Tetrahedron Letters No. 2, pp 159 - 160.
©Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/0108-0159$02.00/0

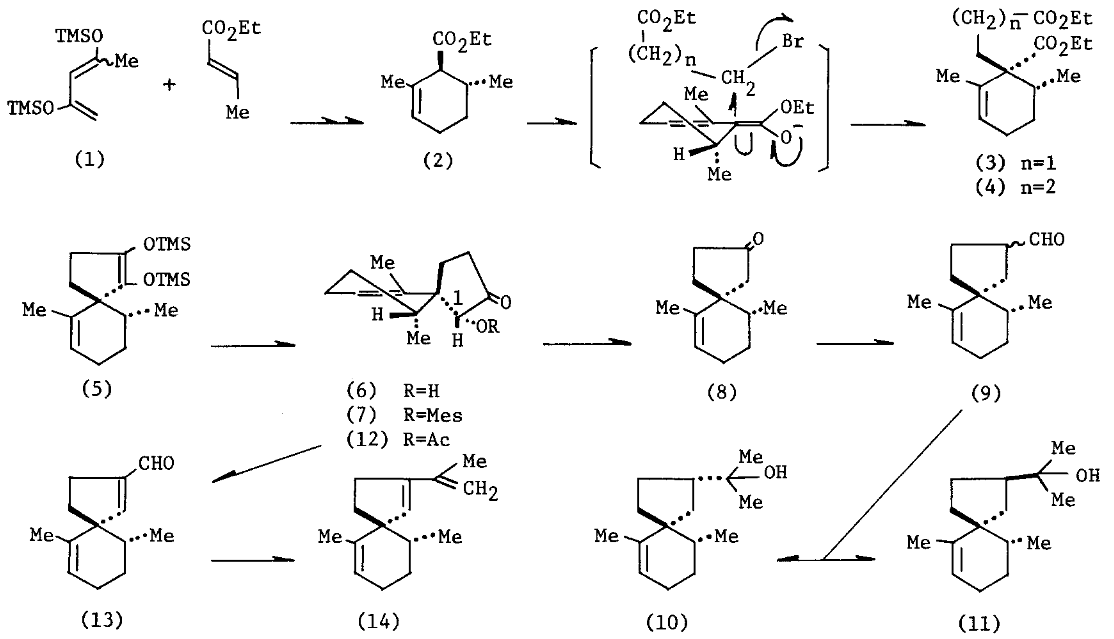
A NEW SYNTHESIS OF SPIROVETIVANES VIA THE SPIRO-ACYLION INTERMEDIATE

Toshiro Ibuka, Kenji Hayashi, Hiroyuki Minakata, and Yasuo Inubushi
Faculty of Pharmaceutical Sciences, Kyoto University
Sakyo-ku, Kyoto 606, Japan

Much attention has been directed recently towards the development of new synthesis of sesquiterpenes with a spiro[4,5]decane carbon skeleton.1) In successful synthesis of these sesquiterpenes, stereoselective construction of the spiro-cycle ring system and regioselective introduction of the double bond into the synthetic intermediate are essential factors. We have been interested in constructing stereoselectively the properly functionalized spiro[4,5]-decane system generally suited for synthesis of spirovetivanes. We now wish to report a new effective synthetic route to some spirovetivanes via spiro-acyloin key intermediate.

Treatment of the β,γ-unsaturated ester (2) (bp 98-101°/28 Torr) prepared from the cycloadduct2) of 2,4-bis(trimethylsiloxy)-1,3-pentadiene (1) with ethyl crotonate, with LDA, followed by alkylation with ethyl 3-bromopropionate or ethyl 4-bromobutyrate proceeded highly stereoselectively to give the diester (3) (bp*1 143-144°/1 Torr) or the diester (4)*2 (bp 153°/5 Torr), respectively as a single product in high yield. The approach of the reagent from the less hindered face opposite the secondary methyl group can be expected and this high stereoselectivity was ascertained finally by identification of synthetic (±)-hinesol with an authentic sample. Treatment of the diester (3) in toluene with Na in the presence of Me_3SiCl afforded the spiro-annelation product (5) (bp 123°/5 Torr, 79% yield), hydrolysis of which provided an effective key intermediate (6) (mp 115-118°, 44% yield; IR ($CHCl_3$) ν 3500, 1742; ^{1}H-NMR ($CDCl_3$) δ 4.05 (1H, s, $>$CH-OH)), and the stereostructure of 6 was confirmed by observation of NOE enhancement (20%) between C_1-H and the secondary methyl protons. Reduction of the mesylate (7) from the acyloin (6) with Zn-NH_4Cl gave tbe spiro-ketone (8) (bp*1 128°/15 Torr, 99% yield), which is a constituent of vetiver oil3) and has been recently synthesized by Büchi1f), Caine1g,h) and Piers.1i) The structure of 8 was ascertained by comparison of the IR and ^{1}H-NMR spectra with those of an authentic sample. Wittig reaction of the spiro-ketone (8) with methoxymethylenetriphenylphosphorane (59% yield), followed by hydrolysis with 10% HCl gave the aldehyde (9) (bp*1 95°/5 Torr; IR ($CHCl_3$) ν 2680, 1718; 84% yield) as an epimeric mixture. This mixture without separation at this stage was converted into (±)-hinesol (10) and (±)-agarospirol (11) (3:2 mixture) in the usual way of three steps. Separation of the mixture of hinesol and agarospirol is known to be troublesome and this was achieved by repeated preparative TLC (silica gel). Synthetic (±)-hinesol was identified with an authentic sample of natural hinesol4) by IR and ^{1}H-NMR spectral comparisons and GC.

On the other hand, synthesis of (±)-α-vetispirene (14) from the common intermediate (6) was completed by regioselective introduction of the double bond at the five membered ring. Thus, the acetate (12) (IR ($CHCl_3$) ν 1757, 1742) of the spiro-acyloin (6) was treated with methoxymethylenetriphenylphosphorane and subsequent hydrolysis with 10% HCl gave the



α,β-unsaturated aldehyde (13) (IR (CHCl$_3$) ν 1678; ^{1}H-NMR (CDCl$_3$) δ 6.62 (C$_1$-H, 1H, t, J=1.5Hz)) The aldehyde (13) was converted into (±)-α-vetispirene (14) in the usual way of four steps. The identity of the synthetic product (14) with an authentic sample was shown by comparisons of their IR and ^{1}H-NMR spectra.$^{1g)}$

Acknowledgements: The authors express their thanks to Prof. D. Caine, School of Chemistry, Georgia Institute of Technology, U. S. A. for authentic IR and NMR spectra of (8) and (14). Thanks are also due to Prof. I. Kitagawa, Osaka University, for authentic natural hinesol.

Notes and References

*1 Distilled from a Büchi Kugelrohr Distillation Apparatus.

*2 The synthesis of a variety of spirovetivanes from the diester (4) through the Dieckmann condensation product will be reported elsewhere. In this Dieckmann reaction, the yield was very low (0-3%) when NaH, NaOMe, NaOEt, MeSOCH$_2^-$, K, and Na were used as a base catalyst. However, the high yield (79%) was obtained , when used KH at -20° in THF.

1) a) J. A. Marshall, St. F. Brady and N. H. Andersen: Fortschritte der Chemie organisher Naturstoffe, 31, 283 (1974), Springer Verlag; C. H. Heathcock: The Total Synthesis of Natural Products, 2, 197 (1973), J. ApSimon, ed., John Wiley & Sons and references cited therein. b) W. G. Dauben and D. J. Hart: J. Am. Chem. Soc., 99, 7307 (1977). c) G. Stork, R. L. Danheiser and B. Ganem: ibid., 95, 3414 (1973). d) E. Wenkert, B. L. Buckwalter, A. A. Craveiro, L. Sanchez and S. S. Sathe: ibid., 100, 1267 (1978). e) K. Yamada, S. Goto, H. Nagase and A. T. Christensen: J. C. S. Chem. Commun., 554 (1977) and references cited therein. f) G. Büchi, D. Berthet, R. Decorzant, A. Grieder and H. Hauser : J. Org. Chem., 41, 3208 (1976). g) D. Caine, A. A. Boucugnani, S. T. Chao, J. B. Dawson and P. E. Ingwalson: ibid., 41, 1539 (1976). h) D. Caine, A. A. Boucugnani and W. R. Pennington: ibid., 41, 3632 (1976). i) E. Piers and C. K. Lau: Synthetic Commun., 495 (1977).

2) T. Ibuka, Y. Ito, Y. Mori, T. Aoyama and Y. Inubushi: Synthetic Commun., 131 (1977).

3) G. Büchi: Koryo, No. 120, 99 (1978).

4) I. Yoshioka and T. Kimura: Chem. Pharm. Bull., 13, 1430 (1965).

(Received in Japan 13 October 1978)