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A FORMAL SYNTHESIS OF MODHEPHENE

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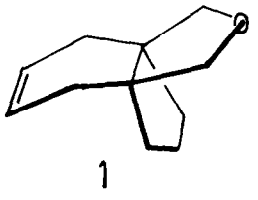
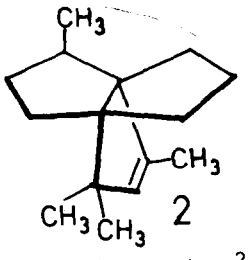
ABSTRACT: A stereo- and regiospecific synthesis of a propellane intermediate that has been previously converted to modhephene is reported.

As part of our research in developing new approaches to propellanes of the type 1[1], we were intrigued by the possibility of a simple entry into modhephene,(2).

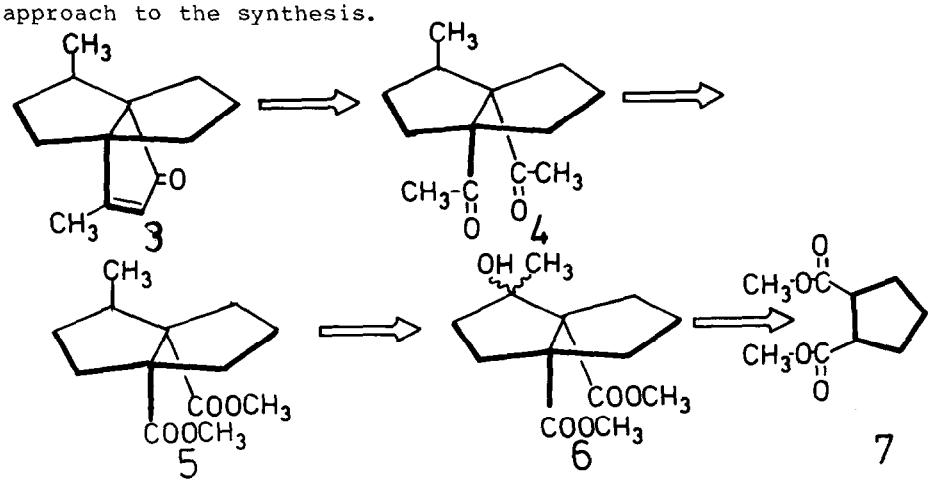


1



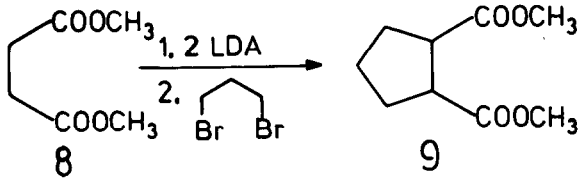
2

Our immediate target was 3, previously shown by Smith[2] to be the key intermediate in his synthesis of 2. Retrosynthetic analysis of 3 summarizes our initial approach to the synthesis.



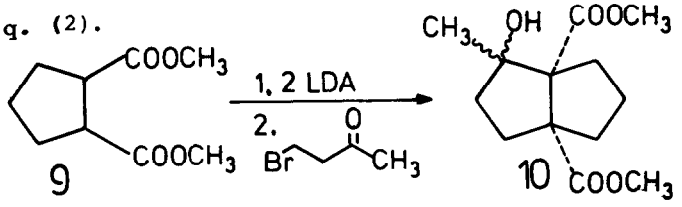
Of key interest in this design was the unambiguous stereochemistry of the ring A methyl group. We did not expect, a priori, that the crotonization of **4** would give only 3; however, this concern became a moot point in that another path from 5 to 3 was employed. We herein report our novel and selective synthesis of the Smith intermediate,(**3**).

The cyclopentane diester, (**9**), was readily prepared by a dianion alkylation of dimethylsuccinate[3] (**Eq. 1**).



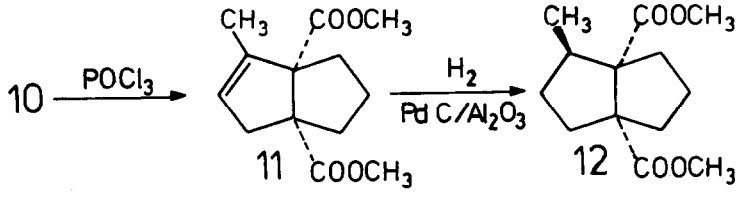
(51%)[8] **(Eq.1)**

Preparation of the dienolate of **9**, followed by addition of 4-bromo-2-butanone (from methylvinyl ketone and HBr), gave the isomeric alcohol mixture,(**10**), as shown in **Eq. (2)**.

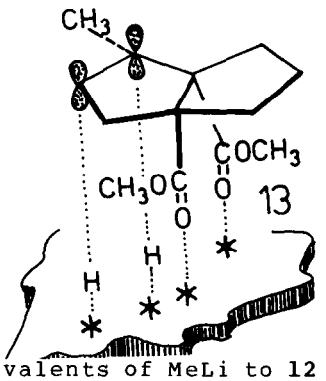


(28%) **(Eq 2)**

Dehydration of **10** with $POCl_3$ gave **11**. This alkene was stereospecifically hydrogenated to **12**. Based on recent reports of hydroxyl group direction of hydrogen delivery[4], as well as unpublished work from our own laboratory[5], we anticipated the reduction of **11** to **12** via **13**. It was predicted that the heteroatom interaction with the catalyst surface would direct the hydrogen delivery cis to the ester functionality, and result in the desired product. **(Eq. 3)**.

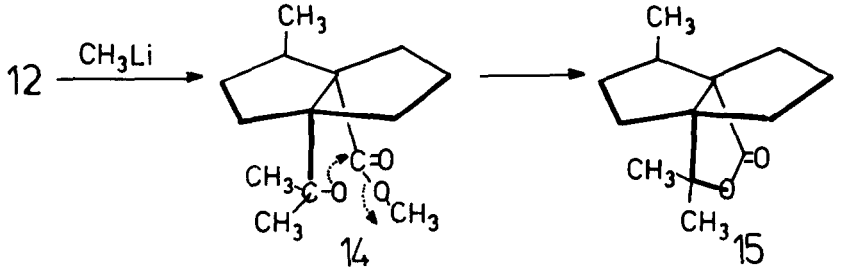


(57%) **(Eq.3)**



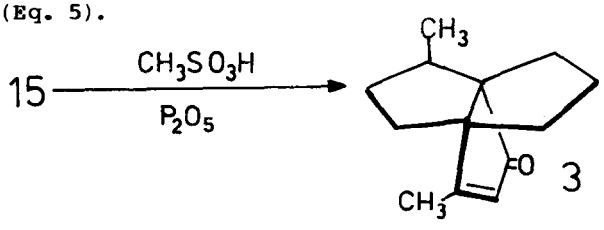
Pd on Alumina

Addition of two equivalents of MeLi to **12** gave **15**, presumably via **14.** To our delight, the regioisomer purity for **15** was greater than 95%. The unambiguous assignment of the lactone structure was confirmed by its conversion to **3.** We suggest that this regiospecificity arises from conformational and steric biases imposed on the system by the C-2 methyl group, and that this bias directs the methyl nucleophile to the C-5 carbomethoxy group. We are currently attempting to determine some precise structural information on an intermediate similar to **12.**



(80%) **(Eq. 4)**

There is literature precedent for conversion of dimethyl lactones to methylcyclopentanones[6]; thus, treatment of **15** with $MeSO_3H$ and P_2O_5 gave the desired **3.** The constitution of the product was unambiguously confirmed by comparison with an authentic sample provided by Prof. A.B. Smith, III. This novel approach to **3** provides regio- and stereospecific entry into the modhephene skeleton[7], **(Eq. 5).**



(30%) **(Eq. 5)**

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2.a. A.B. Smith,III and P.J. Jerris, **J. Org. Chem.**, (1982),**47**, 1845.

b. For other syntheses of modhephene, see for example:

(1) J. Wrobel, K. Takahashi, V. Honkan, G. Lannoye, J.M. Cook and S.H. Bertz, **J. Org. Chem.**,(1983), **48**, 139.
(2) P.A. Wender and G.B. Dreyer, **J. Am. Chem. Soc.**,(1982),**104**, 5805.
(3) M. Karpf and A.S. Dreiding, **Tetrahedron Letters**,(1980), 4569.
(4) H. Schostorez and L.A. Paquette, **J. Am. Chem. Soc.**,(1981),**103**, 722.
(5) W. Oppolzer and F. Marazza,**Helv. Chim. Acta**,(1981),**64**, 1575.
(6) W. Oppolzer and K. Battig, **ibid**,(1981),**64**, 2489.

3. a. D. Wilkening and B. P. Mundy, **Synthetic Communications**, (1984) **13**, 227. This work describes a general cyclopentane, cyclopentene and cyclopentanone annulation methodology.

b. There are other similar reports of a dianion methodology for preparing ring systems. For example, see: K.G. Bilyard, P.J. Garratt, R. Hunter and E. Lete, **J. Org. Chem.**,(1982),**47**, 4731.

4.a. G. Stork and D.E. Kahne, **J. Am. Chem. Soc.**, (1983), **105**, 1072.

b. R.H. Crabtree and M.W. Davis, **Organometallics**, (1983), **2**, 681.

5. a. B.P. Mundy and S. Glancy, Unpublished observations on the influence of remote heteroatoms on the kinetics of alkene reduction.

b. B.P. Mundy and J.J. Theodore, **J. Am. Chem. Soc.**, (1980),**102**, 2005.

6. P.E. Eaton, G.R. Carlson and J.T. Lee, **J. Org. Chem.**,(1973),**38**, 4071.

7. All new compounds prepared in this synthesis have been fully characterized by H-NMR, C-NMR, and MS (including HRMS). The comparison of our 3 with that of Prof. A.B. Smith,III also included capillary GLC retention times.

8. All reported yields are for purified compounds.

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