Pergamon

Tetrahedron Letters, Vol. 35, No. 39, pp. 7151-7154, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01531-7

Improvements in the Synthesis of Adamantane-2,6-dione and Preparation of the Novel Adamantane-2,6-dione *mono*-ketal

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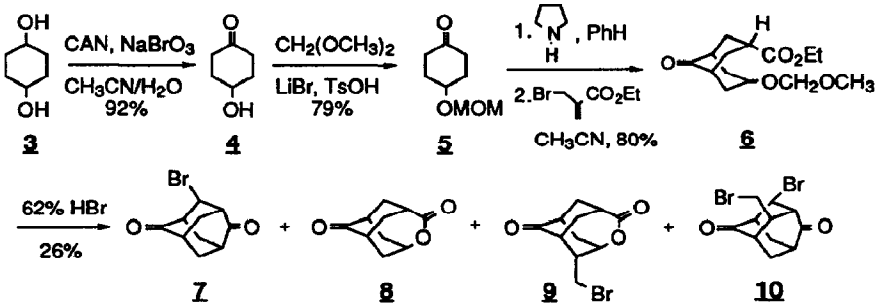
Abstract: A facile seven-step synthesis of adamantane-2,6-dione is presented that involves minimal purification, provides multigram quantities of product, and proceeds in an overall yield of 21%. The *mono*-ketal of adamantane-2,6-dione is obtained in 18% overall yield.

Our interest in adamantane-based molecular architecture[1] requires a ready supply of the crucial building blocks adamantane-2,6-dione (**1**) and its *mono*-ketal **2**. Although several syntheses of **1** have appeared in the literature[2] we sought an alternative route that possessed fewer steps, was amenable to large-scale preparations, and proceeded in higher overall yield.

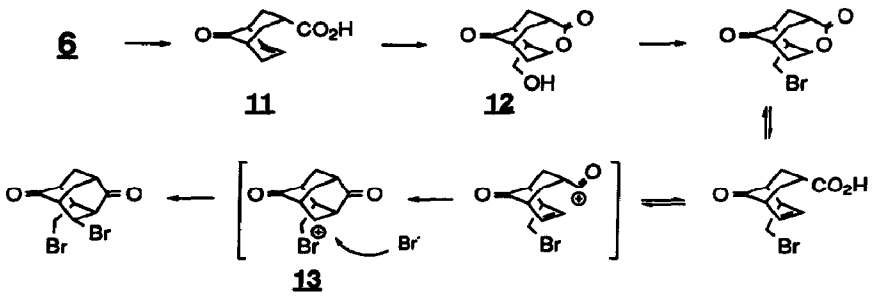
1 **2**

Our initial efforts (Scheme 1) focused on the α,α'-annelation of the pyrrolidinenamine of cyclohexanone-4-methoxymethylether (**5**) with ethyl α-bromomethylacrylate,[3] followed by a π-route cyclization[4] in refluxing 62% HBr, a method that was successfully exploited by Stetter.[2g,h]



Scheme 1

However, analysis of the reaction mixture revealed the presence of two unexpected products that were subsequently identified as the bromolactone **9** and dibromide **10**. Presumably, formaldehyde arising from the decomposition of the methoxymethyl protecting group in **6** adds to the acid **11** in an intramolecular Prin's reaction[5] (Scheme 2) to give the **12** and eventually **10** via the intermediate **13**.

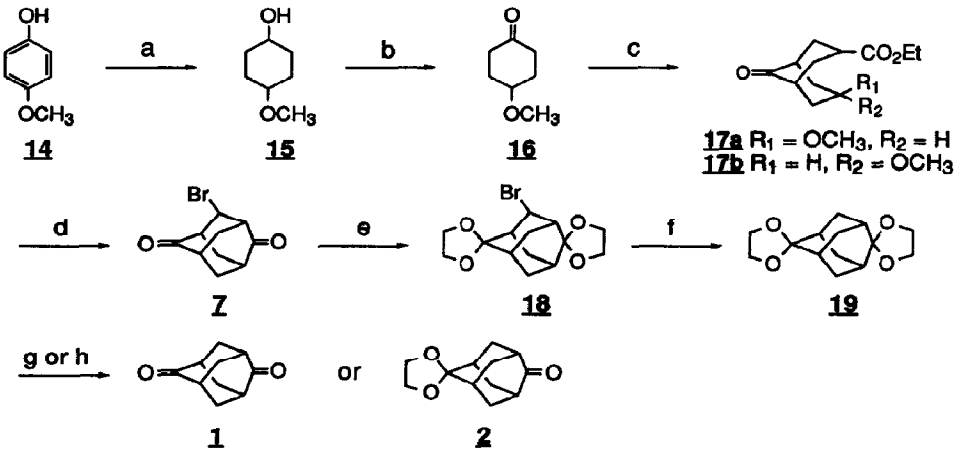


Scheme 2

Conversion of **9** to its ketal offered crystals suitable for X-ray analysis, which confirm the proposed structure (Figure 1). The crystal structure of **10** (Figure 2) reveals that severe 1,3-diaxial interactions during π-route cyclization allow for only *syn*-addition of Br^- to **13** and 4_{ax}-bromomethyl-8_{eq}-bromoadamantane-2,6-dione is isolated as the sole isomer from the reaction mixture.

In view of our initial results we sought an alternative starting material with a protecting group that would be both labile and inert during the cyclization step. *p*-Methoxyphenol (**14**) proved ideal (Scheme 3). Hydrogenation[6] (1000 psi) of **14** over catalytic Rh/Al_2O_3 gave quantitatively the alcohol **15** which was then oxidized under $(NH_4)_2Ce(NO_3)_6/NaBrO_3$[7] conditions to give **16** in 74% yield after distillation (26 °C, 0.1 mmHg). Both reactions were routinely carried out on a 50 g scale.

Scheme 3. Improved synthesis of adamantane-2,6-dione



Reagents and conditions: (a) H_2, Rh/Al_2O_3, EtOH, 100% (b) CAN, $NaBrO_3$, CH_3CN/H_2O, 74% (c) i. pyrrolidine, PhH ii. ethyl α-bromomethylacrylate, CH_3CN iii. H_3O^+, 91% (d) 62% HBr, reflux, 4 h, 40% (e) ethylene glycol, PhH, 100% (f) Na/NH_3, EtOH, Et_2O, 99% (g) 25% HCl, 2 h, 80% (h) actetone, *p*-TsOH, reflux, 69%

The α,α'-annelation of the pyrrolidinenamine of **16** with ethyl α-bromomethylacrylate gave the bicyclo[3.3.1]nonane-3-carboxylates **17a,b** as a mixture of isomers in a ratio of ~40/60. π-Route cyclization of crude **17a,b** in refluxing 62% HBr (5h) proceeded cleanly to **7**, which was then easily purified by sublimation (130 °C, 0.6 mmHg). Following ketalization and removal of bromine, **19** was deprotected in 25% HCl to give **1** in 80% yield. Since **1** shows modest solubility in water, the recovery of additional product required continuous extraction with CH_2Cl_2. We therefore carried out the deprotection in acetone and to our surprise found that the *mono*-ketal **2** was a substantial component of the reaction mixture. Monitoring the course of the reaction by ^1H NMR allowed **2** to be obtained in yields of 69% after chromatography (SiO_2, 3:2 hexanes/EtOAc). Our modified seven-step synthesis provides multigram quantities of **1** and proceeds in an over all yield of 21%. The novel *mono*-ketal **2** is available in an overall yield of 18%.

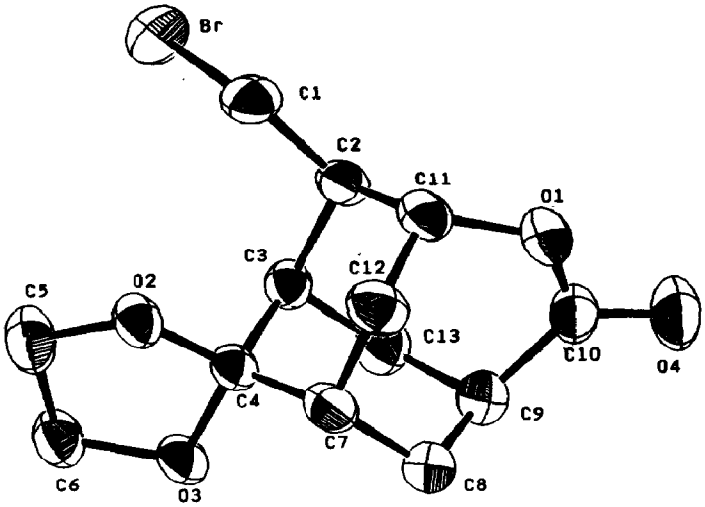


Figure 1. ORTEP represenation of **9**

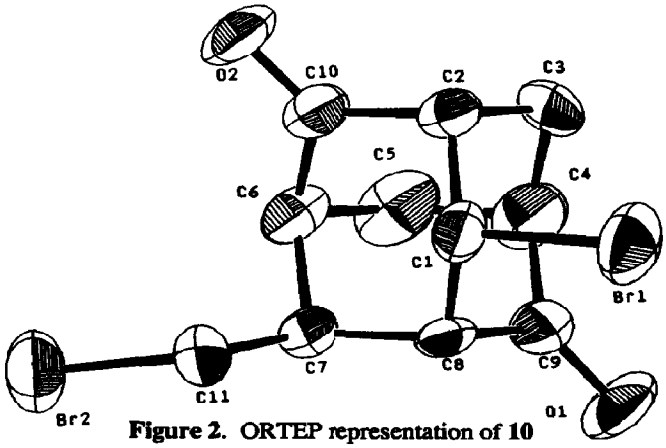


Figure 2. ORTEP representation of **10**

References and Notes

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1. a) Chapman, O. L., to Mobil Oil Corp., U.S. Pat **5,053,434**, 1991. b) Shen, D., Ph.D. dissertation, University of California, Los Angeles, 1990. c) Kaganove, S. N., Ph.D. dissertation, Unversity of California, Los Angeles, 1993.
2. a) Geluk, H. W. *Synthesis* **1972**, 374. b) Barton, D. H. R.; Boivin, J.; Gastiger, M.; Morzycki, J. Hay-Motherwell, R. S.; Motherwell, W. B.; Ozbalik, N.; Schwartzentruber, K. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 947. c) Geluk, H. W.; Schlatmann, J. L. M. A. *Recueil* **1971**, *90*, 516. d) Janku, J.; Landa, S. *Coll. Czech. Chem. Commun.* **1970**, *35*, 375. e) Prelog, V.; Seiwerth, R. *Chem. Ber.* **1941**, *74*, 1644. f) Webster, O. W.; Sommer, L. H. *J. Org. Chem.* **1964**, 29, 3103. g) Stetter, H.; Thomas, H. G.; Meyer, K. *Chem. Ber.* **1970**, *103*, 863. h) Stetter, H.; Dorsch, U. P. *Liebigs Ann. Chem.* **1976**, 1406.
3. a) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924. b) Maier, L; Crutchfield, M. M. *Phosphorus and Sulfur* **1978**, *5*, 45.
4. Faulkner, D. and McKervey, M. A. *J. Chem. Soc. (C)*, **1971**, 3906.
5. Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661.
6. a) Bach, F. L.; Cohen, E.; Kohlbrenner, P. J. **U.S. 3,517,069.**
7. Tomioka, H; Oshima, K; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539.

(*Received in USA* 20 *July* 1994; *accepted* 2 *August* 1994)