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Four-step convergent synthesis of *trans*-fused tetracyclic oxane

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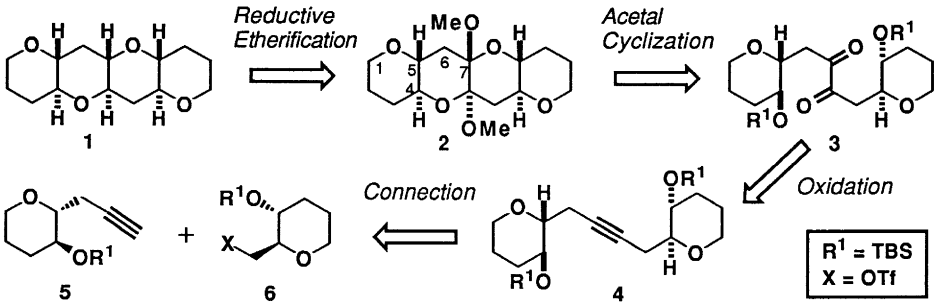
Abstract

Four-step convergent synthesis of *trans*-fused tetracyclic oxane starting from monocyclic ethereal acetylene and triflate segments was achieved, which involved the following sequence: (i) connection of two monocyclic segments; (ii) oxidative formation of α-diketone; (iii) construction of *trans*-fused tetracyclic diacetal; and (iv) reductive etherification of the diacetal.

Keywords: polyethers; etherification; oxygen heterocycles; coupling reactions.

Natural polycyclic ethers represented by brevetoxins and ciguatoxin, which have novel structures and strong biological activities, present the interesting synthetic challenges to chemists.[1] One such challenge which has been actively explored is an efficient convergent strategy for the construction of these large polycycles.[2] In this paper, a four-step convergent synthesis of *trans*-fused tetracyclic oxane **1**, which could enable an efficient synthetic approach to various natural polycyclic ethers, is described.

Our strategy for the construction of **1** (Scheme 1) includes four key steps: (i) connection of monocyclic acetylene **5** and triflate **6** segments; (ii) oxidative formation of α-diketone **3** from acetylene **4**; (iii) construction of *trans*-fused tetracyclic diacetal **2**; and (iv) reductive etherification of **2**. This convergent strategy would strongly rely on the successful cyclization of **3** into the fused system **2**. Although no report



Scheme 1.

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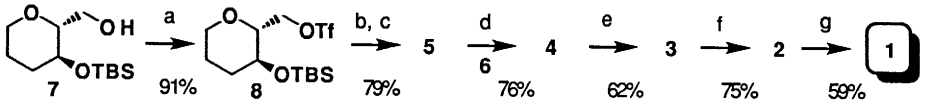
on the cyclization of the 1,8-dihydroxy-4,5-octanedione system have been published, we expected that the desired cyclization could proceed in a system fixed with two oxane rings.

Segment **5** was prepared from **7**[3] through a three-step sequence (conversion to **8**, substitution with ethynyltrimethylsilane, and removal of TMS) (Scheme 2). Lithiated **5** reacted with **6** smoothly to provide **4** in 76% yield,[4] and which was oxidized with RuO_2–$NaIO_4$[5] to afford **3** (62%). Treatment of **3** with TsOH in MeOH–$(MeO)_3CH$ produced the desired *trans*-fused cyclic diacetal **2**[6,7] (75%). Diacetal **2** was reduced with Et_3SiH–$SnCl_4$ to give tetracyclic **1**[6,7] (59%).



Scheme 2. Reagents and conditions: (a) 2,6-lutidine (3 equiv.), Tf_2O (1.1 equiv.), CH_2Cl_2, −78°C, 30 min; (b) TMSC≡CH (1.3 equiv.), BuLi (1.3 equiv.), HMPA (1.3 equiv.), THF, −78°C, then **8**, −78→−20°C, 2 h; (c) K_2CO_3 (2.8 equiv.), MeOH, 24°C, 3.5 h; (d) BuLi (1.2 equiv.), THF–HMPA (10:1), −78°C, then **6** (1.3 equiv.), −78→−20°C, 2.5 h; (e) $RuO_2 \cdot H_2O$ (cat.), $NaIO_4$ (3.8 equiv.), CCl_4–MeCN–pH 7 buffer (1:1:1.5), 26°C, 30 min; (f) $TsOH \cdot H_2O$ (3.1 equiv.), MeOH–$(MeO)_3CH$ (2:1), 24°C, 5 h, then 44°C, 44 h; (g) Et_3SiH (18 equiv.), $SnCl_4$ (8 equiv.), CH_2Cl_2, 0→23°C, 5 h

Thus, an efficient and convergent synthesis of **1** from monocyclic segments **5** and **6** was achieved in only four steps. Application of the present results to the synthesis of natural polycyclic ethers is currently under way in our laboratory.

References

1. For reviews for natural polycyclic ethers, see: (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Yasumono, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
2. For recent convergent approaches to polycyclic oxanes, see: (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (b) Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003. (c) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (d) Fujiwara, K.; Saka, K.; Takaoka, D.; Murai, A. *Synlett* **1999**, 1037.
3. Oxane **7** was prepared from the corresponding benzyl ethereal derivative reported by Hirama (Oishi, T.; Nagumo, Y.; Hirama, M. *Synlett* **1997**, 980).
4. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609.
5. (a) Gopal, H.; Gordon, A. J. *Tetrahedron Lett.* **1971**, 2941. (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (c) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (d) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237.
6. For the reported synthesis and reductive etherification of *trans*-fused tetracyclic dithioacetals, see: Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; Defrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.
7. Spectral data of **1** agreed well with those of the literature.[6] Representative data of **2**: colorless plates, mp 179–180°C (hexane); ^{1}H NMR (300 MHz, C_6D_6, C_6HD_5 as 7.15 ppm): δ 1.13–1.28 (2H, m, H2e), 1.39–1.58 (4H, m, H2a, H3a), 2.38 (2H, dd, *J*=5.0, 12.5 Hz, H6e), 2.45 (2H, dd, *J*=11.2, 12.5 Hz, H6a), 3.02 (6H, s, OMe), 3.06–3.17 (2H, m, H1a), 3.29 (2H, ddd, *J*=5.0, 9.2, 11.2 Hz, H5), 3.53 (2H, ddd, *J*=4.0, 9.2, 11.0 Hz, H4), 3.66–3.75 (2H, m, H1e); ^{13}C NMR (75 MHz, C_6D_6, $^{13}C^{12}C_5D_6$ as 128.0 ppm): δ 26.3 (C2), 29.5 (C3), 30.2 (C6), 46.6 (OMe), 68.2 (C1), 71.1 (C4), 77.0 (C5), 99.1 (C7); IR (KBr): ν 2980, 2894, 2854, 1284, 1142, 1092, 1062, 1048, 1027, 992 cm^{-1}; HR-EIMS calcd for $C_{16}H_{26}O_6$ [M]: 314.1729; found: 314.1731. The fused cyclic structure of **2** was deduced from J_{H5-6a} (11.2 Hz) and J_{H5-6e} (5.0 Hz) which suggested the chair conformations of the central oxane rings.