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PREPARATION OF 2-OXA-3,6-DIOXO-9-VINYL-cis-DECALIN SKELETON, A PRECURSOR OF VERNOLEPIN1)

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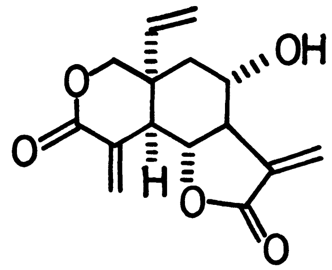
2-Oxa-3,6-dioxo-4-methoxycarbonyl-9-vinyl-cis-decalin (9), a precursor of vernolepin, was synthesized from 3-ethoxy-2-cyclohexenone (3). The condensation of the kinetic enolate of 3 with acetaldehyde and subsequent dehydration afforded 5 in good yield. Deconjugative hydroxymethylation of 5 followed by esterification with methyl malonyl chloride gave 8. Intramolecular Michael addition of 8 provided 9 in 66% yield.

As a current synthetic target, vernolepin (1), a sesquiterpenoid antitumor agent, and the related vernomenin (2) have attracted many attentions of synthetic chemists. A variety of processes for the construction of 2-oxa-3,6-dioxo-9-vinyl-cis-decalin skeleton have been reported.2) We have also investigated stereoselective functionalization of a decalin system including the intramolecular Michael addition of the malonate derivative of 4-substituted cyclohexenone (8).



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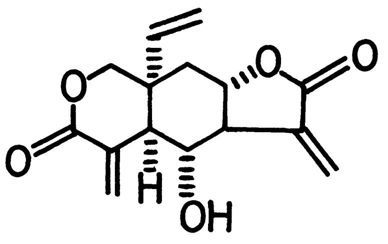

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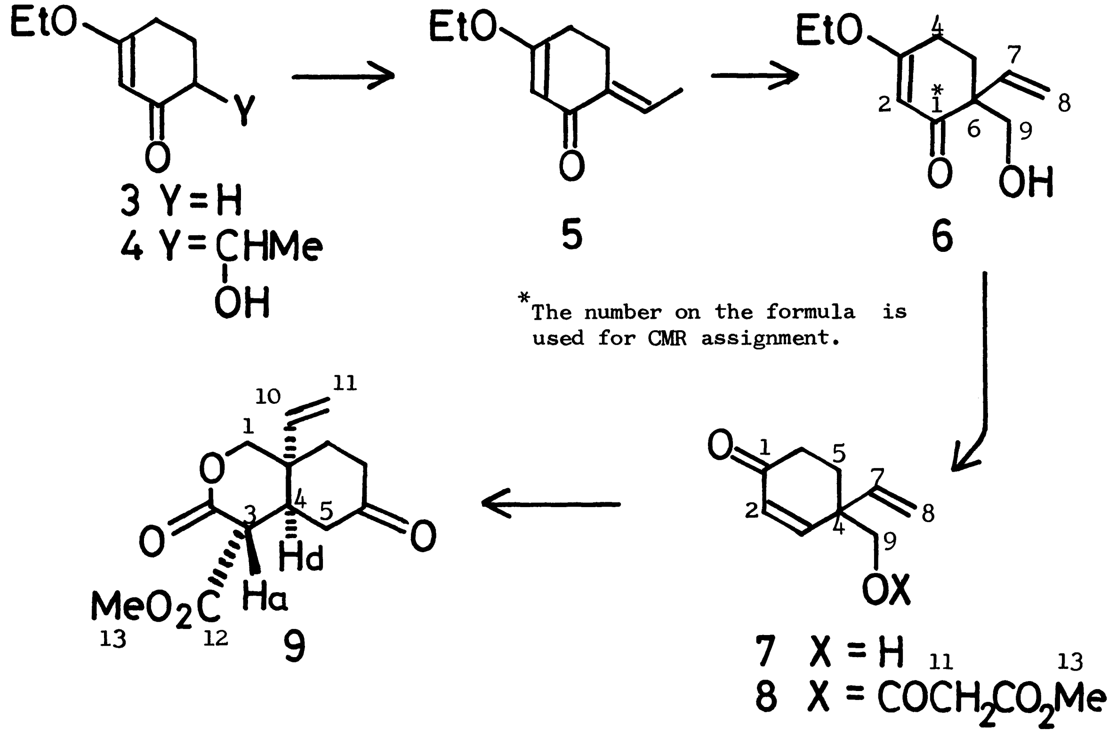
In this communication, we wish to present the preparation of 2-oxa-3,6-dioxo-4-methoxycarbonyl-9-vinyl-cis-decalin (9), a versatile precursor of vernolepin synthesis.

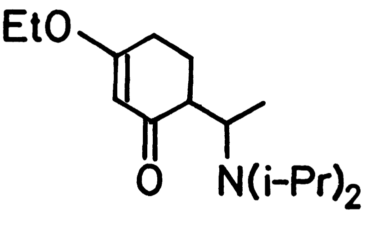
Introduction of the hydroxyethyl substituent at the C-6 position of 3-ethoxy-2-cyclohexenone (3) was achieved by kinetically controlled aldolization.3) Thus, the reaction of the kinetic enolate of 3, generated by lithium diisopropylamide (LDA) in THF at -70 °C, with acetaldehyde for several minutes gave desired aldol 4 in 92% yield,4) without the aid of chelating agent such as zinc chloride.5) The aldol 4 thus obtained was a mixture of diastereomers, which were separated into each pure isomer (4a : 4b = 4 : 1) by column chromatography (SiO_2, hexane-AcOEt).6)



*The number on the formula is used for CMR assignment.

The structure of 4 6) was confirmed by the spectral data 7): 4a, IR (neat) 3400 (OH), 1639 (C=O), 1610 cm^{-1} (C=C); PMR (60 MHz) δ 5.29 (s, 1, H-C=C), 4.04 (m, 1, HC-O), 4.02 (s, 1, OH), 3.89 (q, 2, CH_2O); 4b, PMR (60 MHz) δ 5.33 (s, 1, H-C=C), 4.24 (oct, 1, J = 7 Hz, J = 3 Hz, HC-O), 3.90 (q, 2, CH_2O).

When treated with refluxing pyridine for 12 h, the mesylate of 4 gave the dehydrated product 5 in 80% yield (based on 4). Deconjugative hydroxymethylation of 5 with gaseous formaldehyde was achieved under the condition using lithium dicyclohexylamide in THF at -70 °C for 10 min, affording the desired 6 in 40% yield 8): IR (neat) 3400 (OH), 1636 (C=O), 1626 cm^{-1} (C=C); PMR (60 MHz) δ 5.78 (d,d, 1, J = 18 Hz, J = 10 Hz, H-C=C), 5.34 (s, 1, H-C=C), 5.26 (d,d, 1, J = 10 Hz, J = 1.5 Hz, C=CH_2), 5.07 (d,d, 1, J = 18 Hz, J = 1.5 Hz, C=CH_2), 3.91 (q, 2, CH_2O), 3.86 (brs, 1, OH), 3.88-3.41 (m, 2, CH_2), 2.70-1.65 (m, 4, CH_2), 1.35 (t, 3, CH_3); CMR δ 202.2 (s, C-1), 177.9 (s, C-3), 136.7 (d, C-7), 117.4 (t, C-8), 102.3 (d, C-2), 67.9 (t, C-9), 64.5 (t, C-10), 52.4 (s, C-6), 28.0 (t, C-5), 26.0 (t, C-4), 14.1 (q, C-11). On the other



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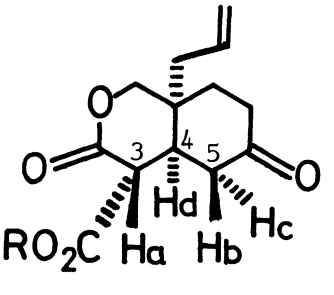
hand, the use of LDA instead of lithium dicyclohexylamide provided the Michael adduct 10 as a major product (40–50% yield) together with 15–20% yield of 6.

The conversion of the enol ether 6 to the enone 7 was performed by reduction with $NaBH_4$ and subsequent hydrolysis with hydrochloric acid in 66% yield. The characteristic functions were elucidated by spectral data: IR (neat) 3400 (OH), 1675 (C=O), 1615 cm^{-1} (C=C); PMR (60 MHz) δ 6.86 (d, 1, J = 10 Hz, H–C=C), 6.10 (d, 1, J = 10 Hz, H–C=C), 5.84 (d,d, 1, J = 18 Hz, J = 10 Hz, H–C=C), 5.28 (d,d, 1, J = 10 Hz, J = 1.5 Hz, $C{=}CH_2$), 5.04 (d,d, 1, J = 18 Hz, J = 1.5 Hz, $C{=}CH_2$), 3.58 (ABq, 2, J = 11 Hz, CH_2O), 3.16 (s, 1, OH), 2.20–1.60 (m, 4, CH_2); CMR δ 200.0 (s, C-1), 152.4 (d, C-3), 138.4 (d, C-7), 130.2 (d, C-2), 117.8 (t, C-8), 68.6 (t, C-9), 45.6 (s, C-4), 33.7 (t, C-6), 29.2 (t, C-5). Esterification of 7 with methyl malonyl chloride in pyridine–ether at 0 °C afforded the ester 8 in 69% yield: IR (neat) 1751 (C=O), 1736 (C=O), 1681 (C=O), 1636 cm^{-1} (C=C); PMR (60 MHz) δ 3.73 (s, 3, CH_3O), 3.40 (s, 2, CH_2CO); CMR δ 198.6 (s, C-1), 166.5 (s, C-10 or C-12), 166.1 (s, C-12 or C-10), 150.1 (d, C-3), 137.1 (d, C-7), 130.7 (d, C-2), 117.9 (t, C-8), 69.9 (t, C-9), 52.5 (q, C-13), 43.6 (s, C-4), 41.2 (t, C-11), 33.5 (t, C-6), 29.6 (t, C-5). Treatment of 8 with potassium fluoride in refluxing methanol afforded the chromatographically and spectroscopically single isomer of the intramolecular Michael adduct, the bicyclic δ-lactone 9 in 66% yield: IR (neat) 1753 (C=O), 1734 (C=O), 1719 (C=O), 1640 cm^{-1} (C=C); PMR (100 MHz) δ 5.88 (d,d, 1, J = 18 Hz, J = 11 Hz, H–C=C), 5.48 (d, 1, J = 11 Hz, $C{=}CH_2$), 5.42 (d, 1, J = 18 Hz, $C{=}CH_2$), 4.14 (ABq, 2, J = 11 Hz, CH_2O), 3.82 (s, 3, CH_3O), 3.34 (d, 1, J = 10 Hz, $CHCO_2$), 2.96 (m, 1, CH), 2.68–1.64 (m, 6, CH_2); CMR δ 208.1 (s, C-6), 168.3 (s, C-2 or C-12), 166.4 (s, C-12 or C-2), 138.8 (d, C-10), 118.6 (t, C-11), 74.0 (t, C-1), 53.3 (q, C-13), 50.8 (d, C-3), 41.9 (t, C-5), 38.7 (s, C-9), 38.3 (d, C-4), 36.0 (t, C-7), 27.2 (t, C-8). Intramolecular Michael addition of 8 using sodium hydride in THF [9] also afforded 9 in 60–65% yield under reflux for 30 min, whose IR, PMR, and CMR spectra were identical in every fine details with those of the specimen obtained in the above experiment. Additionally, in the PMR spectrum of 11a[10] (R = Me, J_{ad} = 9 Hz),[11] prepared similarly from 3, a long-range coupling (J_{ab} = 1.6 Hz) was observed. This result supports the assigned stereostructures for 11a, and hence for 9.



11a (R = Me)
11b (R = Et)

CMR of 11a
51.0 (d, C-3)
38.3 (d, C-4)
41.5 (t, C-5)

REFERENCES AND FOOTNOTES

1) Preliminary results were presented to the 20th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Akita-City, Japan Oct. 4th, 1976.

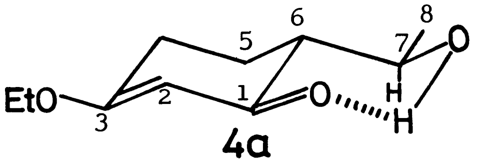
2) (a) P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, J. Am. Chem. Soc., 98, 1612 (1976); (b) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, J. Am. Chem. Soc., 98, 3028 (1976); (c) P. M. Wege, R. D. Clark, and C. H. Heathcock, J. Org. Chem., 41, 3144 (1976); (d) R. D. Clark and C. H. Heathcock, J. Org. Chem., 41, 1396 (1976); (e) J. A. Marshall and D. E. Seitz, J. Org. Chem., 40, 534 (1975).

3) G. Stork and R. L. Danheiser, J. Org. Chem., 38, 1775 (1973).

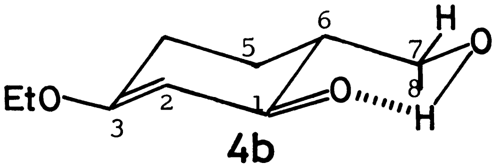
4) Satisfactory elemental analyses were obtained for all new compounds.

5) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973).

6) Due to the effect of the steric compression between C-5 and C-8 carbons on 4b in comparison with that of 4a, the signals ascribable to the C-5 and C-8 carbons of 4b were observed in 1.0-1.3 ppm higher fields than those of 4a: 4a, δ_c ppm (multiplicity) 23.4 (t, C-5), 20.1 (q, C-8); 4b, 22.1 (t, C-5), 19.0 (q, C-8).



4a



4b

7) IR spectra were determined with a Japan Spectroscopic Co. Ltd., IRA-I infrared recording spectrophotometer. PMR spectra were determined at 60 MHz with a Hitachi R-24 and at 100 MHz with a JEOL MH-100 spectrometers. CMR spectra were taken at 25.05 MHz in the Fourier mode using a JEOL FX-100 spectrometer. Samples were dissolved in $CDCl_3$ containing TMS as an internal standard (ppm downfield from TMS).

8) For aldol condensation of carbanions with formaldehyde: see G. Stork and M. Isobe, J. Am. Chem. Soc., 97, 4745 (1975).

9) H. Iio, T. Kawai, M. Isobe, and T. Goto,"The Symposium Papers of 20th Symposium on The Chemistry of Natural Products", Sendai, p 147 (1976); Tetrahedron Lett., 703 (1977).

10) The spectral data of 11a are as follows: IR (neat) 1753 (C=O), 1730 (C=O), 1718 (C=O), 1635 cm^{-1}(C=C); PMR (60 MHz) δ 6.16-5.49 (m, 1, H-C=C), 5.31 (brs, 1, $C=CH_2$), 5.09 (d,d, 1, J = 7 Hz, J = 2 Hz, $C=CH_2$), 4.10 (ABq, 2, J = 12 Hz, CH_2O), 3.79 (s, 3, CH_3O), 3.34 (d,d, 1, J = 9 Hz, J = 1.6 Hz, $CHCO_2$), 2.71-2.20 (m, 7, CH_2, CH), 2.00-1.75 (m, 2, CH_2).

11) The coupling constants (J_{ad}) of 9 and 11b 9) are as follows: 9, 10 Hz; 11b, 9.5 Hz.

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