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TOTAL SYNTHESIS OF (±)-FORSYTHIDE AGLUCONE DIMETHYL ESTER

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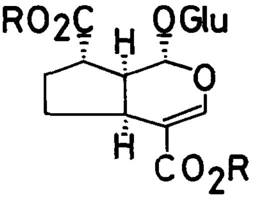
Forsythide (1) is a naturally occurring iridoid glucoside isolated from fresh leaves of *Forsythia viridissima* Lindl.[1] We now wish to report a total synthesis of the aglucone (3) of (±)-forsythide dimethyl ester (2).

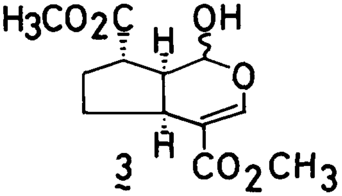
The bromolactone carboxylic acid 4,[2] which is easily available from commercial cyclopentadiene-maleic anhydride adduct,[3] was chosen as the starting material. The first step of the synthesis is conversion of 4 into a keto lactone 9, a key intermediate for the secoiridoid synthesis.[4] Treatment of the acid 4 with thionyl chloride in boiling benzene gave an acid chloride 5, mp 99-100°, which was transformed to a diazoketone 6, mp 145° (dec), by treatment with diazomethane. Irradiation of 6 in 1% aqueous acetonitrile (1 : 1) solution gave a homo acid 7, mp 171.5-172.5°.[5,6] The overall yield of the acid 7 based on 4 was 71%. The homo acid 7 was reduced with diborane in tetrahydrofuran to give the corresponding alcohol 8 (75%) with unchanged acid (24%). Alkaline hydrolysis of bromolactones of norbornane type is known to give keto acids instead of the expected epoxy acids.[7] Treatment of 8 with 1.5*N* sodium hydroxide (50-55°, 8 h), followed by warming the acidified solution (80°, 1 h), gave a keto lactone 9 (55%): mp 136-137°; ir ($CHCl_3$) 1748, 1730 cm^{-1}.

Methanolysis of the keto lactone 9 with sodium methoxide in boiling methanol (1 h) gave a hydroxy ester 10 (98%); *p*-nitrobenzoate, mp 102-103°. The epimerization accompanied by the methanolysis was confirmed by difficult lactonization of the resulting acid by the hydrolysis of the hydroxy ester 10.[8] The



1 R = H

2 R = CH_3



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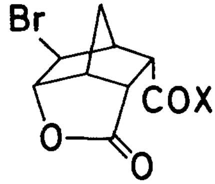
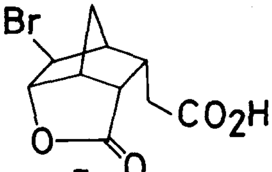


4 X = OH

5 X = Cl

6 X = CHN_2



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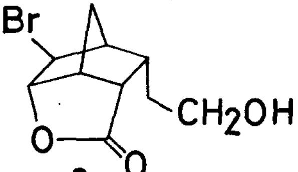

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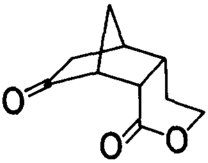

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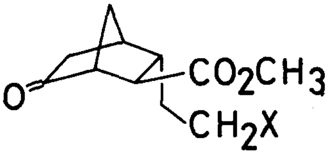
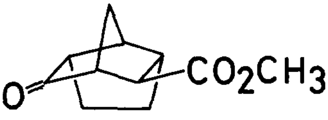


10 X = OH

11 X = OTs



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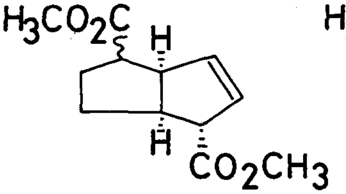
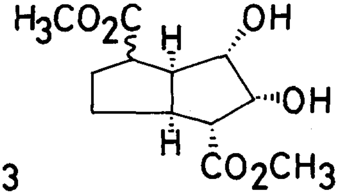


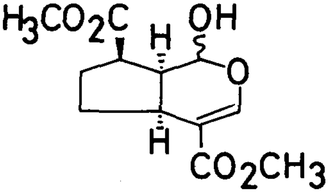
13 α-CO_2CH_3

14 β-CO_2CH_3



15 α-CO_2CH_3

16 β-CO_2CH_3



17

hydroxy ester **10** was treated with tosyl chloride and pyridine in methylene chloride to give a tosylate **11** (93%): ir (neat) 173o, 1595, 1370, 1178 cm^{-1}. The tosylate **11**, on treatment with potassium t-butoxide in t-butyl alcohol (30°, 2.5 h, under Ar), gave a tricyclic ketoester **12** (47%): ir (neat) 1725 cm^{-1}.[9]

The keto ester **12**, on irradiation with a medium pressure mercury lamp (500 w) in 0.17% acetonitrile solution (24 h), gave a bicyclic aldehyde,[10] which was immediately oxidized with the Jones' reagent. The acid fraction was esterified with diazomethane to give a methyl ester **14** (47% based on **12**): nmr (CDCl$_3$) δ 3.66 (s, 6), 5.52 (m, 1), 5.72 ppm (m, 1). The neutral fraction of the oxidation gave 45% of unchanged **12**. Contrary to forsythide, **14** has the newly-formed ester function in trans relationship to the hydrogen atoms on the ring junction. The epimeric ester was prepared as follows. The crude aldehyde from the photolysis was treated with 0.1*N* aqueous-methanolic sodium hydroxide (5°, 1.5 h), followed by esterification with diazomethane and subsequent oxidation with the Jones' reagent. Repeated esterification with diazomethane of the acid fraction gave a dimethyl ester **13** (16% based on **12**): nmr (CDCl$_3$) δ 3.68 (s, 6), 5.58 (m, 1), 5.78 ppm (m, 1). The low yield of the ester **13** is apparently due to the fact that the epimerization was accompanied by the internal aldol condensation.

When the methyl ester **13** was oxidized with osmium tetraoxide in ether and the resulting osmate cleaved with hydrogen sulfide, a diol **15** (94%), mp 116-118°, was obtained. Oxidation of the diol with lead tetraacetate in benzene in the presence of potassium carbonate gave the aglucone (**3**) of forsythide dimethyl ester (86%): uv (95% EtOH) 238 nm (log ε 3.90), addition of 0.1 *N* NaOH shifts max to 273 nm; ir (CHCl$_3$) 3400, 1720, 1705, 1630 cm^{-1}; nmr (CDCl$_3$) δ 3.72 (s, 6), anomeric proton (1H in total): 4.86 (d, J = 7 Hz), 5.28 (d, J = 1H), vinyl proton (1H in total): 7.43 (d, J = 1 Hz), 7.45 (d, J = 1 Hz).

Fresh leaves (3 kg) of Forsythia viridissima collected in our campus in May was extracted with hot methanol (40 ℓ). Work-up of the extracts by a procedure simplified from the method of Inouye[1] gave forsythide dimethyl ester (**2**) (3.56 g), mp 142-143°, $[\alpha]^{26}_{\underline{D}}$ -56.6° (*c* = 1, MeOH), which was identified with the authentic sample. Hydrolysis of the glucoside ester in a buffer solution (pH =

4.85) in the presence of Naringinase[11] gave forsythide aglucone dimethyl ester (**3**) as an oil (67%), $[\alpha]^{26}_{D}$ +40.5° (*c* = 1, $CHCl_3$), which was completely identical with the synthetic specimen in ir and nmr spectra.

On the other hand, oxidation of the dimethyl ester **14** with osmium tetraoxide gave a diol **16** (80%), mp 112-114°, which was further oxidized with lead tetraacetate to give **17** (78%). The ir spectrum is similar to, but the nmr spectrum [($CDCl_3$) δ 3.72 (s, 6), anomeric proton (1H in total): 5.01 (d, J = 10 Hz), 5.80 (d, J = 3 Hz), vinyl proton: 7.38 ppm (bs, 1)] is distinctly different from that of **3**. This result sufficiently verify the epimerization of the photolysis aldehyde by base, at least, at the formyl group as expected.

Acknowledgement We are indebted to Professor Hiroyuki Inouye of the Kyoto University for a kindest gift of the authentic sample of forsythide dimethyl ester.

REFERENCES AND FOOTNOTES

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2. K. Alder and G. Stein, *Ann. Chem.*, **514**, 1 (1934).
3. A generous supply of this material from the Hitachi Chemical Co. Ltd. is gratefully acknowledged.
4. Total synthesis of (±)-swerogenin from this material will be reported later.
5. A. Padwa and R. Layton, *Tetrahedron Lett.*, 2167 (1965).
6. Satisfactory elemental analyses were obtained for 7 and all the solid compounds described hereafter.
7. R. M. Moriarty and T. Adama, *Tetrahedron Lett.*, 3715 (1969).
8. Heating the acid (150°, 1 h) resulted in recovery, azeotropic dehydration in benzene with *p*-toluenesulfonic acid (1 h) gave a lactone different from 9.
9. A. Nickon, H. Kwansnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Amer. Chem. Soc.*, **87**, 1613 (1963).
10. Another possible cleavage of the carbonyl group may be unfavorable because of necessity for the radical to abstract ε-hydrogen to make a double bond.
11. S. Okada, K. Kishi, M. Higashihara, and J. Fukumoto, *Nippon Nōgeikagaku Kaishi*, **37**, 84 (1963).