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Crystal structure of the tritylated product of 3-hydroxymethylbicyclo[3.3.1]nonan-2-on-7-ol ethylene acetal cyclization

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A tritylated product of 3-hydroxymethylbicyclo[3.3.1]nonan-2-on-7-ol ethylene acetal cyclization, 4-hydroxymethyl-3-[2-(trityloxy)-ethoxy]-2-oxatricyclo[4.3.1.0^{3,8}]decane, was found to have a crystal structure comprising close packed molecular layers intersected by infinite tubes filled with solvent molecules.

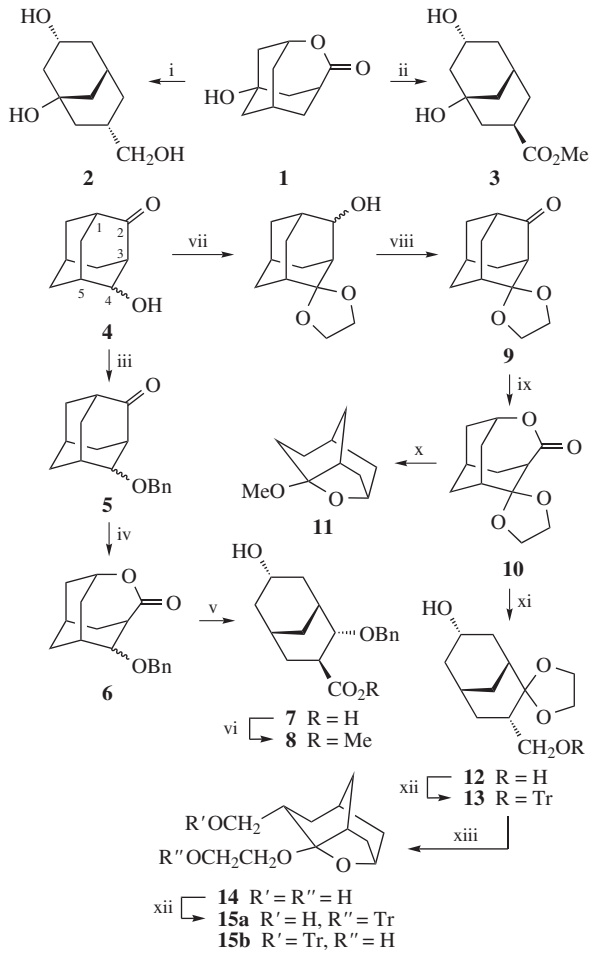
Bridgehead systems are frequent structural elements in natural and synthetic organic compounds possessing different biological activities. Our particular interest to the synthesis of 1,3,7- and 2,3,7-trisubstituted bicyclo[3.3.1]nonanes was connected with the development of simplified Taxol® analogues.[1]

1,3,7-Trisubstituted bicyclo[3.3.1]nonanes were easily synthesised from kemantane lactone **1** by ring-opening reaction[2–4] either reductive with the formation of triol **2** or by alkaline that afforded after subsequent methylation compound **3** (Scheme 1). Compounds **2** and **3** offer a suitable handle for the installation of different functionalities on the bicyclic framework.†

The synthesis of 2,3,7-substituted bicyclo[3.3.1]nonane derivatives required an extra procedure at the step of the initial lactone preparation, namely, the introduction of a bulkier substituent in the C(4) position of 4-hydroxyadamantan-2-one **4** [otherwise, its Bayer–Villiger oxidation affords two regioisomers with a slight domination of a product with C(1)–C(2) insertion of oxygen atom, see Online Supplementary Materials]. The use of benzyloxy derivative **5** after its oxidation and alkaline ring opening of resulted benzyloxylactone **6** furnished expected acid **7** (Scheme 1) in a good yield (the reductive ring opening of **6** has been carried out by Ganesh *et al.*[5]).

The alternative way of ketol **4** C(4) modification by ethylene acetal (compound **9**) leads to lactone **10** in the Bayer–Villiger reaction. Interestingly, the ring opening of lactone **10** either by alkaline with subsequent methylation or by $LiAlH_4$‡ with further removal of the ethylene acetal group leads to structurally analogous oxatricyclo[4.3.1.0^{3,8}]decane derivatives **11** and **14** (Scheme 1). Tricyclic hemiacetal **11**, evidently obtained by decarboxylation of the transient β-ketoacid under the treatment with methanolic $BF_3{\cdot}Et_2O$, has been previously described[6] but synthesised by a more complicated and less effective method. To confirm the structure of compound **14** (and the formation of compound **11**), one of its trityl derivatives (**15a**) was studied by X-ray analysis [Figure 1(*a*)].§

The analysis of the crystal structure of **15a** revealed an unusual characteristic of its molecular packing. In the absence of specific intermolecular contacts, the main molecules form close packed molecular layers. The parallel conjunction of the



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, 3 h, reflux, 83%; ii, NaOH, MeOH + H_2O, reflux, 26 h, then $Et_2O{\cdot}BF_3$, MeOH, reflux, 4 h, 30% (the simultaneous formation of the elimination reaction by-product was detected); iii, NaH, DMF, then BnCl, room temperature, 1 h, 97%; iv, H_2O_2, SeO_2, Bu^{t}OH, 80 °C, 1.5 h, 94%; v, NaOH, MeOH + H_2O, reflux, 26 h, 83%; vi, MeOH, $CHCl_3$, *p*-TSA, reflux, 6 h, 37% from **6**; vii, ethylene glycol, *p*-TSA, toluene, reflux, 6 h, 89%; viii, PCC/Al_2O_3, benzene, room temperature, 12 h, 90%; ix, *m*-CPBA, $CHCl_3$, $NaHCO_3$, reflux, 24 h, 72%; x, NaOH, MeOH + H_2O, reflux, 26 h, then $Et_2O{\cdot}BF_3$, MeOH, reflux, 4 h, 70%; xi, $LiAlH_4$, Et_2O, room temperature, 3 h, 91%; xii, TrCl, DMF, DMAP, room temperature, 8 h, 55% for **13**, 26% for **15a**, 32% for **15b**; xiii, HCl, Et_2O, room temperature, 95%.

† For the synthetic details and characteristics of all the compounds see Online Supplementary Materials.

‡ For the X-ray structure of tritylated derivative of **12**, *i.e.*, compound **13** see ref. 7.

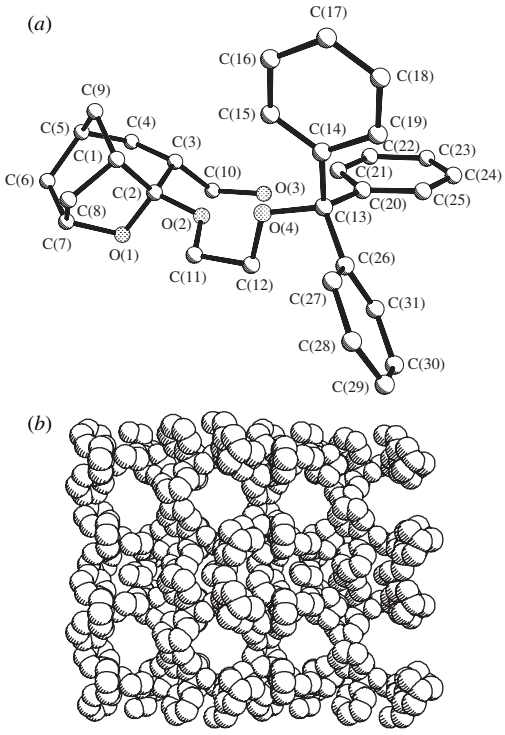


Figure 1 (*a*) X-ray structure of compound **15a**; (*b*) 'the tubes'.

layers gives us the infinite periodic quasicylindrical void spaces. These 'tubes' are filled by statistically irregular molecules of the solvent, acetonitrile [Figure 1(*b*)]. To study the possible mechanism of the 'tubes' formation the calculations of intermolecular interactions energy by the atom-atomic potential method was carried out. The molecular contacts rigidity[8] was

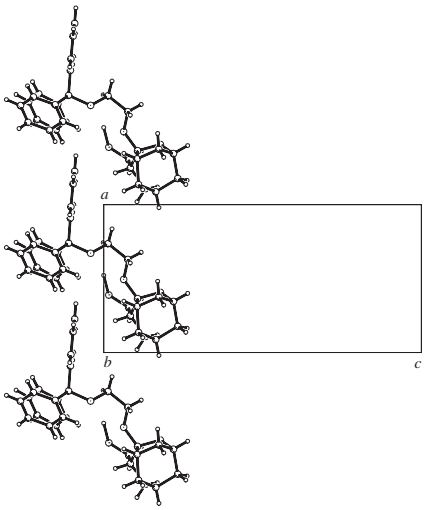


Figure 2 Molecular chain $P_{c(X)}1,Z = 1(1)$.

§ For **15a**: mp 156–157 °C. ^{1}H NMR, δ: 1.13–2.16 (m, 10H), 2.38 (m, 1H), 3.16–3.28 (m, 3H, CH_2 + OH), 3.51 (m, 2H), 3.81 (m, 2H), 4.46 [m, 1H, C(2)HO], 7.18–7.43 (m, 15H, arom.). ^{13}C NMR, δ: 27.90, 31.00, 32.05, 38.81, 39.86, 40.12, 40.54, 60.93, 63.11, 64.04, 76.68, 86.54 (*C*Ph_3), 110.71 [*C*O(*C*H_2)$_2$], 126.92, 127.78, 128.65, 143.98. IR (ν/cm^{-1}): 1450, 1475, 1600, 3430 (br.). MS (ESI): 503 $[M + Na]^{+\cdot}$.

Crystallographic data for **15a**: colourless, transparent crystals were obtained from acetonitrile; $C_{31}H_{34}O_4 \cdot 0.75C_2H_3N$, M = 501.37; space group $Pca2_1$, orthorhombic, a = 8.885(5), b = 15.820(8), c = 19.067(10) Å, V = 2680(2) Å^3, Z = 4, d_{calc} = 1.243 g cm^{-3}, μ(MoKα) = 0.079 cm^{-1}, R = 0.0780.

CCDC 626665 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

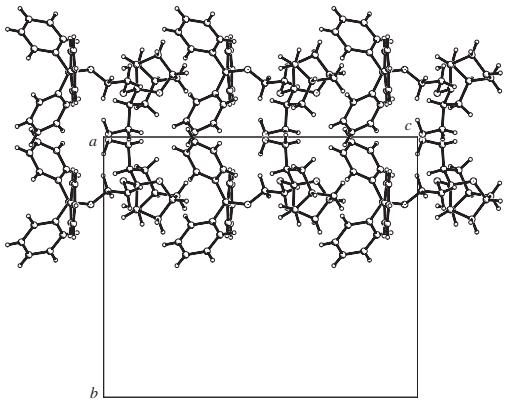


Figure 3 Molecular layer $P_{l(XZ)}ac,Z = 4(1)$.

also studied to reveal primary and secondary molecular agglomerate[9,10] formation.

The investigation indicated that, at the first step, the steady molecular chains $P_{c(X)}1,Z = 1(1)$ (for nomenclature, see ref. 9) are formed due to the packing of the 'buttress-cavity' type. 'Buttress' is represented by a benzene ring C(26)–C(31), while the 'cavity' is formed by two other benzene rings C(14)–C(19) and C(20)–C(25) and tetracyclic framework [orientation of the framework is stabilised by the intramolecular hydrogen bond O(3)–H···O(2)] (Figure 2). Then, energetically effective and rigid contacts of molecular chains stabilise the close packed molecular layers $P_{l(XZ)}ac,Z = 4(1)$ (Figure 3). Finally, these molecular layers are packed by parallel translation along the crystallographic axis *b*. The stability of the molecular layers interaction is provided by the arrangement (disposition) of the benzene rings C(14)–C(19) and C(20)–C(25) coming out of the layers and interacting at the 'buttress-cavity' type. These interactions lead to the formation of infinite quasicylindrical tubes throughout close packed molecular layers (Figure 4).

The period of translation along the tube is a = 8.885 Å. Besides, a glide plane passes along the tube with a glide by half of the translation vector along the axis *a*. This glide divides the translation in two times. The linear size of an acetonitrile molecule (including van der Waals radii) is about 5.9 Å. Therefore, the tube cannot be filled with these molecules without void spaces and intersections (otherwise, it leads to the distortion of the translation symmetry). This explains the statistical irregularity of solvent molecules in the tubes. It is interesting that three

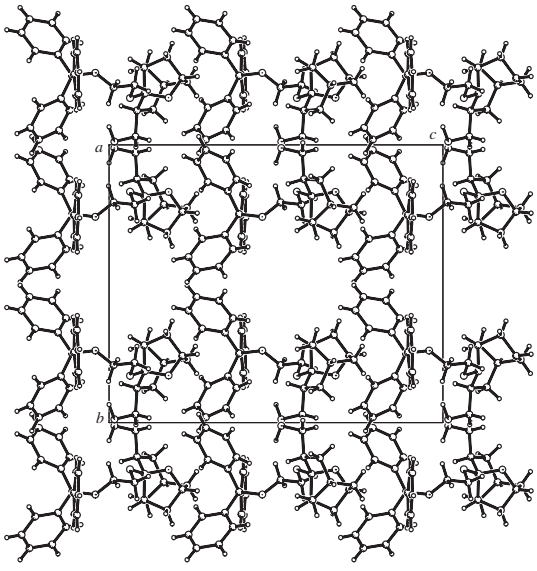


Figure 4 Projection of the structure of **15a** along the axis *a* (solvent molecules are not shown).

acetonitrile molecules can exactly occupy two periods along the axis *a* (2*a* = 17.770 Å; 3×5.9 = 17.7 Å). This fact indicates that the tube might be rather closely packed by solvent molecules (three solvent molecules per each two translations along the axis *a*).

In summary, the preparation of novel 2,3,7- and 1,3,7- bicyclo-[3.3.1]nonanes scaffolds suitable for further functionalization led to the observation that 2-oxo-7-hydroxybicyclo[3.3.1]nonanes undergo an easy transformation into oxatricyclic frameworks. The analysis of the X-ray data of oxatricyclo[4.3.1.$0^{3,8}$]decane derivative **15a** revealed its specific molecular packing comprising the infinite tubes filled with the solvent molecules. The role of the solvent type in the tube formation will be studied in the near future.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2007.11.011.

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