72. Tricyclo[3.3.0.0^{2,8}]octanones as Building Blocks in Natural Products Synthesis. II. A New Synthesis of Loganin

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Dedicated to Emeritus Professor *Takeo Sakan* on the occasion of his 70th birthday

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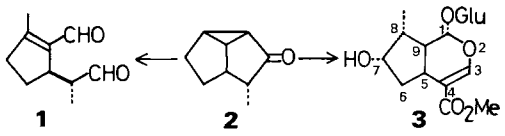
Summary

The stereocontrolled synthesis of loganin from 4-methyltricyclo[3.3.0.0^{2,8}]octan-3-one is described.

In the previous paper [1], we have reported the stereocontrolled synthesis of chrysomelidial (**1**) starting from 4-methyltricyclo[3.3.0.0^{2,8}]octan-3-one (**2**). We now have used the versatile intermediate **2** in the synthesis of loganin (**3**) [2], a typical iridoid which plays an important role in the biosynthesis of other natural products [3].

Scheme 1



Ring cleavage of **2** with 99% formic acid at 70–80° for 30 min, followed by methanolysis and acetalization in the usual manner gave in 87% yield a mixture of the expected acetal **4** (2,8-bond cleavage) and its structural isomer **5** (1,2-bond cleavage) in a ratio of 4:1 (by ^{1}H-NMR.). These isomers were easily separated by column chromatography. Oxidation of **4** with CrO_3/pyridine in CH_2Cl_2, followed by treatment with *p*-toluenesulfonohydrazide and molecular sieves (3 Å) in CH_3OH under reflux for 45 min gave tosylhydrazone **6**. The latter was treated with butyllithium in *N, N, N′, N′*-tetramethylethylenediamine, followed by trapping of the produced vinyl anion with DMF to give the α,β-unsaturated aldehyde **7** in 36% yield [4]. The oxidation of **7** with active MnO_2 in the presence of HCN in CH_3OH

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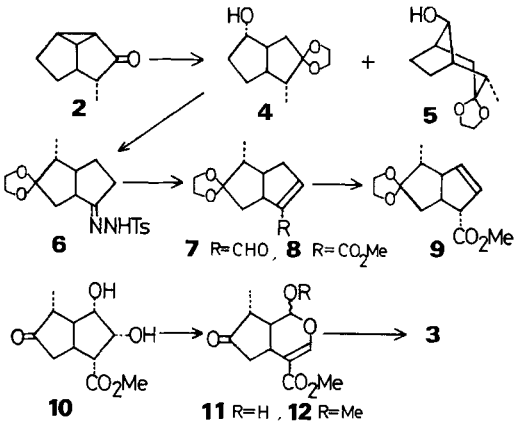
Scheme 2



at room temperature for 18 h afforded the α,β-unsaturated ester **8** in 82% yield [5]. On the other hand, direct conversion of **6** to **8** was also accomplished in 32% overall yield by treatment of **6** with BuLi and then trapping of the produced vinyl anion with methyl chloroformate instead of DMF.

Deprotonation of **8** with lithium diisopropylamide in THF at $-78°$ produced the lithium enolate of **8** *in situ*, which was kinetically protonated by the exposure to aqueous acetic acid in a *Teflon* tube at 0° to give β,γ-unsaturated ester **9** in 96% yield. Oxidation of **9** with OsO_4 in ether at 25° for 48 h, followed by decomposition with $NaHSO_3$, and deprotection of the ethylene acetal with *p*-toluenesulfonic acid in aqueous THF at 30° for 24 h gave the dihydroxy-keto derivative **10** in 89% overall yield from **9**. Oxidation of **10** with sodium periodate in ether/water 1:1 at 4° for 24 h afforded 7,*O*-didehydrologanin aglycone (**11**) in 90% yield.

Didehydrologanin aglycone **11** was transformed into the corresponding 1-*O*-methyl derivative **12** in 85% yield by treatment with cation exchange resine in CH_3OH at 25° for 48 h. The ^{1}H-NMR. and IR. spectrum of the synthetic methyl ester **12** were consistent with those of the reported methyl ether; this methyl ester **12** has already been converted into (±)-loganin by *Büchi et al.* [2a]. Thus, a new synthetic route to loganin was established.

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