Tetrahedron Letters,Vol.25,No.20,pp 2167-2170,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# STEREOCONTROLLED CONSTRUCTION OF A SPIRO FUSED BICYCLO[2.2.2]OCTANE RING SYSTEM BY THE INTRAMOLECULAR DOUBLE MICHAEL REACTION

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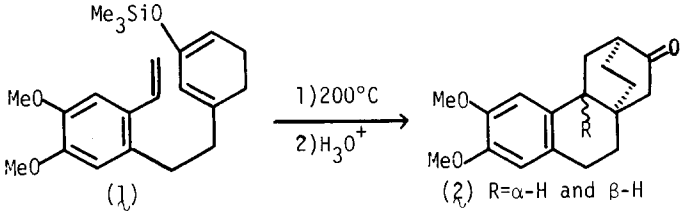
Summary: The lithium enolate from the cyclohexenone (8) possessing the α,β-unsaturated ester moiety caused an intramolecular double Michael reaction to produce stereoselectively the spiro fused bicyclo[2.2.2]-octane (10).

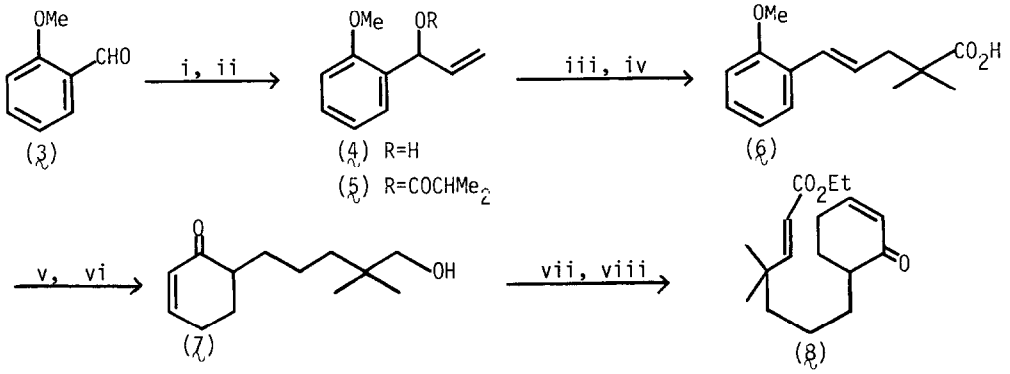
Spiro fused bicyclo[2.2.2]octane ring system is a skeleton of some tetra- and penta-cyclic diterpenoids such as atisirene and atisine. Recently it has been demonstrated that compounds possessing such frameworks are usefull synthetic intermediates of complicated natural products. For example, chasmanine[1], aphidicolin[2,3], maritimol[3,4] and stemarin[5] have been ingeneously synthesized through the rearrangement from bicyclo[2.2.2]octane derivatives. Keeping in mind the synthesis of natural products, we have searched the general method for the construction of the above ring system. In the previous study, the atisane skeleton (2) was assembled by intramolecular Diels-Alder reaction of the triene (1) but a poor stereoselectivity was observed.[6] Intending to find out a high stereoselective synthesis of the desired cyclic compound, we planned the novel intramolecular double Michael reaction[7], since it was anticipated that a metal chelated intermediate would lead to a selective formation of the natural type ring system. Here we wish to report our successful result by this strategy.



(1) (2) R=α-H and β-H

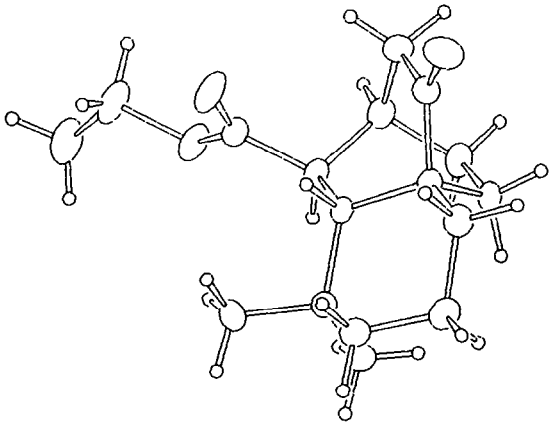
As a model experiment of intramolecular double Michael reaction, cyclization of the α,β-unsaturated enone ester (8) was examined under a variety of conditions. The substrate (8) was prepared as follows. Grignard reaction of o-anisaldehyde (3) gave in 91% the alcohol (4)[8], which was esterified with isobutyric acid in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine[9]. The ester (5)[8] obtained in 85% yield was silylated with trimethyl-

chlorosilane in the presence of lithium diisopropylamide and hexamethylphosphoric triamide at -78°C and then subjected to the [3,3] sigmatropic rearrangement[10] followed by hydrolysis with 10% hydrochloric acid to give the acid (6)[8] in 69% yield. After reduction of the acid (6) with lithium aluminum hydride, the resulting alcohol was treated with excess metallic lithium in liquid ammonina in the presence of isopropanol and then hydrochloric acid in methylene chloride. Oxidation of the enone (7)[8], obtained in 70% yield form 6, with pyridinium chlorochromate, followed by the reaction of the resulting aldehyde with the Wadsworth-Emmons reagent[11] gave the unsaturated ester (8)[8] as the E-isomer in 90% yield.



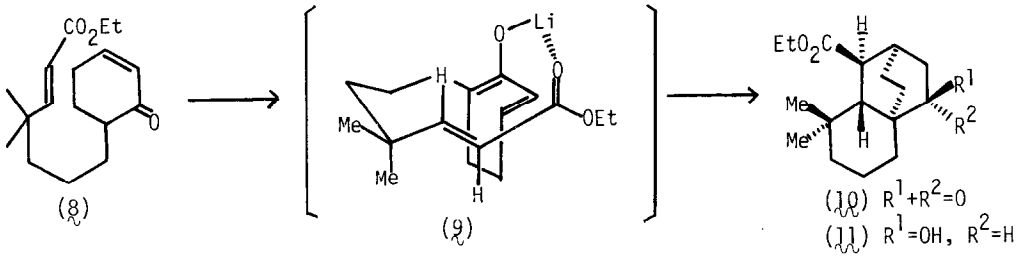

Reagents: i) $CH_2$=CHMgBr. ii) $Me_2CHCO_2H$, DCC, DMAP. iii) LDA, HMPA then TMSCl. iv) 10% HCl. v) $LiAlH_4$. vi) Li, liq. $NH_3$, $^iPrOH$ then 10% HCl. vii) PCC. viii) $(EtO)_2P(O)CH_2CO_2Et$, NaH.

Some of the conditions and yields examined for cyclization of 8 are listed in the Table. The desired tricyclic compound (10)[8] was produced as a single isomer by the lithium enolate formation of 8 under the kinetically controlled conditions[12] at -78°C followed by reaction under the indicated conditions. Best result, 60% yield, was obtained on the reaction utilizing lithium hexamethyldisilazide (LHMDS) as the entry 2. Stereochemistry of the product (10) was deduced by the reduction with sodium borohydride. Namely, IR spectrum of the alcohol (11)[8] formed in 83% yield as a sole product showed the presence of hydroxyl and ester groups, which are intramolecularly hydrogen-bonded. Furthermore the chemical shifts of two methyl groups in $^1$H-NMR spectrum were not significantly changed by the reduction. The above assignment was further confirmed by the X-ray analysis of the tricyclic compound (10), mp 97 - 98°C[13]. The molecular structure of one of enantiomer of 10 is shown in the Figure.



Figure

The stereoselective formation of (10), which has the suitable stereochemical arrangement for the synthesis of natural products, can be accounted by the conjugated addition via the endo mode intermediate (9) in which the two oxygens are held closely to the metal cation. Although this highly stereocontrolled reaction could be regarded as the sequential Michael reaction, the anion-accelerated Diels-Alder mechanism could not be ruled out[7]. Application of this new method to the synthesis of natural products is in progress[14].




Conditions and Yields of Formation of the Tricyclic Compound (10) from (8)

| entry | base | eq. | solvent | temp.(°C) | time(h) | Yield(%) |
|---|---|---|---|---|---|---|
| 1 | NaH | 1.5 | THF | 66 | 24 | — |
| 2 | LHMDS | 1.3 | THF | -78 ∿ r.t. | 20 | 30 ∿ 60 |
| 3 | LHMDS | 1.3 | THF-HMPA | -78 ∿ r.t. | 20 | 10 |
| 4 | LDA | 2.0 | THF | -78 | 2 | 22 |
| 5 | LDA | 1.3 | THF | -78 | 16 | 24 |
| 6 | LDA | 1.3 | THF | -78 ∿ -20 | 2 | 45 |

Acknowledgment We thank Prof. Y. Iitaka and Dr. A. Itai, Faculty of Pharmaceutical Sciences, University of Tokyo, for X-ray analysis and Dr. M. Koizumi, Chugai Pharmaceutical Co. for his help. A part of this work was financially supported by Grant-in-Aid for Special Project No.57118006 from the Ministry of Education, Science and Culture, Japan.

References and Notes

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7) Intermolecular double Michael reaction has been studied by several workers: (a) R. A. Lee, Tetrahedron Lett., 1973, 3333. (b) K. B. White and W. Reusch, Tetrahedron, 34, 2439 (1978). (c) E. G. Gibbons, J. Org. Chem., 45, 1540 (1980). (d) M. R. Roberts and R. H. Schlessinger, J. Am. Chem. Soc., 103, 724 (1981). (e) M. Asaoka, K. Ishibashi, N. Yanagida, and H. Takei, Tetrahedron Lett., 24, 5127 (1983).

8) All compounds have been characterized by elemental analysis and/or high resolution mass spectra. Their purity was established by TLC and/or HPLC using a Hitachi 635 instrument. Significant spectral data are recorded below: (4) $^1$H-NMR ($CCl_4$) δ 5.98 (1H, ddd, J 5, 10 and 17 Hz, -CH=$CH_2$). (5) $^1$H-NMR ($CCl_4$) δ 1.15 (6H, d, J 7 Hz, 2 × Me), 2.20 - 2.80 (1H, m, $CHMe_2$). (6) $^1$H-NMR ($CCl_4$) δ 1.23 (6H, s, 2 × Me), 2.45 (2H, d, J 7 Hz, =$CHCH_2$-). (7) $^1$H-NMR ($CCl_4$) δ 0.83 (6H, s, 2 × Me), 3.20 (2H, s, $OCH_2$), 5.85 (1H, dt, J 1 and 10 Hz, COCH=CH-), 6.70 - 7.00 (1H, m, COCH=CH-). (8) IR $\nu_{max}$ ($CHCl_3$) 1700 and 1660 $cm^{-1}$ (C=O); $^1$H-NMR ($CCl_4$) δ 1.07 (6H, s, 2 × Me), 1.27 (3H, t, J 7 Hz, $CH_2CH_3$), 4.10 (2H, q, J 7 Hz, $CH_2CH_3$), 5.57 (1H, d, J 16 Hz, =$CHCO_2$Et), 5.80 (1H, dt, J 1 and 10 Hz, COCH=CH-), 6.50 - 6.90 (1H, m, CO-CH=CH-), 6.73 (1H, d, J 16 Hz, CH=$CHCO_2$Et). (10) IR $\nu_{max}$ ($CHCl_3$) 1720 $cm^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$) δ 0.77 and 1.06 (each 3H, each s, 2 × Me), 1.25 (3H, t, J 7 Hz, $CH_2CH_3$), 4.14 (2H, q, J 7 Hz, $CH_2CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 14.50, 18.14, 21.78, 24.01, 26.13, 29.34, 32.00, 32.17, 34.93, 39.28, 41.21, 43.92, 44.97, 45.15, 60.82, 175.19, 214.00. (11) IR $\nu_{max}$ ($CHCl_3$) 3400 (OH), 1700 $cm^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$) δ 0.76 and 0.97 (each 3H, each s, 2 × Me), 1.27 (3H, t, J 7 Hz, $CH_2CH_3$), 4.16 (2H, q, J 7 Hz, $CH_2CH_3$).

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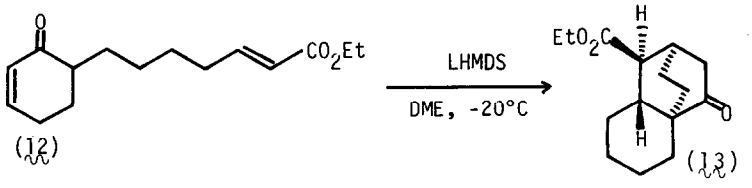
13) Triclinic, space group $P\bar{1}$ with a=13.853 (4), b=8.492 (2), c=7.163 (2) Å: α=108.87°(5), β=95.37°(4), γ=94.88°(4) for Z=2. Final R value was 0.062 for 2786 observed reflections.

14) Intramolecular Double Michael reaction of 12, prepared from 4 via ortho-acetate Claisen rearrangement[15], also afforded the tricyclic compound (13) as a single diasteroisomer. The details will appear on a full paper.




(12) (13)

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(Received in Japan 13 February 1984)