Tetrahedron Letters No. 49, pp 4967 - 4970, 1973. Pergamon Press. Printed in Great Britain.

SYNTHETIC STUDIES ON SPIROVETIVANES. II. STEREOSPECIFIC TOTAL SYNTHESIS OF dl-HINESOL,[1] dl-α-VETISPIRENE, AND dl-β-VETISPIRENE (dl-β-ISOVETIVENENE).

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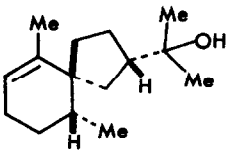
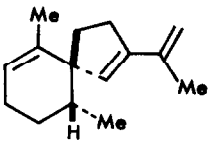
(Received in Japan 26 September 1973; received in UK for publication 29 October 1973)

In the previous communication,[2] we reported the facile method of constructing the spiro[4.5]decane system by acid-catalyzed spirocondensation of a 4-(3'-formylpropyl)-3-cyclohexenone derivative and its application to the stereospecific synthesis of dl-β-vetivone, one of the representative spirovetivanes.[3]

We report here the stereospecific synthesis of three spirovetivanes, hinesol 1,[4] α-vetispirene 2,[5] and β-vetispirene 3[5,6] (β-isovetivenene[7]), in racemic form, using the intermediates prepared in the synthesis[2] of β-vetivone.



1



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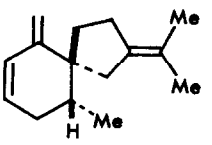


3

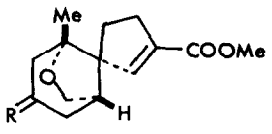
dl-Hinesol 1 ——— The saturated ester 6,[2] obtained by catalytic hydrogenation of the conjugated ester 4[2] was selected as the starting compound. In view of the steric course of catalytic hydrogenation, stereochemistry of the asymmetric center alpha to the ester group was assigned as depicted in 6, which was unambiguously confirmed by the chemical means.[8] Deketalization of 6 (aqueous oxlic acid - DME, 25°) afforded the ketone 12,[9,10] which was converted [$(PhO)_3PMe \cdot I$ - $BF_3 \cdot OEt_2$ in MeCN, 25°, 5 hr] to the conjugated ketone 13.[10]

The iodomethyl group of 13 was reduced (Zn - AcOH, 25°, 1 hr) affording 14,[10] which was converted to the thioketal 15,[9,10] mp 84.5 - 85.5° (~70% from 6). The ester 16,[10] obtained on desulfurization of 15 [Raney Ni (W-2), EtOH, reflux, 4 hr] was treated with methyl lithium (DME, 40°, 2 hr) affording a liquid (~70%), which was purified by preparative glpc (5% SE-30 on Chromosorb W, 160°) to give dl-hinesol 1,[9,10] identical with natural hinesol[11] by spectral (ir, 100 MHz nmr, mass spectrum) and chromatographic comparison. This was further converted to dl-hinesol acetate (identical with natural material by spectral and chromatographic comparison).

dl-α-Vetispirene 2 ———— The conjugated ester 4[2] was treated with acid (2N HCl - DME, 25°, 3 hr) affording the ketone 5,[9,10,12] mp 116 - 118°, (85%), which was converted [$(PhO)_3PMe \cdot I$ - $BF_3 \cdot OEt_2$ - MeCN, 25°, 15 hr] to the iodomethyl derivative 19,[13] [νmax($CHCl_3$) 1710, 1660 cm^{-1}]. Reduction of 19 (Zn - AcOH, 25°, 1 hr) gave the ketone 20,[13] which was transformed into the thioketal 21,[9,10] mp 93 - 94° (74% from 5). Desulfurization of 21 [Raney Ni (W-2), EtOH, reflux, 5 hr] afforded the diene ester 22,[9,10] [65% after preparative glpc purification (5% SE-30 on Celite 545, 160°)], which was subsequently treated with methyl lithium (DME, 40°, 40 min) giving the rather unstable alcohol 23.[10] Dehydration of 23 (camphorsulfonic acid - benzene, 50°, 16 hr) afforded a liquid, which was purified by preparative tlc[14a] to give dl-α-vetispirene 2,[9,10] (85% from 22), identical with natural α-vetispirene[15] by spectral (ir, uv, 100 MHz nmr, mass spectrum) and chromatographic comparison.

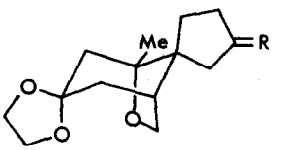
dl-β-Vetispirene (dl-β-Isovetivenene) 3 ———— Starting from the conjugated ketone 14, the conjugated diene system present in β-vetispirene was constructed by two ways. First, the conjugated ketone 14 was reduced ($NaBH_4$ - MeOH, 0°, 40 min) giving the allyl alcohol 17,[10] which was dehydrated (camphorsulfonic acid - benzene, 25°, 15 hr)[16] to afford the conjugated diene 24,[9,17] (68% from 14 after preparative tlc purification[14b]). In the second route, acetylation of 14 (Ac_2O - $BF_3 \cdot OEt_2$ - DME, 25°, 3 hr) produced the enol acetate 26,[18] (68% based on reacted 14,[19] after preparative tlc purification[14b]), which was reduced[20] [$Fe(CO)_5$ - Bu_2O, 146°, 6 hr] affording the conjugated diene 24 (40% after preparative tlc purification[14b]). On treatment of 24 with methyl lithium (DME, 40°, 1 hr) the alcohol 25[10] was obtained. Subsequent dehydration of 25 ($POCl_3$ - pyridine, 25°, 3 hr) gave a liquid, which was purified by preparative glpc (5% SE-30 on Celite 545, 150°) affording

dl-β-vetispirene 3,[9,10] (~60% from 24), spectroscopically (ir, uv, 100 MHz nmr, mass spectrum) and chromatographically identical with natural β-vetispirene.[15]



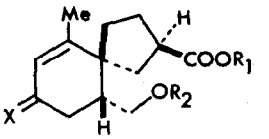
4, R = 

5, R = O



6, R = 

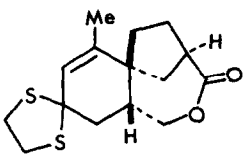
7, R = 



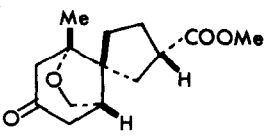
8, X = O; R_1 = Me; R_2 = Ac

9, X = ; R_1 = Me; R_2 = Ac

10, X = ; R_1 = R_2 = H



11



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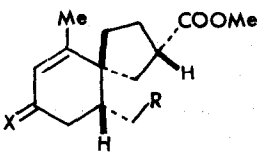


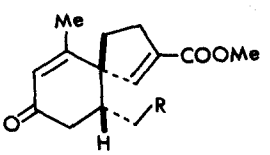
13, X = O; R = I

14, X = O; R = H

15, X = ; R = H

16, X = H_2; R = H

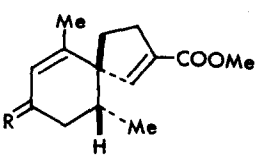
17, X = ; R = H



18, R = OH

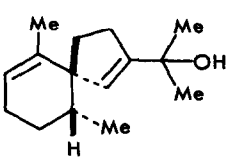
19, R = I

20, R = H

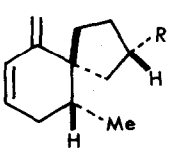


21, R =

22, R = H_2

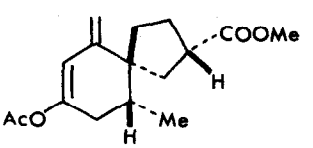


23



24, R = COOMe

25, R = $C(OH)Me_2$



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REFERENCES AND FOOTNOTES

1. Taken in part from the M. S. Thesis presented to Nagoya University, January 1973 by H. N.
2. K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, Tetrahedron Lett., in the press.
3. Spirovetivane, a name suggested for the skeleton related to β-vetivone: J. A. Marshall and S. F. Brady, Tetrahedron Lett., 1387 (1969).
4. J. A. Marshall and S. F. Brady, J. Org. Chem., 35, 4068 (1970), for the structure and the total synthesis.
5. N. H. Andersen, M. S. Falcone, and D. D. Syrdal, Tetrahedron Lett., 1759 (1970).
6. P. M. McCurry, Jr. and R. K. Singh, Tetrahedron Lett., 3325 (1973).
7. M. Romaňuk and V. Herout, Coll. Czechoslov. Chem. Commun., 25, 2540 (1960): this sesquiterpene was first isolated by Romaňuk and Herout, who designated as β-isovetivenene, and later the structure was deduced by the Andersen's group and designated as β-vetispirene.[5]
8. The following sequence of reactions were employed for the proof of stereochemistry on the asymmetric center formed by catalytic hydrogenation: (1) epimerization of 6 to 7 (NaOMe - MeOH, reflux); (2) deketalization (aqueous oxalic acid - DME, 25°); (3) formation of 8 (Ac_2O - $BF_3 \cdot OEt_2$ - DME, 25°, 3 hr); (4) thioketalization to give 9;[9,10] (5) hydrolysis (KOH - MeOH, 25°) affording 10; and (6) dehydration (DCC - pyridine, 25°, 14 hr) leading to 11,[9,10] [νmax($CHCl_3$) 1730 cm^{-1}]. The same sequence of reactions [(2) through (6)] were applied to pure 6, and no lactone was formed.
9. The composition of the new compounds was confirmed by elemental analysis or by high resolution mass spectroscopy.
10. Structure assignments are based on ir, nmr and mass spectral evidence.
11. We thank Professors F. Sǒrm and J. A. Marshall for (-)-hinesol, and Professor I. Yosioka for the ir and nmr spectra of (-)-hinesol.
12. In the deketalization, the alcohol 18[10] (oil) was obtained as the minor product (~10%), which could be used for the preparation of 19 under the conditions of converting 5 to 19.
13. Since this compound formed an inseparable mixture, the product was used without further purification in the next step.
14. Performed on silica gel with: (a) 1:1 $CHCl_3$ - hexane; (b) 4:1 $CHCl_3$ - EtOAc.
15. Natural α- and β-vetispirenes were isolated in our laboratory from vetiver oil, kindly provided from Professor A. Yoshikoshi.
16. We thank Professor P. Deslongchamps for informing us of his results of the dehydration experiments on the similar system.
17. νmax($CHCl_3$) 1727, 1635, 1600, 892 cm^{-1}; λmax(MeOH) 232 nm (ε 13,800); δ($CDCl_3$, 60 MHz) 0.85 (3H, d, J = 6.5 Hz), 3.74 (3H, s), 4.97 (1H, br.s), 5.05 (1H, br.s), 5.69 (1H, m), 6.09 (1H, dd, J = 9.0, 3.0 Hz); m/e 220 (M^+).
18. νmax($CHCl_3$) 1745(sh.), 1732, 1658, 1612, 899 cm^{-1}; δ($CDCl_3$, 60 MHz) 0.91 (3H, d, J = 6.5 Hz), 2.13 (3H, s), 3.71 (3H, s), 4.98 (1H, br.s), 5.04 (1H, br.s), 5.83 (1H, d, J = 2.0 Hz); m/e 278 (M^+).
19. The starting compound 14 was recovered (~35%) under these conditions. Although 14 reacted entirely under forcing conditions, the yield of 26 was remarkably lowered owing to decomposition of 26.
20. S. J. Nelson, G. Detre, and M. Tanabe, Tetrahedron Lett., 447 (1973).