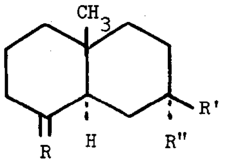
Tetrahedron Letters No.6, pp. 501-503, 1971. Pergamon Press. Printed in Great Britain.

# A STEREOSELECTIVE NONANNELATION SYNTHESIS OF EUDALENE SESQUITERPENES.

J. W. Huffman & M. L. Mole
Department of Chemistry and Geology
Clemson University
Clemson, South Carolina 29631

(Received in USA 24 November 1970; received in UK for publication 5 January 1971)

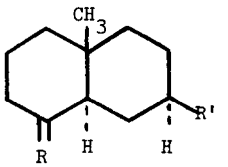
Although a number of syntheses of eudalene type sesquiterpenes have been described[1-5] every approach reported to date has utilized the Robinson annelation sequence to construct the bicyclic skeleton common to this group of natural products. We report at this time the first fruitful synthetic approach to these sesquiterpenes which does not utilize the annelation reaction* and which results in a short, efficient and highly stereoselective synthesis of trans-8-methylene-10-methyl decalin-2β-carboxylic acid (**1**)[2,3]. Since this acid has been converted to β-eudesmol[2,3] (**2**), which has in turn been converted to cryptomeridiol[6] (**3**) and neointermedeol[7](**4**) this work constitutes formal total syntheses of



**1** R = $CH_2$, R' = $CO_2H$, R" = H

**8** R = O, R', R" = $CO_2H$, H

**9** R = $CH_2$, R' = H, R" = $CO_2H$



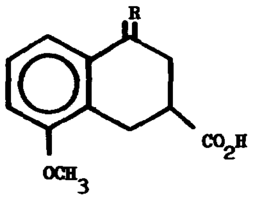
**2** R' = $CH_2$, R' = $CH(CH_3)_2OH$

**3** R = αOH, β$CH_3$, R' = $CH(CH_3)_2OH$

**4** R = βOH, α$CH_3$, R' = $CH_2$ = CH $CH_3$

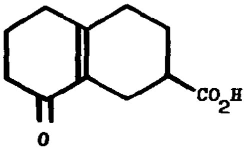
---

*The stereochemical problems and general perversity inherent in the Robinson annelation become apparent if one considers the multi-step sequences utilized, and generally mediocre yields obtained in, the synthesis of a relatively simple compound such as β-eudesmol (refs. 1, 2 and 3).



5 R = O

6 R = $H_2$



7

these sesquiterpenes.

Clemmensen reduction of 5-methoxy-1-tetralone-3-carboxylic acid[8] (5) affords 8-methoxytetralin-2-carboxylic acid (6, 57%, mp 141-143°)[9] which on Birch reduction[10] followed by treatment with acid gave a mixture of four compounds from which the desired unsaturated keto acid (7, 49%, mp 145-146°)[9] could be obtained by chromatography on silica gel. The angular methyl group was introduced by means of lithium dimethyl cuprate[11] to give a mixture of approximately equal amounts of three isomers of 10-methyl-1-decalone-7-carboxylic acid (8, no stereochemistry implied) in nearly theoretical yield. From this mixture one isomer, mp 152-154° could be obtained in a pure state.*

Since it has been shown that the Wittig reaction of both *cis* and *trans*-1-decalones leads predominantly to products having a *trans* ring fusion[3,12], reaction of the mixture of isomeric keto acids (8) with methylenetriphenylphosphorane was carried out, and there was obtained a mixture of three acids in a ratio of 1:3:6. Direct crystallization gave *trans*-8-methylene-10-methyldecalin-2α-carboxylic acid (9, mp 123-125°)[9], while esterification, equilibration with methanolic sodium methoxide and hydrolysis gave the desired 2β-acid (1, 75% from 8), identical in all respects to a sample prepared by the method of Marshall[3,13].

## REFERENCES

1. D. C. Humber, A. R. Pinder and R. A. Williams, *J. Org. Chem.* 32, 2335 (1967).

---

* This compound is almost certainly one of the two isomers with a *cis* ring fusion, but is probably not the same *cis*-acid reported by Heathcock (ref. 2).

2. C. H. Heathcock and T. R. Kelly, Tetrahedron, 24, 1801 (1968).

3. J. A. Marshall, M. T. Pike and R. D. Carroll, J. Org. Chem. 31, 2933 (1966).

4. J. A. Marshall and M. T. Pike, J. Org. Chem., 33, 435 (1968).

5. J. M. Mellor and S. Munavalli, Quart. Rev. (London) 18, 270 (1964) describe earlier synthetic approaches to these compounds.

6. M. Sumimoto, H. Ito, H. Hirai and K. Wada, Chem. Ind. (London) 780 (1963).

7. V. B. Zalkow, A. M. Shaligran and L. H. Zalkow, Chem. Ind. (London), 194 (1964).

8. A. Sieglitz and C. Jordanides, Ann. Chem. 702, 94 (1967).

9. Satisfactory analytical data were obtained for all new compounds, and all compounds were characterized by infrared and nmr spectroscopy and thin layer and/or gas chromatography.

10. H. L. Dryden, Jr., O. M. Webber, R. R. Burtner and J. A. Cella, J. Org. Chem., 26, 3237 (1961).

11. H. O. House, W. L. Respess and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966).

12. M. D. Soffer and L. A. Burke, Tetrahedron Lett., 211 (1970).

13. We would like to thank Prof. J. A. Marshall, Northwestern University, for a sample of this compound.