Tetrahedron Letters 50 (2009) 5751–5753

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 9-oxa-noradamantane derivative, an aesthetically pleasing 'oxa-basket'

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ARTICLE INFO

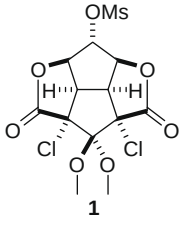
Article history:
Received 2 July 2009
Revised 26 July 2009
Accepted 29 July 2009
Available online 3 August 2009

ABSTRACT

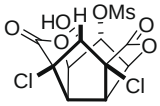
A simple protocol for the synthesis of an aesthetically pleasing 'oxa-basket' (5-methoxy-2,8,13-trioxapentacyclo[7.2.1.1.^{5,12}0.^{4,11}0^{6,10}]tridecane-3,7-dione), possessing 9-oxa-noradamantane core, is described. The readily available diquinane based dichloro bis-γ-lactone precursor upon treatment with $MeSO_3H$ furnished dichloro 'oxa-basket' which was dechlorinated using TBTH/AIBN to obtain the title compound. The key role of the chlorines was demonstrated by replacement with hydrogen or allyl substituents which redirects the cascade to simple hydrolysis products.

The design and synthesis of aesthetically pleasing and architecturally challenging unnatural products has stimulated synthetic chemists to construct marvelous scaffolds.[1–5] In this context, the first tactical synthesis of cubane[2] by Eaton et al. is a landmark in the synthesis of topologically demanding unnatural products which continues to fascinate with its rich chemistry and novel applications.[6] Various architecturally interesting unnatural products, oxa-bowls,[3a–c] thia-bowls,[3d] ladderanes,[3e,3f] prismanes,[3g] dodecahedrane,[4,3g] and other cage compounds[5] were synthesized by ingenuous strategies. Our interest in this area led us to the synthesis of interesting oxa-bridged compounds[7] and, more recently, constrained bowl shaped molecules, starting from norbornyl α-diketone building blocks.[8] In continuation of our efforts we herein report a short synthesis of an aesthetically pleasing molecule possessing the 9-oxa-noradamantane core (Fig. 1). The two-atom bridges between C2–C4 and C6–C8 on either side of this core with a C1–C5 oxa-bridge gives rise to a molecular shape resembling a basket.

We envisioned that 'oxa-basket' (R = H, Fig. 1) should be amenable via S_N2 displacement of a mesylate by an *endo*-hydroxy group in **2**. We have demonstrated previously an efficient route to ketal **1** and other related diquinane based bis-γ-lactones in a few steps from an easily available starting material.[8a] It was envisaged that hydrolysis of ketal **1** followed by a stereoselective reduction from the sterically accessible *exo*-face would furnish *endo*-alcohol **2** or even the target 'oxa-basket' directly.



1



2

The ketal moiety in **1** was found to be inert under usual hydrolytic conditions. Further, being sparingly soluble in common organic solvents, it posed problems of handling and monitoring the reaction progress using routine methods. Therefore, β-hydroxy bis-lactone **3**, obtained from a different route compared to **1**,[8a] was subjected to $MeSO_3H$ reaction. In this case, the starting

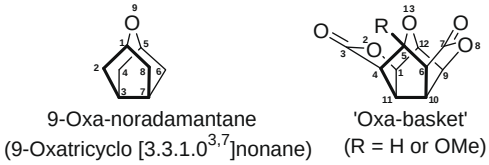
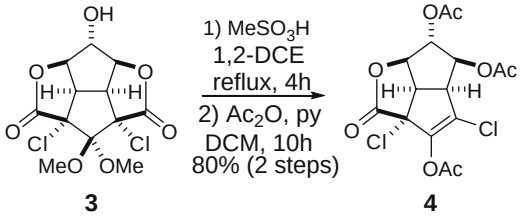


Figure 1.



3 **4**

Scheme 1. Acid mediated reaction of **3**.

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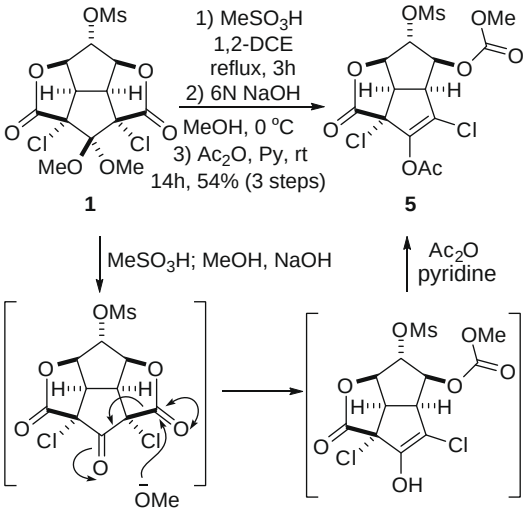
doi:10.1016/j.tetlet.2009.07.143



Scheme 2. A plausible mechanism for the formation of **5**.

material was consumed to furnish a sparingly soluble reaction mixture which was treated with excess Ac_2O and pyridine. Interestingly, a triacetate derivative **4** was isolated in very good yield (Scheme 1).[9] Acid mediated hydrolysis of the ketal **3** followed by decarboxylation and subsequent acylation of the enolizable species thus formed under Ac_2O–pyridine conditions is a likely route to **4**.

After realizing that the methanesulfonic acid mediated hydrolysis of the ketal occurs smoothly in the case of **3**, we revisited **1** and exposed it to identical reaction conditions. Earlier we had established that the mesylate group in **1** could be displaced by a hydroxyl using NaOH in a S_N2 fashion to obtain the corresponding α-hydroxy derivative.[8a] Based on this observation, the reaction mixture obtained after reacting **1** with methanesulfonic acid was treated with NaOH in MeOH in order to replace the mesylate with a hydroxyl group with inversion of stereochemistry prior to acylation. However, to our surprise, a carbonate derivative **5** was obtained (Scheme 2).[9] This was evident from one extra carbon signal at δ 153.1 in ^{13}C NMR spectrum while the ^{1}H NMR spectrum showed characteristic methyl resonances for carbonate, mesylate and acetate groups, in addition to other peaks. Finally, the structure of carbonate derivative **5** was unambiguously secured from single crystal X-ray analysis (Figure 2).[10] A plausible mechanism depicting the formation of product **5** appears in Scheme 2. After the initial acid mediated ketal hydrolysis to the corresponding ketone, opening of the lactone by methoxide gives the enolate. Subsequent treatment with Ac_2O–pyridine furnishes the carbonate **5** as shown in Scheme 2.

The difficulty encountered in intercepting the ketal prompted us to change our strategy. Instead of synthesizing *endo*-alcohol **2** to eventually form the oxa-bridge of the target through an intramolecular displacement, we thought of shifting the *endo*-alcohol functionality to the other terminus to form an oxa-bridge through a mixed ketal. For this purpose, we turned our attention to *endo*-hydroxy bis-γ-lactone **6**, accessible in excellent yield from mesylate **1** simply by a brief exposure to NaOH/MeOH at room temperature.[8a] When **6** was subjected to methanesulfonic acid in 1,2-dichloroethane as solvent and refluxed over a period of 3 h, an insoluble and highly crystalline compound **7** was obtained in high yield (Scheme 3).[11] The presence of four ^{1}H NMR and seven ^{13}C NMR signals strongly hinted at the symmetric nature of the molecule. Disappearance of one OMe signal at $\delta \sim 53$ and the emergence of a signal at δ 107.2 in the ^{13}C NMR spectrum indicated the formation of a mixed ketal. Unequivocal proof for the proposed

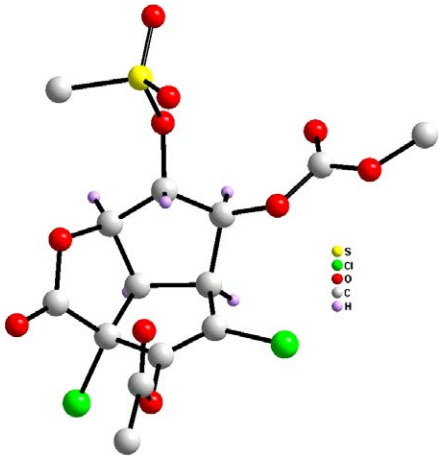
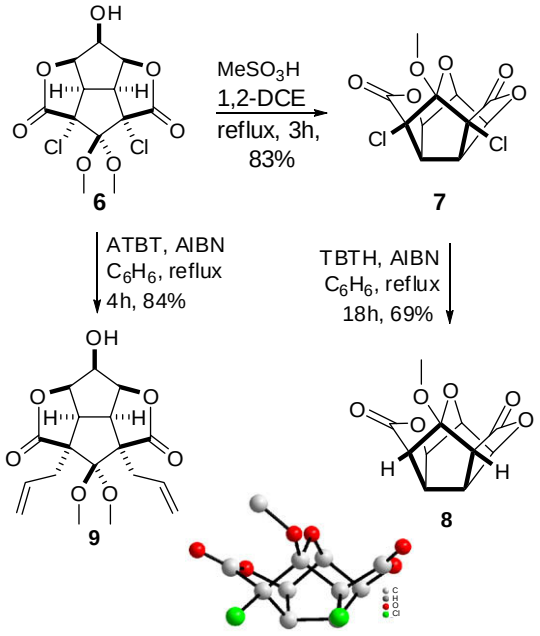
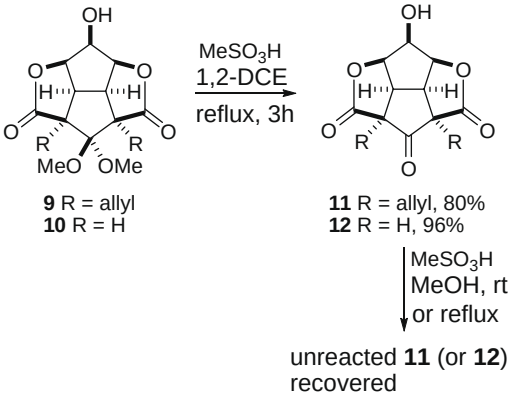


Figure 2. X-ray structure of methyl carbonate **5**.



Scheme 3.



Scheme 4.

structure **7** was obtained by performing a single crystal X-ray analysis (Scheme 3).[10]

Radical mediated dechlorination of **7** furnished the title compound. Subjecting **7** to TBTH/AIBN reduction in benzene gave bis-reduced oxa-basket **8** (Scheme 3).[9] To probe the role, if any, of two chlorine atoms in **6** on the key cyclization, two reactions were set up with *endo*-hydroxy bis-γ-lactones **9** and **10**[8a] lacking chlorines under identical conditions (Scheme 4). Bis-allyl derivative **9** was synthesized in good yield via radical mediated allylation employing allyl tri-*n*-butyltin (ATBT) in presence of catalytic AIBN (Scheme 3).[12] Surprisingly the hydrolyzed products **11** and **12** rather than the expected cyclized products were formed in high yield. This clearly demonstrated the pivotal role played by the chlorines in steering the key cyclization. The symmetric nature of **11** and **12** was obvious from NMR spectral data and characteristic carbonyl signals at δ 200.5 and 199.5 in ^{13}C NMR spectra further confirmed the assigned structures.[9] Further, separately treating **11** or **12** with $MeSO_3H$ in methanol under reflux conditions also failed to furnish the cyclized products as shown in Scheme 4.

In conclusion, an aesthetically pleasing 'oxa-basket' possessing the 9-oxa-noradamantane core has been synthesized in a single transformation. Halogen substituents steer the crucial ring closure to oxa-basket while allyl and proton substituents do not.

Acknowledgements

We are grateful to the Department of Science and Technology (DST), New Delhi, for the financial assistance. F.A.K. acknowledges DST for a Swarnajayanti Fellowship. C.N.R. thanks CSIR, New Delhi for a fellowship.

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9. All new compounds were fully characterized on the basis of their spectral data. Spectral data for **4**, **5**, **8**, **11** and **12**. Compound **4**: colorless crystalline compound, mp 210–211 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (dd, 1H, J = 4.1, 6.6 Hz), 5.27 (t, 1H, J = 6.6 Hz), 4.81 (dd, 1H, J = 4.1, 8.2 Hz), 3.86 (t, 1H, J = 8.2 Hz), 3.79 (t, 1H, J = 8.2 Hz), 2.24 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6, 5:1) δ 169.2, 168.5, 168.2, 165.6, 140.1, 126.4, 79.5, 77.0, 74.2, 68.4, 49.8, 45.3, 20.2, 20.1, 19.5; IR (KBr) 1785, 1740, 1655, 1470, 1220, 1160, 1030 cm^{-1}; Calcd for $C_{15}H_{14}O_8Cl_2$: C, 45.82; H, 3.59. Found: C, 45.66; H, 3.43. Compound **5**: mp 190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (t, 2H, J = 5.4 Hz), 4.98 (dd, 1H, J = 5.4, 10.0 Hz), 4.02 (t, 1H, J = 6.6 Hz), 3.83 (s, 3H, OMe), 3.81 (dd, 1H, J = 10.0, 11.2 Hz), 3.12 (s, 3H, OMs) 2.29 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6, 5:1) δ 167.3, 165.6, 153.1, 140.1, 125.9, 82.7, 77.7, 76.6, 67.7, 54.6, 48.1, 43.6, 37.6, 18.9; IR (KBr) 3050, 1790, 1755, 1660, 1450, 1270, 1020, 840 cm^{-1}; Calcd for $C_{14}H_{14}O_{10}Cl_2S$: C, 37.77; H, 3.17. Found: C, 37.54; H, 2.93. Compound **8**: mp 182–183 °C, ^1H NMR (400 MHz, acetone-d_6) δ 5.12 (q, 2H, J = 2.4, 3.3 Hz), 4.4 (s, 1H), 3.68 (m, 2H), 3.52 (s, 3H, OMe), 3.30 (d, 2H, J = 5.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.3, 105.8, 81.1, 77.4, 55.5, 53.2, 46.5; IR (KBr) 2950, 1770, 1450, 1350, 1070, 910 cm^{-1}; ESI-MS m/z 239.0557 [(M+H)$^+$ 239.0555 calcd for $C_{11}H_{10}O_6$]. Compound **11**: mp 212–214 °C, yield 80% (100 mg, 0.29 mmol); ^1H NMR (400 MHz, $CDCl_3$:DMSO-d_6, 5:1) δ 5.65- 5.57 (m, 2H), 5.22 (d, 2H, J = 15.4 Hz), 5.19 (d, 2H, J = 9.2 Hz), 4.86 (dd, 2H, J = 4.5, 6.4 Hz), 4.37 (t, 1H, J = 4.5 Hz), 3.46 (t, 2H, J = 3.9 Hz), 2.75 (dd, 2H, J = 7.3, 13.7 Hz), 2.60 (d, 1H, OH, J = 16.3 Hz), 2.46 (dd, 2H, J = 7.6, 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6, 5:1) δ 200.5, 171.6, 130.6, 120.4, 83.2, 74.8, 63.3, 44.5, 36.1; IR (KBr) 3518, 2929, 1788, 1736, 1640, 1412, 1151, 1108, 1008, 929, 696 cm^{-1}; ESI-MS m/z 327.0840 [(M+Na)$^+$ 327.0845 calcd for $C_{16}H_{16}O_6$]. Compound **12**: mp 200 °C (decomp.), yield 89% (40 mg, 0.15 mmol); ^1H NMR (500 MHz, DMSO-d_6) δ 4.92 (s, 2H), 4.23 (s, 1H), 3.60 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.5, 170.8, 84.3, 73.6, 56.1, 42.6; IR (KBr) 3454, 3019, 2982, 1787, 1723, 1370, 1049, 990, 934, 699 cm^{-1}; Anal. Calcd for $C_{10}H_8O_6$: C, 53.58; H, 3.60. Found: C, 53.45; H, 3.50.
10. Crystallographic data (excluding structure factors) for **5** and **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 738579 and CCDC 738580, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax : +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
11. *Procedure for synthesis of* **7**: to a stirred solution of sparingly soluble substrate **6** (40 mg, 0.118 mmol) in 1,2-dichloroethane (2 mL), was added methanesulfonic acid (113 mg, 1.19 mmol) at 0 °C. After 3 h reflux, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with 50% aqueous $NaHCO_3$ (2 mL) solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. Pure colorless crystals of **7** were obtained in good yield (83%) without any further column purification. mp 140 °C (decomp.); ^1H NMR (400 MHz, DMSO-d_6) δ 5.36 (d, 2H, J = 5.6 Hz), 4.70 (s, 1H), 4.04 (d, 2H, J = 5.6 Hz), 3.50 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 107.2, 79.8, 77.7, 74.0, 53.3, 52.9; IR (KBr) 2995, 1800, 1350, 1265, 1030, 940, 820, 760 cm^{-1}; Calcd for $C_{11}H_8O_6Cl_2$: C, 43.02; H, 2.63. Found: C, 42.95; H, 2.49.
12. *Procedure for bis-allylated compound* **9**: to a stirred solution of substrate **6** (50 mg, 0.147 mmol) in benzene (4 mL), was added freshly distilled allyl tri-*n*-butyltin (ATBT) (121 mg, 0.369 mmol) followed by AIBN (few crystals, 5–10 mol %). After refluxing the reaction for 4 h, the solvent was removed under reduced pressure. The crude reaction mass was purified by silica gel column chromatography to furnish bis-allylated product **9**. R_f (70% ethyl acetate in hexane) 0.4, colorless crystalline compound, mp 212–214 °C; yield 84%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75–5.64 (m, 2H), 5.25 (d, 2H, J = 16.8 Hz), 5.19 (d, 2H, J = 10.0 Hz), 4.60 (dt, 2H, J = 2.4, 4.3 Hz), 4.15 (td, 1H, J = 4.3, 8.0 Hz), 3.79 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.29 (d, 1H, J = 11.7 Hz , OH), 3.03 (dd, 2H, J = 2.4, 3.8 Hz), 2.82 (dd, 2H, J = 6.3, 12.7 Hz), 2.63 (dd, 2H, J = 8.9, 12.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 131.7, 120.8, 109.3, 81.6, 76.1, 63.8, 54.4, 52.1, 48.4, 37.9; IR (KBr) 3400, 2950, 1770, 1640, 1440, 1220, 1040, 920 cm^{-1}; ESI-MS m/z 373.1267 [(M+Na)$^+$ 373.1264 calcd for $C_{18}H_{22}O_7$].