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TRICYCLO[3.3.0.$0^{2,8}$]OCTANONES AS BUILDING BLOCKS IN NATURAL PRODUCTS SYNTHESIS. -- SYNTHESIS OF (±)-FORSYTHIDE AGLYCON DIMETHYL ESTER --

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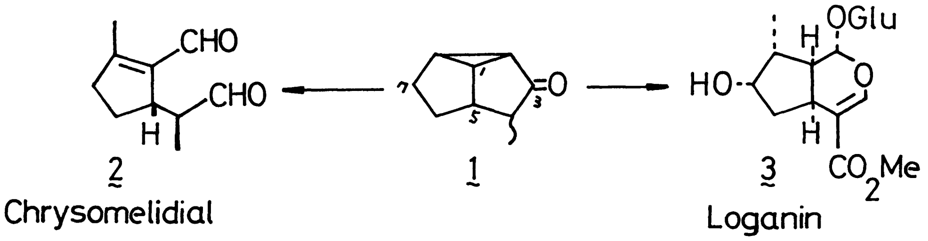
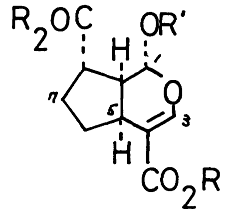
The stereocontrolled synthesis of (±)-forsythide aglycon dimethyl ester from 4-methoxycarbonyl-tricyclo[3.3.0.$0^{2,8}$]octan-3-one (6) is described.

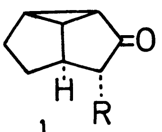
The various methodologies have been extended towards the synthesis of cyclopentanoid natural products. We recently identified the potential utility of 4-methyl-tricyclo[3.3.0.$0^{2,8}$]octan-3-one (1) as a versatile intermediate in the synthesis of chrysomelidial$^{1)}$ (2) and loganin$^{2)}$ (3). In this paper we wish to report the stereocontrolled synthesis of (±)-forsythide aglycon dimethyl ester (4b), starting from an another versatile synthon, 4-methoxycarbonyl-tricyclo[3.3.0.$0^{2,8}$]-octan-3-one (6). Forsythide (4a)$^{3)}$ is a naturally occurring iridoid glucoside isolated from fresh leaves of Forsythia viridissima Lindl.





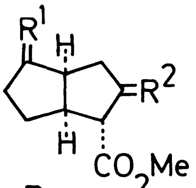
4a: R=H, R'=Glu., Forsythide.
4b: R=Me, R'=H, Forsythide aglycon dimethyl ester.

The key intermediate 6 was prepared from tricyclo[3.3.0.$0^{2,8}$]octan-3-one (5)$^{4)}$ by methoxycarbonylation with dimethyl carbonate and sodium hydride in dimethoxyethane at reflux temperature in 84 % yield. Although the cyclopropane ring cleavage of 1 or 5 with 99 % formic acid at 70-80°C afforded the corresponding formate (C_{2-8} bond cleavage) and its isomer (C_{1-2} bond cleavage)$^{5)}$, in the case of 6 with methoxycarbonyl group at C-4 position, the only C_{2-8} bond was selectively cleaved with 99 % formic acid in the presence of conc. sulfuric acid at room temperature to the desired formate and a subsequent treatment with sodium methoxide afforded the hydroxyl keto ester 7 in 88 % yield from 6. Deoxygenation of ketone at C-3 position was achieved by the thioketalization followed by reduction with Raney Ni



5: R = H

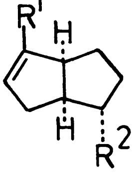
6: R = CO_2Me



7: R^1=H,OH; R^2=O

8: R^1=H,OH; R^2=H_2

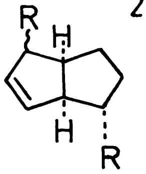
9: R = O ; R^2 = H_2



10: R^1=CN

R^2=CO_2Me

11: R^1=R^2=CO_2Me



12: R = CO_2Me

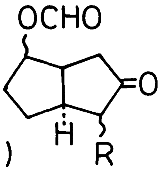
(αβ/βγ = 1.0/10.4)

(W-2). Thus, 7 gave the hydroxy ester 8 in 80 % yield from 7. 8 was oxidized with Jones reagent to give the keto ester 9 which was converted into the corresponding cyanohydrin by a treatment with KCN and AcOH in EtOH at 30°C in good yield. This was dehydrated with phosphoryl chloride in pyridine to give αβ-unsaturated nitrile 10 in 84 % yield. 10 was hydrolyzed with potassium hydroxide in ethylene glycol at 160-180°C to its dicarboxylic acid which was treated with diazomethane to give the corresponding diester 11 in 79 % yield. 11 was deprotonated with lithium diisopropyl amide-hexamethylphosphoramide complex in THF at -78°C to produce the lithium enolate of 11 in situ, which was quenched with acetic acid to give the βγ-unsaturated ester 12 in 84 % yield (ratio: αβ/βγ = 1.0/10.4 by pmr). Ozonolysis of the mixture of 12 followed by reductive workup with Zn/AcOH directly led to (±)-forsythide aglycon dimethyl ester (4b) after purification by preparative TLC as an oil, which was epimeric mixture at C-1 position in 66 % yield (ratio: α-OH/β-OH = 3.5/1.0 by pmr).

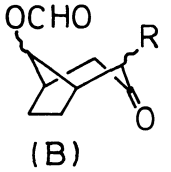
The pmr and ir spectra of synthetic 4b were consistent with those of the compound(6) derived from natural forsythide. As described above, the stereo-controlled and facile synthesis of (±)-forsythide aglycon dimethyl ester (4b) was achieved starting from versatile synthon 6.

References

1. K. Kon and S. Isoe, Tetrahedron Lett., 1980, 3399.
2. K. Kon and S. Isoe, "Abstracts of Papers", 23rd Symposium on the Chemistry of Natural Products, Japan, 1980, 49.
3. Isolation: H. Inoue and T. Nishioka, Chem. Pharm. Bull. (Japan), 21, 497 (1973).
   Synthesis: K. Furuichi and T. Miwa, Tetrahedron Lett., 1974, 3689.
4. S. A. Monti, David J. Bucheck, and John C. Shepard, J. Org. Chem., 34, 3080 (1969).
5. The ratio of C_{2-8} bond cleavage (A) and C_{1-2} bond cleavage (B) was 4 : 1 in either case of 1 and 5.



(A)



(B) R=H,Me

6. We thank Prof. T. Miwa and Dr. K. Furuichi for kindly providing copies of the pmr and ir spectrum of (±)-forsythide aglycon dimethyl ester.

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