

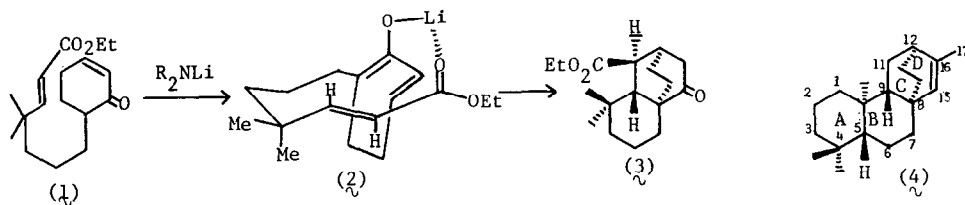
INTRAMOLECULAR DOUBLE MICHAEL REACTION. PART II.¹
 SYNTHESIS OF ISOATISIRENE TYPE COMPOUND

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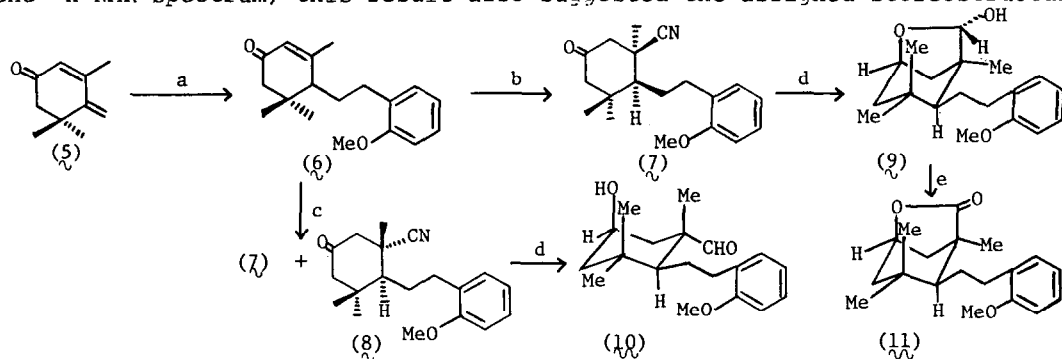
Summary: Intramolecular double Michael reaction of the α,β -unsaturated enone ester (16), prepared from the dienone (5), stereoselectively gave the tetracyclic product (17), which was converted into the isoatisirene type compound (20).

In the previous paper,¹ we disclosed the stereoselective construction of a spiro fused bicyclo[2.2.2]octane ring system (3) by the novel intramolecular double Michael reaction.² It was considered that the control of the diastereoselection was achieved by cyclization through the lithium chelated intermediate (2). As a part of a program designed to develop this method into a general stereocontrolled construction of polycyclic ring systems, we have investigated the synthesis of several natural products including isoatisirene and its related compounds. The structural feature of isoatisirene (4)³ is the perhydroethanophenanthrene skeleton in which the ethano bridge is trans to the hydrogen at the angular C₉ position. The assembly of this part is expected to be accomplished by this methodology and herein we wish to report the application of the intramolecular double Michael reaction to the synthesis of the isoatisirene type compound.



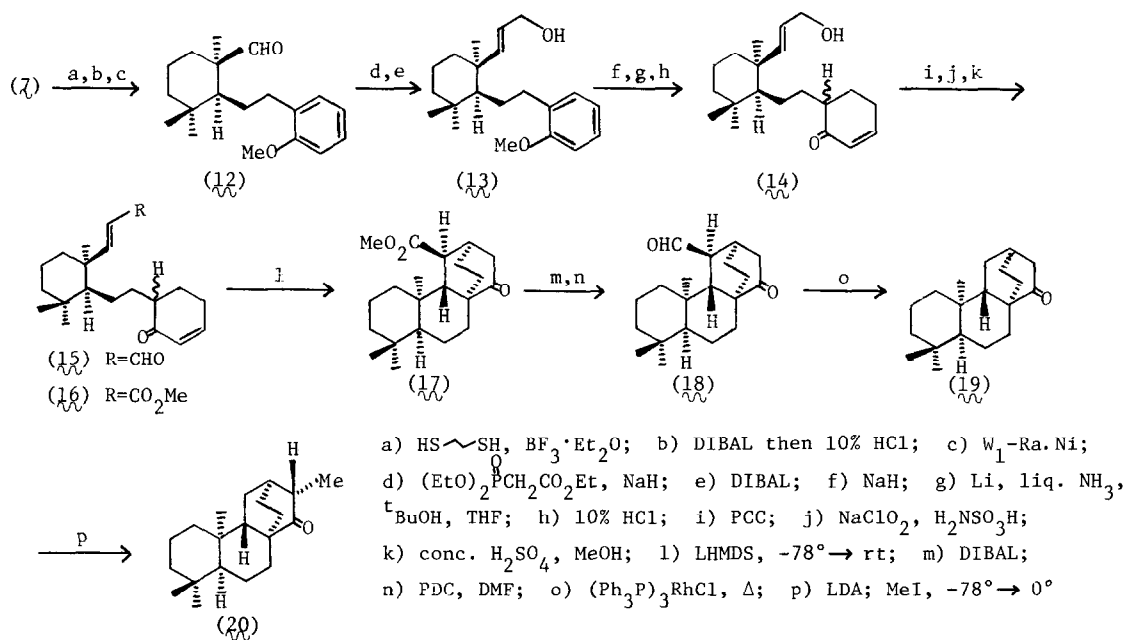
Reaction of the dienone (5)⁴ with 2-methoxybenzylmagnesium bromide in the presence of copper(I) bromide caused the 1,6-conjugate addition to give the enone (6)⁵ in 65% yield after isomerization. Introduction of carbon unit at the β -position of the enone (6) was rather difficult probably due to the steric hindrance and this was done by hydrocyanation.^{6a} Under the thermodynamically controlled reaction conditions using potassium cyanide - ammonium chloride in

dimethylformamide,^{6b} potassium cyanide - acetone cyanohydrin - 18-crown-6,^{6c} or diethylaluminum cyanide,^{6d} only single isomer (λ)⁵ was obtained in 75 - 78% yield. On the other hand, the kinetically controlled hydrocyanation using hydrogen cyanide - triethylaluminum^{6e} afforded λ in 71.4% yield along with the stereoisomer (δ)⁵ in 4.5% yield. Since the cyanide is less bulky than the methyl group, the compound (λ), which is also expected to be a favored product from stereoelectronic consideration,⁷ is more thermodynamically stable isomer. The structures of λ and δ were further supported by the following reactions. Reduction of λ with diisobutylaluminum hydride (DIBAL) followed by acidic treatment gave in 65% yield the cyclic hemiacetal (ρ)⁵, mp 88 - 89°C, while the hydroxy aldehyde ($\lambda\rho$)⁵ was gained from δ by the same treatments. Oxidation of ρ with silver carbonate - celite⁸ produced the lactone ($\lambda\rho\rho$)⁵ in 80% yield. Furthermore one of the methyl groups of the aldehyde ($\lambda\rho\rho$)⁵, which was synthesized from δ by dithioketalization (75%), reduction with DIBAL (85%) and desulfurization with Raney nickel (60%), was resonated at a high field, 0.73 ppm, in the ¹H-NMR spectrum; this result also suggested the assigned stereostructure.



- a) 2-Methoxybenzylmagnesium bromide, Cu₂Br₂, 0°; b) Et₂AlCN or KCN, NH₄Cl, DMF-H₂O or KCN, Me₂C(OH)(CN), 18-crown-6; c) HCN, AlEt₃, rt; d) DIBAL, -78°→rt then 10% HCl; e) Ag₂CO₃-celite

Reaction of $\lambda\rho\rho$ with the Wadsworth-Emmons reagent, followed by reduction of the resulting unsaturated ester (95%) with DIBAL furnished in 94% yield the alcohol ($\lambda\rho\rho$)⁵, which was firstly treated with sodium hydride and then subjected to the Birch reduction with lithium in liquid ammonia in the presence of tert.-butanol. After treatment with dil. hydrochloric acid, the enone ($\lambda\rho\rho$)⁵, obtained in 50% yield from $\lambda\rho\rho$, was converted into the requisite α,β -unsaturated enone ester ($\lambda\rho\rho$)⁵ by the sequential reactions; oxidation of $\lambda\rho\rho$ with pyridinium chlorochromate to the aldehyde ($\lambda\rho\rho$)⁵ (83%), further oxidation with sodium chlorite in the presence of sulfamic acid⁹ to the acid (70%), and esterification (72%). The double Michael reaction of $\lambda\rho\rho$ was conducted with lithium hexamethyldisilazide at -78°~rt^{1,10} in *n*-hexane - ether (8 : 1 v/v) to give the tetracyclic compound ($\lambda\rho\rho$)⁵ in 17% yield.¹¹ It is noteworthy that no other stereoisomer formed and the cyclized product was obtained in spite of a crowded intermediate.¹²



The ester moiety of 17 was removed by the following three steps; reduction of 17 with DIBAL followed by oxidation with pyridinium dichromate to the keto aldehyde (18)⁵, mp 121 ~ 123°C, and the decarbonylation with tris(triphenylphosphine)chlororhodium. Methylation of the ketone (19)⁵, mp 80 ~ 82°C, with methyl iodide in the presence of lithium diisopropylamide at -78 ~ 0°C furnished the isoatisirene type compound (20)⁵ as a single isomer.¹⁴ The signal of the methyl group at the angular C₁₀ position of compounds (19 and 20) was observed at a lower field, 1.14 ppm; this fact supported the stereochemistry of the framework.¹⁵

Application of the intramolecular double Michael reaction to polycyclic natural products is further in progress.

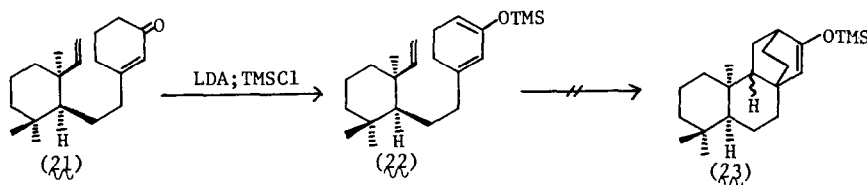
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References and Notes

- 1) Part I; M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, Tetrahedron Lett. in press.
- 2) Intermolecular double Michael reaction has been studied by several workers: K. B. White and W. Reusch, Tetrahedron, **34**, 2439 (1978); M. R. Roberts and R. H. Schlessinger, J. Am. Chem. Soc., **103**, 724 (1981).
- 3) A. H. Kapadi, R. R. Sobti, and S. Dev, Tetrahedron Lett., 1965, 2729.
- 4) B. R. Davis and S. J. Johnson, J. Chem. Soc., Perkin I, 1979, 2840.
- 5) All compounds have been characterized by elemental analysis and/or high

resolution mass spectra. Significant spectral data are recorded below:

- (7) $^1\text{H-NMR}$ (CDCl_3) 1.04, 1.07, 1.54 (each 3H, each s, 3 \times Me). (8) $^1\text{H-NMR}$ (CDCl_3) 0.90, 1.16, 1.23 (each 3H, each s, 3 \times Me). (9) $^1\text{H-NMR}$ (CDCl_3) 0.91, 1.03, 1.23 (each 3H, each s, 3 \times Me), 4.43 (1H, br t, J 5.7 Hz, >CH-O-). (12) $^1\text{H-NMR}$ (CCl_4) 0.73, 0.99, 1.02 (each 3H, each s, 3 \times Me), 9.67 (1H, s, $-\text{CHO}$). (16) IR ν_{max} (CHCl_3) 1670, 1710 cm^{-1} (CO); $^1\text{H-NMR}$ (CDCl_3) 0.74, 0.89, 1.01 (each 3H, each s, 3 \times Me). (17) IR ν_{max} (CHCl_3) 1715, 1730 cm^{-1} (CO); $^1\text{H-NMR}$ (CDCl_3) 0.93, 1.05, 1.13 (each 3H, each s, 3 \times Me). (19) $^1\text{H-NMR}$ (CDCl_3) 0.91, 0.97, 1.14 (each 3H, each s, 3 \times Me). (20) $^1\text{H-NMR}$ (CDCl_3) 0.91, 0.99, 1.14 (each 3H, each s, 3 \times Me), 1.17 (3H, d, J 7 Hz, Me).
- 6) a) W. Nagata and M. Yoshioka, Org. React., Vol. 25, p. 255 (1977); b) W. Nagata, M. Narisada, and T. Sugawara, J. Chem. Soc. C, 1967, 648; c) C. L. Liotta, A. M. Dabdoub, and L. H. Zalkow, Tetrahedron Lett., 1977, 1117; d) W. Nagata, M. Yoshioka, and S. Hirai, J. Am. Chem. Soc., 94, 4635 (1972); e) W. Nagata and M. Yoshioka, Org. Synth., 52, 100 (1972).
- 7) P. Deslongchamps "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford (1983), p. 221.
- 8) V. Balogh, M. Fétizon, and M. Golfier, J. Org. Chem., 36, 1339 (1971).
- 9) B. O. Lindgren and T. Nilsson, Acta Chem. Scand., 27, 888 (1973).
- 10) Reaction of the α,β -unsaturated enone aldehyde (15) under the same conditions gave no desired product.
- 11) The yield is not optimized.
- 12) The olefinic enone (21), prepared from the dienone (5) in the similar way, was transformed into the silyl enol ether (22), which was then subjected to Diels-Alder reaction¹³ but no tetracyclic compound (23) formed.



- 13) Intramolecular Diels-Alder reaction to bicyclo[2.2.2]octanes: T. Kametani, T. Honda, K. Fukumoto, M. Toyota, and M. Ihara, Heterocycles, 16, 1673 (1981); H. Nemoto, M. Hashimoto, K. Fukumoto, and T. Kametani, J. Chem. Soc., Chem. Comm., 1982, 699.
- 14) It was assumed on the basis of the CPK model consideration that the kinetically controlled alkylation would occur from the less hindered α -side.
- 15) P. A. Gunn, R. McCrindle, and R. C. Roy, J. Chem. Soc. C, 1971, 1018; J. MacMillan and E. R. H. Walker, J. Chem. Soc. C, 1972, 1274.

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