Tetrahedron Letters No. 49, pp 4963 - 4966, 1973. Pergamon Press. Printed in Great Britain.

SYNTHETIC STUDIES ON SPIROVETIVANES. I. SPIROCONDENSATION OF A 4-(3'-FORMYLPROPYL)-3-CYCLOHEXENONE AND STEREOSPECIFIC TOTAL SYNTHESIS OF dl-β-VETIVONE.[1]

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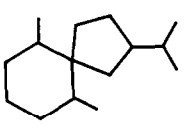
The structural feature of spirovetivanes,[2] a group of sesquiterpenes is that they are the spiro[4.5]decane derivatives 1. We have been interested in constructing the spiro[4.5]decane system generally suited for the synthesis of these sesquiterpenes.

We are reporting here a facile method of preparing the properly functionalized spiro[4.5]decane system by acid-catalyzed condensation of a 4-(3'-formylpropyl)-3-cyclohexenone derivative 7, and the stereospecific synthesis of β-vetivone 28,[3] in racemic form, using this type of condensation as a crucial step (8 → 14). The acid 2[4] was converted to the aldehyde 3,[5] (~60%) by reduction ($LiAlH_4$ - ether, 25°) and the subsequent oxidation (DMSO - DCC - H_3PO_4, 25°). Acetalization of 3 gave the acetal 4,[5,6] bp 160 - 161° (2 mm), (95%), and the reduction of 4 (Li in liquid NH_3 - t-BuOH - THF, -33°) followed by hydrolysis (aqueous oxalic acid) afforded the cyclohexenone 7,[5,6] (~90%). Two modes of condensation of 7 were found to take place under the acidic conditions. While the cyclohexenone 7 afforded mainly a diastereomeric mixture (ratio, ca. 4:1, estimated by nmr spectrum) of the conjugated ketone 9,[5,6] (77% after preparative tlc purification on silica gel with EtOAc), together with the saturated ketone 11,[6,7] mp 105° (15%) under rather mild conditions [6N HCl - DME (1:2), 50°, 1 hr], the saturated ketone 11 was formed as the sole product in the condensation of 7 under forcing conditions [6N HCl - DME (1:2), reflux, 2 hr]. The spiro structure 9 of the conjugated ketone was established by the ir spectrum [νmax($CHCl_3$) 1740 cm^{-1} (five-membered ring ketone)] of the ketone 10,[6,8] obtained by oxidation of 9 (CrO_3 - pyridine), excluding the alternative possible structure 12. The structural assignment of the saturated ketone 11 based on the spectral evidence was confirmed by the stepwise synthesis of this compound.[9] Further, the spiro compound 9 was found to be transformed quantitatively into the saturated ketone 11 under forcing conditions [6N HCl - DME (1:2), reflux, 2 hr]. This finding suggests

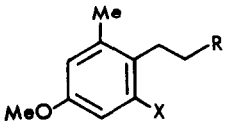
that, although the two modes of condensation of 7 occur, only the desired spiro compound 9 would be synthesized by protecting, during the condensation, the hydroxyl group of 9. For this purpose, the cyclohexenone 8 was prepared, the condensation of which was performed.

The reaction of the aldehyde 5[10] with methoxymethylene triphenylphosphorane (DMSO - DME, -20°) followed by acetalization afforded the acetal 6,[5,6] mp 120 - 122° (73%), which was converted to the desired cyclohexenone 8,[5,6] (~80%) by reduction (Li in liquid NH_3 - t-BuOH - THF, -33°) and the subsequent hydrolysis (aqueous oxalic acid). Under the acidic conditions [6N HCl - DME (1:2), reflux, 4 hr], condensation of 8 took place to give a lactone 14,[6,11,12] mp 137 - 139° (90%) as the sole product. Assignment of the stereochemistry of 14 was based on: i) the inspection of the Dreiding models by considering the fact that 14 was the more stable isomer;[12] and ii) conversion of 14 to dl-β-vetivone 28. The lactone 14 was converted to the ketone 16,[6,13] mp 108 - 110° (77%) by the sequence: (1) ketalization; (2) reduction ($LiAlH_4$ - THF, 25°, 2 hr); and (3) treatment with acid [2N HCl - DME (1:5), 25°, 1.5 hr]. Further, the ketone 16 was transformed into the ketal 17,[5,6] mp 131.5 - 132° (83%) by the following sequence;[14] (1) acetylation (Ac_2O - pyridine, 25°, 16 hr); (2) ketalization; and (3) hydrolysis (KOH - MeOH, 25°, 2 hr). Oxidation of 17 (CrO_3 - pyridine, 25°, 2 hr) afforded the ketone 19,[5,6] mp 72 - 74° [νmax($CHCl_3$) 1735 cm^{-1}], which was converted (NaH - dimethyl carbonate, 50°, 14 hr) to the β-keto ester 20,[5,6] (~90% from 17 after preparative tlc purification on silica gel with 95:5 $CHCl_3$ - MeOH). Conversion of 20 to the conjugated ester 21,[5,6] mp 135 - 136° (82%) was effected by the following sequence: (1) reduction ($NaBH_4$ - MeOH, 0°, 30 min); (2) mesylation (MsCl - pyridine, 5°, 17 hr); and (3) elimination (NaOMe - MeOH, 25°, 2 hr). Catalytic hydrogenation of 21 (PtO_2 - MeOH, 25°) afforded the saturated ester 22,[5,6,15] (98%). The ester 22 was converted to the isopropylidene ketone 25,[5,6] mp 93 - 94° in 71% overall yield by the sequence: (1) treatment with methyl lithium (DME, 40°, 1 hr) to give 23;[5] (2) dehydration ($POCl_3$ - pyridine, 25°, 2 hr) affording 24,[5,6] mp 73.5 - 75.5°; and (3) deketalization [2N HCl - DME (1:3), 25°, 2 hr]. Regeneration[16] of the double bond in the six-membered ring of 25 without migration of the labile double bond of the isopropylidene group was effected by treating 25 with triphenylphosphine dibromide (MeCN, 25°, 3 hr) to give the bromomethyl derivative 26,[5,6] mp 126 - 127° (88% based on reacted 25) with 25 recovered (~20%). The bromomethyl derivative 26 was converted (NaI - MeCOEt, 50°, 20 hr) to the iodomethyl compound 27,[5,6] mp 118 - 119° (80%), which was reduced (Zn - AcOH, 25°, 1 hr) to give dl-β-vetivone 28,[5,6] mp 48 - 49° (90%), mixture mp[17] 47.5 - 49°, spectroscopically

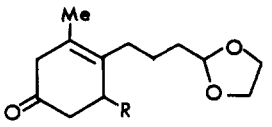
(ir, 100 MHz nmr, mass spectrum) and chromatographically identical with natural β-vetivone.[18]



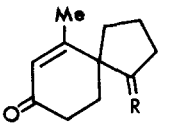
1



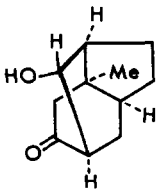
2, X = H; R = CH_2COOH
3, X = H; R = CH_2CHO
4, X = H; R = CH_2CH(O,O)
5, X = COOH; R = CHO
6, X = COOH; R = CH_2CH(O,O)



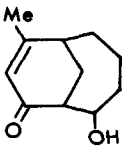
7, R = H
8, R = COOH



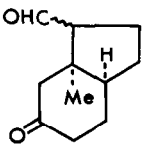
9, R = <H,OH
10, R = O



11



12



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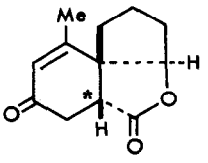
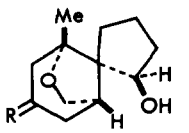
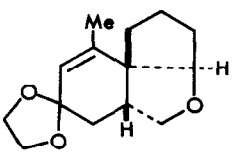


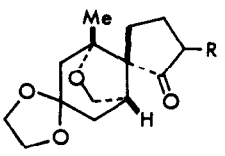
14
15, epimer at the asterisked carbon



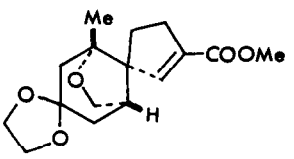
16, R = O
17, R = (O,O)



18



19, R = H
20, R = COOMe



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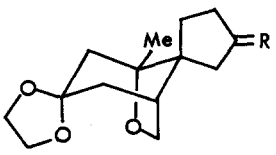
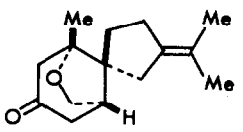


22, R = <COOMe,H
23, R = <C(OH)Me_2,H
24, R = CMe_2



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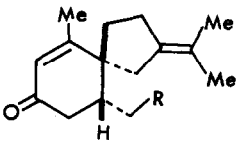

26, R = Br
27, R = I
28, R = H (β-vetivone)

REFERENCES AND FOOTNOTES

1. Taken in part from the M. S. Thesis presented to Nagoya University, January 1973 by H. N.
2. Spirovetivane, a name suggested for the skeleton related to β-vetivone: J. A. Marshall and S. F. Brady, Tetrahedron Lett., 1387 (1969).
3. (a) J. A. Marshall and P. C. Johnson, J. Org. Chem., 35, 192 (1970), for the structure and the total synthesis; (b) G. Stork, R. L. Danheiser, and B. Ganem, J. Amer. Chem. Soc., 95, 3414 (1973), for the stereospecific total synthesis; (c) P. M. McCurry, Jr. and R. K. Singh, Tetrahedron Lett., 3325 (1973), for the total synthesis.
4. W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, J. Org. Chem., 27, 2015 (1962).
5. This compound has been fully characterized by ir, nmr, and mass spectra confirmatory of the structure presented.
6. Elemental analysis or high resolution mass spectral data for this compound are in accord with theory.
7. νmax($CHCl_3$) 3450, 1720 cm^{-1}; δ($CDCl_3$, 60 MHz) 0.95 (3H, s), 2.30 (2H, br.s), 2.63 (1H, br.s, OH), 3.86 (1H, d, J = 5.0 Hz); m/e 180 (M^+).
8. νmax($CHCl_3$) 1740, 1667, 1620 cm^{-1}; δ($CDCl_3$, 60 MHz) 1.80 (3H, d, J = 1.2 Hz), 5.94 (1H, q, J = 1.2 Hz); m/e 178 (M^+).
9. (i) Conversion of 7 (NaOMe - MeOH, 25°) to the corresponding conjugated ketone; (ii) deacetalization; (iii) intramolecular Michael addition (Et_2NH - MeOH, 25°, 15 hr) to give a diastereomeric mixture of the cis-hydrindane derivative 13;[5] and (iv) intramolecular aldol condensation (NaOMe - MeOH, 25°) of 13 to afford 11.
We thank Mr. H. Nakamura for his technical assistance in some of the above sequence of reactions.
10. K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, and Y. Hirata, J. Amer. Chem. Soc., 94, 8278 (1972).
11. νmax($CHCl_3$) 1780, 1670, 1620 cm^{-1}; λmax(MeOH) 237 nm (ε 15,400); δ($CDCl_3$, 60 MHz) 2.00 (3H, d, J = 1.2 Hz), 4.87 (1H, m), 6.00 (1H, q, J = 1.2 Hz); m/e 206 (M^+).
12. The less stable lactone 15,[6] mp 107 - 109° [νmax($CHCl_3$) 1780, 1660, 1610 cm^{-1}; λmax(MeOH) 240 nm (ε 12,200); δ($CDCl_3$, 60 MHz) 2.00 (3H, d, J = 1.2 Hz), 4.87 (1H, m), 5.76 (1H, q, J = 1.2 Hz); m/e 206 (M^+)], the epimer at the asterisked carbon of 14 was formed in 5 - 15% yield, if the reaction time was short [e.g., 6N HCl - DME (1:2), reflux, 30 min]. Isomerization of 15 to 14 under forcing conditions (see text) proceeded quantitatively.
13. νmax($CHCl_3$) 3400, 1715 cm^{-1}; δ($CDCl_3$, 60 MHz) 1.15 (3H, s), 1.79 (1H, s, OH), 4.12 (1H, d, J = 8.2 Hz), 4.20 (2H, m); m/e 210 (M^+).
14. Since the direct ketalization of 16 under the standard conditions afforded the product 18,[5] the hydroxyl group of 16 was protected prior to ketalization.
15. The proof of the stereochemistry of the new asymmetric center is described in the accompanying communication: K. Yamada, K. Aoki, H. Nagase, Y. Hayakawa, and Y. Hirata, Tetrahedron Lett., in the press.
16. Other methods examined for effecting the regeneration of the double bond consisted of treatment of 25 with: (a) methanesulfonic acid anhydride ($BF_3 \cdot OEt_2$ - MeCN, 25°, 12 hr); and (b) triphenylphosphite methiodide ($BF_3 \cdot OEt_2$ - MeCN, 25°, 12 hr). Although the regeneration of the conjugated keto system was achieved in isolated yield more than 90% in each case, complete migration of the double bond of the isopropylidene group into the cyclopentane ring took place.
17. Performed with dl-β-vetivone[3b] (mp 47.5 - 49° after glpc purification) kindly provided by Professor G. Stork.
18. Natural β-vetivone was kindly provided by Professors G. Stork and J. A. Marshall. We thank Professors J. Tanaka and S. Ito, and Dr. K. Endo for the ir spectra of natural β-vetivone.