on the methylene C−H bonds α to the cyclopropyl group at C(6) and C(11); these are the positions where a developing radical or carbocation would be stabilized by the cyclopropyl group because of the favorable "bisected" orientation presented by the prominent p character of the orbital generated at the cyclopropylcarbinyl carbon.[4e,12] Apparently, the mentioned methylene C−H bonds would become cyclopropyl-activated also in a concerted "oxenoid" O-insertion by dioxiranes.[3,4]

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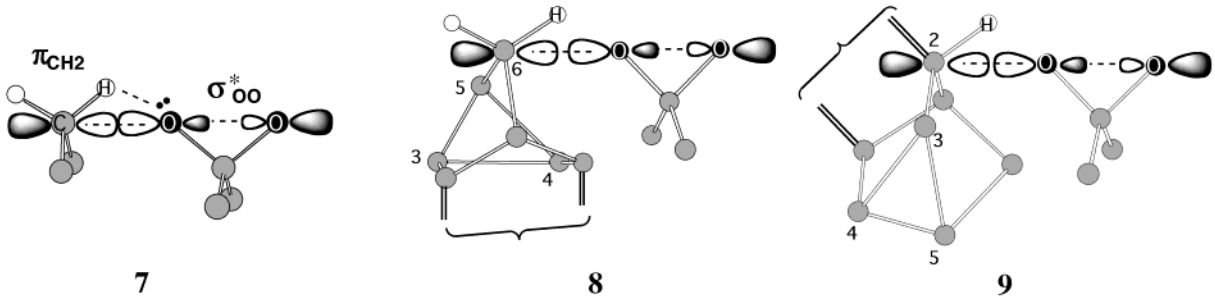

7 8 9

Figure 2. FMO interaction of a saturated alkane filled π_{CH} fragment orbital with the dioxirane electrophilic empty σ^*_{O-O} (**7**) and feasible orientation of "oxenoid" O-insertion into C(6)−H and into the C(2)−H bond of Binor S (**8** and **9**, respectively). For clarity, all but one of the H atoms are omitted and just one of the two Binor S nortricyclane subunits is shown.

In fact, Bach and co-workers[13] have produced careful ab initio calculations in support of a frontier molecular orbital theory (FMO) that provides a unique rationale for both the stereospecificity and the stereoselectivity of O-insertion into the hydrocarbon C−H bond by electrophiles and dioxiranes. In this FMO, the electrophilic attack is directed along the peroxide O−O bond axis toward the relevant carbon atom[13] of the substrate, so that the dioxirane electrophilic oxygen approaches a filled C−H fragment orbital containing both a carbon 2p and a hydrogen 1s orbital. For dioxirane attack at a generic CH_2, this should produce a FMO geometry such as **7** (Figure 2); here, we use the filled π_{CHR} fragment orbital of the hydrocarbon interacting with the dioxirane empty σ^*_{O-O} orbital, since Bach's calculations suggest that this produces a preferred orientation of approach.[13]

The analogous FMO interaction for dioxirane attack at CH_2 of **2** should take place as sketched in **8** (Figure 2). It is seen that the π fragment of the pertinent hydrocarbon C−H orbital array is forced to lie almost parallel to the cyclopropyl C(3)−C(4) bond (i.e., the favored "bisected" arrangement)[14] due to the rigid tricyclic framework.

Despite this α-cyclopropyl activation of CH_2, it is clear that the TFD oxyfunctionalization of **2** proceeds preferentially at the bridgehead tertiary C−H (Scheme 2). In fact, GC/MS monitoring of the reaction and control experiments using isolated diol **4** have shown that preferential oxyfunctionalization at C(6) occurs only after hydroxylation at the bridgehead C(1)−H and C(9)−H takes place in the facing nortricyclane subunit. Actually, inspection of transition structure **9** (Figure 2) reveals that these C−H bonds are not necessarily deactivated by the α-cyclopropyl moiety; instead, in the shown π_{RCH} orientation, the fragment p orbital component would lie in a nearly "bisected" orientation.[14] However, the two hydroxy groups initially introduced should deplete electron density at the neighboring C(2)−H and C(8)−H, hence making oxyfunctionalization of diol **4** at the C(6) methylene compete effectively with further hydroxylation at the residual bridgehead tertiary C−H bonds.

Be the mechanistic details as they may, results herein show that the application of the powerful dioxirane **1b** to Binor S leads in reasonable yield to the valuable highly regiospecific transformation of the methylene group into a carbonyl in one of the substrate nortricyclane subunits. Binor S oxygenated derivatives such as **5** and **6** may be quite difficult to obtain by other routes; it is likely that they can find fruitful application in the synthesis of other useful synthons of this hyperenergetic target.

(14) Instead, in the didehydroadamantane (**3**) case (Scheme 1), the C-5 and C-7 bridgehead C−H become "deactivated" since they are forced to adopt just about the unfavorable "perpendicular" orientation (ref 12). We verified that comparable selectivity is attained in the oxyfunctionalization of **3** on going from DMD to the more powerful TFD (**1b**); in fact, just didehydroadamantan-2-one and 7-hydroxy didehydroadamantane are formed (cf. Scheme 1) in ca. 40 and 60% yields, respectively. However, the oxidation by TFD is remarkably faster, i.e., 80% conversion during 1 h.

Experimental Section

Materials and Methods. Commercial 1,1,1-trifluoro-2-propanone (TFP) (bp 22 °C), methylene chloride, *tert*-butyl alcohol, and other common solvents were purified by standard methods, stored over 5 Å molecular sieves, and routinely redistilled prior to use.[1,4c] Curox triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Peroxid-Chemie GmbH, Munich, Germany) was our source of potassium peroxymonosulfate employed in the synthesis of dioxirane. Solutions of 0.8−1.0 M methyl(trifluoromethyl)dioxirane (**1b**) in TFP were obtained by following described procedures and precautions using the described equipment.[4c] Heptacyclo-[8.4.0.0.^{2,7}0.^{3,5}0.^{4,8}0.^{9,13}0^{12,14}]tetradecane (**2**) (Binor S), a gift from prof. P. E. Eaton's laboratories (University of Chicago), was recrystallized from EtOH/Et_2O: mp 64−65 °C.[8] High-Resolution MS spectra were run on a VG Autospec instrument (EI^+, source temperature 200 °C, trap current 150 μA, EE 30 eV, DIP).

Oxidation of Binor S (2) with Methyl(trifluoromethyl)-dioxirane. The following procedure is representative. To a stirred solution of **2** (380 mg, 2.06 mmol) dissolved in 40 mL of CH_2Cl_2/*t*-BuOH (ca. 50:50 v/v) and kept at 0 °C was added excess methyl(trifluoromethyl)dioxirane (18 mL of 0.7 M **1b** in TFP, 12.5 mmol) in one portion. The reaction was monitored by GC (SE 30, 30 m × 0.25 μm i.d., from 80 to 280 °C, 10 °C/min). After 15 min, removal of the volatile solvents in vacuo and column chromatography (silicagel, 230−400 mesh, elution gradient: from 9:1 to 1:9 Et_2O/MeOH) afforded products **4** (147 mg, 0.68 mmol, yield 33%), **5** (185 mg, 0.8 mmol, yield 39%), and **6** (24 mg, 0.103 mmol, yield 5%).

The heptacyclo[8.4.0.0.^{2,7}0.^{3,5}0.^{4,8}0.^{9,13}0^{12,14}]tetradecan-1,9-diol (**4**) that was isolated (mp 210−214 °C) gave ^{1}H and ^{13}C NMR spectra practically identical to those reported by Eaton et al.[8]

Heptacyclo[8.4.0.0^{2,7}.0^{3,5}.0^{4,8}.0^{9,13}.0^{12,14}]tetradecane-1,9-diol-6-one (5): white solid, uncorrected mp 233−5 °C; ^{1}H NMR (CD_3OD, 400 MHz): δ 2.34 (m, 2H), 2.27 (d, 2H, J = 5.2), 1.80 (m, 1H), 1.74 (m, 1H), 1.48 (t, 1H, J = 4.8), 1.45 (d, 2H, J = 4.8), 1.40 (t, 1H, J = 5.2), 1.21 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 214.94, 82.24 (2C), 49.97 (2C), 46.26, 40.47, 29.52, 26.58, 25.84 (2C), 25.31 (2C), 19.46; IR (KBr) ν 3373, 3063, 3049, 2942, 2929, 1758, 1736, 1431, 1371, 1306, 1280, 1209, 1133, 1105, 1083, 1062, 844, 817 cm^{-1}; GC/MS (70 eV) *m*/*z* (rel intensity) 230 (M^+, 22), 231 (4), 212 (10), 185 (34), 184 (20), 171 (16), 149 (30), 123 (79), 95 (100), 82 (89); HRMS calcd for $C_{14}H_{14}O_3$ 230.0943, found 230.0945.

Heptacyclo[8.4.0.0^{2,7}.0^{3,5}.0^{4,8}.0^{9,13}.0^{12,14}]tetradecan-1,2,8-triol (6): white solid, uncorrected mp 216 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.8−1.78 (three overlapping multiplets, 3H), 1.64 (br, 1H), 1.46 (apparent d, 1H), 1.38 (m, 2H), 1.36 (complex m, 2H), 1.30 (complex m, 2H), 1.22 (td, 2H, J = 4.9, 5.7); ^{13}C NMR (CD_3OD, 125 MHz) δ 83.48, 81.46, 81.35, 51.77, 45.21, 38.66,

32.26, 30.28, 26.57, 26.32, 23.40, 20.06, 17.48, 17.35; GC/MS (70 eV) *m*/*z* (rel intensity) 232 (M^+, 8), 231 (4), 214 (95), 185 (29), 171 (33), 149 (38), 107 (58), 105 (45), 77 (100), 69 (20), 66 (35).

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Supporting Information Available: Characterization ^1H and ^{13}C NMR spectra for compound **5**; X-ray crystallographic data and an ORTEP drawing for triol **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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