

PENTACYCLIC TRITERPENE SYNTHESIS. II. PREPARATION OF AN AB SYNTHON<sup>1</sup>

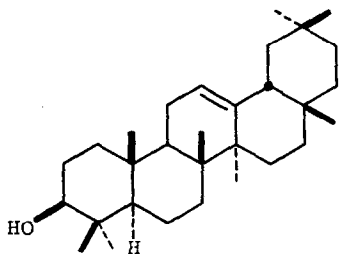
John S. Dutcher, James G. Macmillan, and Clayton H. Heathcock\*

Department of Chemistry, University of California

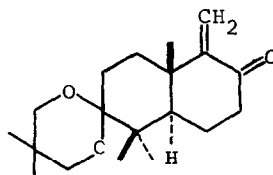
Berkeley, California 94720

(Received in USA 16 January 1974; received in UK for publication 5 February 1974)

As part of our program to devise a convergent synthesis of pentacyclic triterpenes, e.g.,  $\beta$ -amyrin (1),<sup>1</sup> we have developed an efficient route to the racemic bicyclic enone 2. Compound 2 is a ring AB synthon which may be useful in the synthesis of pentacyclic triterpenes of the oleanane, ursane, or lupane families.



1



2

The enedione 3<sup>2</sup> is reduced by NaBH<sub>4</sub> in ethanol to obtain the hydroxyenone 4 (m.p. 88-89°)<sup>3,4</sup> in 73% yield. Compound 4 is treated with 3.0 equivalents of lithium in a mixture of THF and liquid ammonia for 30 minutes, then with 10 equivalents of CH<sub>3</sub>I for 30 minutes to give a product containing 85-90% hydroxyketone 5 (m.p. 54.5-60°; lit., liquid<sup>5</sup>) in quantitative yield.<sup>6</sup> Compound 5 is ketalized by treatment with 2,2-dimethyl-1,3-propanediol and  $\beta$ -naphthalenesulfonic acid ( $\beta$ -NpSO<sub>3</sub>H) in benzene to yield hydroxy ketal 6 (m.p. 148.5-149°), which is oxidized by bispyridinechromium(VI)oxide<sup>8</sup> in CH<sub>2</sub>Cl<sub>2</sub> to give the dione monoketal 7 (m.p. 135-138°) in an overall yield of 56% from compound 4.

Ketone 7 reacts with methyllithium in ether at  $-78^{\circ}$  to give in quantitative yield a mixture of the stereoisomeric alcohols 8a (m.p.  $106-111^{\circ}$ ) and 8b (m.p.  $92-98^{\circ}$ ) in a ratio of 3:2. Alcohol mixture 8 is dehydrated and deketalized by stirring a 0.3 M solution in pentane over 25% aqueous  $H_2SO_4$  at  $25^{\circ}$  for 7 hrs. The dehydration product is reketalized with 2,2-dimethyl-1,3-propanediol and  $\beta$ -NpSO<sub>3</sub>H to afford a product from which unsaturated ketal 9 (m.p.  $112-113^{\circ}$ ) is crystallized in 60% yield.<sup>9</sup>

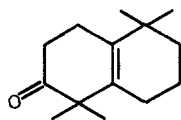
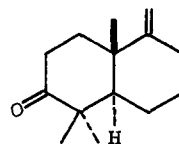
Alkene 9 reacts with m-chloroperoxybenzoic acid in  $CHCl_3$  to afford an equimolar mixture of stereoisomeric epoxides 10a (m.p.  $145.4-146.5^{\circ}$ ) and 10b (m.p.  $123.5-126^{\circ}$ ) in quantitative yield. Isomer 10a reacts with lithium di-n-propylamide in THF-hexane<sup>10</sup> to give allylic alcohol 11a (m.p.  $103.5-105^{\circ}$ ) in 89% yield. Similar treatment of epoxide 10b affords a 3:2 mixture of the stereoisomeric allylic alcohol 11b (m.p.  $128-129^{\circ}$ ) and allylic alcohol 12 (m.p.  $96-102^{\circ}$ ) in 94% yield. Oxidation of 11a or 11b by bispyridinechromium-(VI) oxide in  $CH_2Cl_2$ <sup>8</sup> gives enone 2 (m.p.  $124-126^{\circ}$ ). Alternatively, the conversion of 9 into 2 may be accomplished without separating the stereoisomeric epoxides 10 or allylic alcohols 11. The overall yield for such a three-stage conversion is 78-83%. The final product is a 70:30 mixture of enones 2 and 13 (m.p.  $189-189.5^{\circ}$ ), which is separated by column chromatography. The complete synthetic scheme is outlined in the chart.

Acknowledgement: We gratefully acknowledge financial support by the National Science Foundation.



## REFERENCES

1. For part I see C.H. Heathcock and J.E. Ellis, Chem. Comm., 1474 (1971).
2. Y. Kitahara, A. Yoshikoshi, and S. Oida, Tetrahedron Letters, 1763 (1964); we prepare compound 3 in 70-75% overall yield by a modification of the procedure of S. Ramachandran and M.J. Newman, Org. Syn., 41, 38 (1962).
3. With the exception of structure 1, all structures refer to racemic substances, although only one enantiomer is depicted. In the following communication, we report the resolution of compound 4.
4. All new compounds have been completely characterized by ir and nmr spectroscopy, and by accurate combustion analyses or by high resolution mass spectrometry.
5. F. Sondheimer and D. Elad, J. Amer. Chem. Soc., 80, 1967 (1958).
6. The reductive methylation step<sup>7</sup> also yields about 7% of polyalkylated material and variable amounts of reduced, unalkylated 4.
7. G. Stork, P. Rosen, N. Goldman, R.V. Coombs, J. Tsuji, J. Amer. Chem. Soc., 87, 275 (1965).
8. a. J.C. Collins, W.W. Hess, F.J. Frank, Tet. Lett., 3363 (1968).  
b. R. Ratcliffe, R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
9. The dehydration also affords the rearranged enone i, and the exocyclic isomer ii, each in about 5% yield. The amount of i produced in the reaction is dependent on the concentration of acid used in the heterogeneous medium, rising to 8% with 30% H<sub>2</sub>SO<sub>4</sub> and 60% with 50% H<sub>2</sub>SO<sub>4</sub>. At the higher acid concentrations, isomer ii is not observed.

iii

10. C.L. Kissel and B. Rickborn, J. Org. Chem., 37, 2060 (1972).