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Synthetic Studies on Lignans and Related Compounds. VII.[1] Synthesis of β-Apoplicatitoxin Trimethyl Ether[2]

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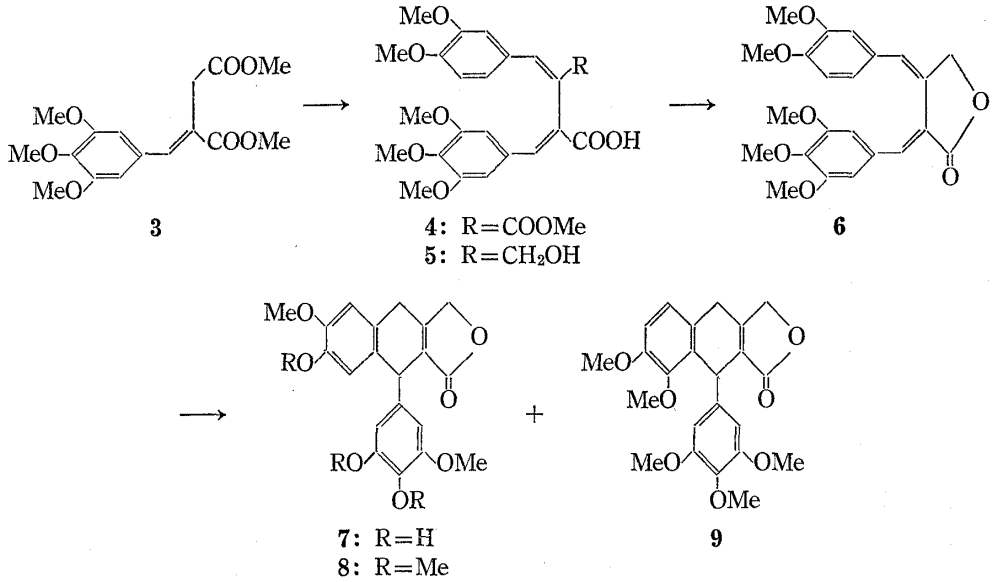
β-Apoplicatitoxin trimethyl ether (**8**) was synthesized by selective photocyclization of a dibenzylidenebutyrolactone (**6**). The photocyclization was preliminarily examined in various solvents by use of a model compound (**1**), and the total yield of resulting isomeric β-apolignans (**2a** and **2b**) and the ratio of **2a**/**2b** were shown to increase with increasing solvent polarity.

Keywords——β-apoplicatitoxin trimethyl ether; synthesis; β-apolignan; 2,3-dibenzylidenebutyrolactone; photocyclization; solvent effect; β-apopicrosikkimotoxin

We recently reported the regiospecific photocyclization[4] of 2,3-dibenzylidenebutyrolactones to β-apolignans which was investigated as a chemical model for the biogenetic pathway to natural naphthalide lignans. This method has now been applied to the synthesis of the trimethyl ether (**8**) of β-apoplicatitoxin (**7**).[5] The lignan (**7**) is the first natural β-apolignan found in plants, and is of interest in relation to its biogenetic role among the coexisting lignans.[2]



3 **4**: R=COOMe, **5**: R=CH_2OH **6** **7**: R=H, **8**: R=Me **9**

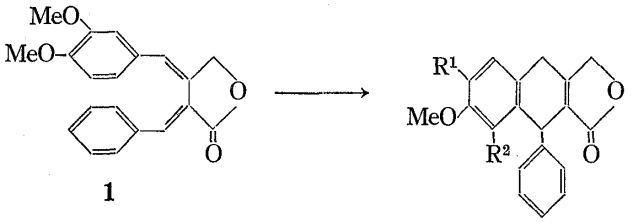
Chart 1

As a design, the 1-aryl-2,3-naphthalide β-apolignan such as **8** is expected to arise selectively from the photocyclization of a dibenzylidenebutyrolactone (**6**), despite a disadvantage due to the dual mode of substitution on the benzene ring unsymmetrically substituted by two methoxyls. The effect of the solvent on the orientation of substitution was first exam-

1) Part VI: T. Momose, K. Kanai, and T. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **26**, 1592 (1978).
2) Presented in part at the 25th Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kobe, Nov. 1975, Abstracts of Papers, p. 31. A preliminary communication has appeared in *Heterocycles*, **6**, 277 (1977).
3) Location: *133-1, Yamada-kami, Suita, Osaka 565, Japan.*
4) T. Momose, K. Kanai, T. Nakamura, and Y. Kuni, *Chem. Pharm. Bull.* (Tokyo), **25**, 2755 (1977).
5) B.F. MacDonald and G.M. Barton, *Can. J. Chem.* **51**, 482 (1973).

ined using a model compound (**1**). As previously mentioned,[4] irradiation of **1** in dimethylformamide (DMF) with the light filtered through ordinary borosilicate glass gave a pair of isomeric β-apolignans (**2a**) (30% yield) and (**2b**) (20% yield). Further study of the photocyclization of **1** in various solvents showed that the total yield of **2** and the ratio of **2a**/**2b** tended to increase with increasing solvent polarity (see Table I). The possibility of interconversion between **2a** and **2b** during the course of their formation in the photocyclization was excluded by the experiment where no conversion into **2a** was observed on irradiation of **2b** in DMF. The result is likely to reflect the sensitivity of excited states of **1** to the solvent polarity.

Table I. Photocyclization of **1** in Various Solvents



1

2a: R^1=OMe, R^2=H
2b: R^1=H, R^2=OMe

Solvent	Product yield (%)	
	2a	**2b**
Benzene	6	15
Acetone	18	10
Dioxane	15	22
DMF	30[a]	20[a]

a) Quoted from ref. 4.

In view of the foregoing result in the photocyclization of **1**, we then proceeded to the synthesis of **8**. The Stobbe condensation of dimethyl succinate with 3,4,5-trimethoxybenzaldehyde and subsequent treatment of the product with diazomethane gave a dimethyl ester (**3**). The second Stobbe condensation of **3** with veratraldehyde afforded a half ester (**4**), which was reduced with lithium aluminum hydride at −15° to a hydroxy acid (**5**). Treatment of **5** with *p*-toluenesulfonic acid in the dark completed the synthesis of **6**.

A solution of **6** in DMF was irradiated with a 100 W high-pressure mercury lamp through a filter of ordinary borosilicate glass in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), and simultaneously bubbled with dry, oxygen-free nitrogen. Preparative thin-layer chromatography (TLC) of the crude product gave **8** (34% yield) and **9** (15% yield). The synthetic sample (**8**) was identical, on mixture melting point and infrared (IR) spectral comparison, with authentic β-apopicrosikkimotoxin,[6] which was reported[5] to be identical with β-apoplicatitoxin trimethyl ether. The structure of another photo-product (**9**) was established on the basis of the following observations. It showed IR spectrum absorption at 1748 (C=O) and 1690 (C=C) cm^{-1}, and proton magnetic resonance (^{1}H-NMR) signals for aromatic protons as two doublets (J=8 Hz) at 6.90 and 6.99, which were closely similar to those of **2b**.

Experimental

Melting points and boiling point are uncorrected. ^{1}H-NMR spectra were obtained with a Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard, IR spectra with a Hitachi EPI-G3 spectrophotometer, Ultraviolet (UV) spectra with a Shimadzu MPS-50L spectrophotometer, and Mass Spectra (MS) with a Hitachi RMU-6E spectrometer (direct inlet, at 70 eV). All organic extracts were dried over Na_2SO_4 before evaporation. Column chromatography was effected using Mallinckrodt silicic acid.

6) E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963).

Preparative TLC was performed on Merck Kieselgel 60 PF_{254}. The photochemical reactions were carried out in an immersion apparatus fitted with an Eikosha 100 W high-pressure mercury lamp.

Irradiation of 2-Benzylidene-3-veratrylidene-4-hydroxybutyric Acid γ-Lactone (1)[4]——A solution of **1** (50 mg) and DABCO (10 mg) in benzene, acetone, or dioxane (50 ml) was irradiated through an ordinary borosilicate glass sleeve (1.5 mm wall thickness) at 5° for 40 min under a stream of dry, oxygen-free N_2. The solvent was removed *in vacuo* to yield a residue, which was purified by preparative TLC on silica gel using $CHCl_3$ as solvent to give a mixture of 1,4-dihydro-6,7-dimethoxy-3-hydroxymethyl-1-phenyl-2-naphthoic acid γ-lactone (**2a**)[4] and 1,4-dihydro-7,8-dimethoxy-3-hydroxymethyl-1-phenyl-2-naphthoic acid γ-lactone (**2b**).[4] Their ratios were determined by ^{1}H-NMR spectra as in Table I.

Irradiation of 2b——A solution of **2b** (30 mg) in DMF (30 ml) was irradiated for 30 min in a similar manner to that for **1**. After evaporation of the solution, **2b** was recovered quantitatively.

Dimethyl 3,4,5-Trimethoxybenzylidenesuccinate (3)——Metallic Na (5.3 g) was dissolved in dry MeOH (92 ml), and to this was added a solution of dimethyl succinate (16.1 g) and 3,4,5-trimethoxybenzaldehyde (20.4 g) in dry MeOH (45 ml) with stirring at room temperature over 40 min. After heating under reflux for 2 hr, the solution was evaporated and poured into ice-water, and the separated oil was taken in ether. The aqueous layer was acidified with 5% H_2SO_4, and the separated oil was extracted with AcOEt. The extract was washed with satd. NaCl and evaporated to give a yellow oil (26 g). The crude acid (26 g) was methylated with CH_2N_2 in ether in a usual manner to give **3** (13.8 g, 41%) as a pale yellow oil, bp 154—155° (0.043 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1743, 1720 (C=O), 1635 (C=C), 1582 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.55 (2H, s, $-C\underline{H}_2CO_2Me$), 3.70, 3.80, 3.81, and 3.83 (15H, each s, $-CO_2Me$ and OMe), 6.56 (2H, s, Ar–H), 7.76 (1H, s, $-CH=\underset{|}{C}-$). MS *m/e*: 324 (M^+, 100%). *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.10; H, 6.26.

Methyl Hydrogen α-(3,4-Dimethoxybenzylidene)-β-(3,4,5-trimethoxybenzylidene)succinate (4)——A solution of **3** (5.6 g) and veratraldehyde (2.8 g) in dry *t*-butanol (15 ml) was added to a stirred solution of potassium *t*-butoxide [from metallic K (1.3 g)] in dry *t*-butanol (30 ml) at room temperature over 40 min, and the solution was refluxed for 1 hr. Usual working-up similar to the foregoing afforded a brown glass (9.0 g), which was chromatographed on silica gel (225 g) in $CHCl_3$ to give **4** (4.2 g, 54%) as a pale yellow glass. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1692 (C=O), 1631 (C=C), 1600, 1582 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, $-CO_2Me$), 3.71 (9H, s, OMe), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 6.33 (1H, broad, $-CO_2H$), 6.6—7.1 (5H, m, Ar–H), 7.83 (2H, s, $-CH=\underset{|}{C}-$). MS *m/e*: 458 (M^+, 5%), 427 (100%).

3-(3,4-Dimethoxybenzylidene)-4-hydroxy-2-(3,4,5-trimethoxybenzylidene)butyric Acid (5)——A solution of **4** (1.0 g) in dry tetrahydrofuran (8 ml) and dry ether (25 ml) was added to a stirred suspension of $LiAlH_4$ (1.5 g) in dry ether (45 ml) at −50° over 0.5 hr, and the suspension was stirred at −15° for 4 hr. After addition of AcOEt and subsequently of 5% H_2SO_4, the organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with satd. NaCl and evaporated *in vacuo* below room temperature to give a pale yellow glass (1.0 g), which was purified by preparative TLC on silica gel using benzene–acetone (3:1) as a developing solvent to give **5** (0.45 g, 47%) as a pale yellow glass. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1682 (C=O), 1601, 1580 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.71 (9H, s, OMe), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 4.27 (2H, broad s, $-C\underline{H}_2OH$), 4.83 (2H, broad, $-CH_2O\underline{H}$ and $-CO_2H$), 6.6—7.4 (6H, m, Ar–H and $-CH=\underset{|}{C}-$), 7.70 (1H, s, $-CH=\underset{|}{C}-$).

3-(3,4-Dimethoxybenzylidene)-4-hydroxy-2-(3,4,5-trimethoxybenzylidene)butyric Acid γ-Lactone (6)——A solution of **5** (0.45 g) and *p*-toluenesulfonic acid (0.50 g) in dry ether (100 ml) was stirred in the dark for 48 hr at room temperature. The solution was washed with satd. $NaHCO_3$ and then satd. NaCl and evaporated *in vacuo* below room temperature to give **6** (0.29 g, 71%) as a yellow solid, mp 128—135°. IR ν_{max}^{KBr} cm^{-1}: 1759 (C=O), 1627 (C=C), 1612, 1580 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.53 (3H, s, OMe), 3.60 (6H, s, OMe), 3.73 (3H, s, OMe), 3.74 (3H, s, OMe), 4.99 (2H, d, J=2 Hz, $-CH_2OCO-$), 6.54 (1H, t, J=2 Hz, $-CH=\underset{|}{C}-$), 7.54 (1H, s, $-CH=\underset{|}{C}-$). UV λ_{max}^{EtOH} nm (log ε): 357 (3.83), 271 (4.04), 261 (4.04).

1,4-Dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3,4,5-trimethoxyphenyl)-2-naphthoic Acid γ-Lactone (β-Apoplicatitoxin Trimethyl Ether) (β-Apopicrosikkimotoxin) (8) and 1,4-Dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3,4,5-trimethoxyphenyl)-2-naphthoic Acid γ-Lactone (9)——A solution of **6** (73 mg) and DABCO (20 mg) in DMF (100 ml) was irradiated for 2 hr in a similar manner to that for **1**. After evaporation of the solution *in vacuo*, the crude product (124 mg) was purified by repeated preparative TLC on silica gel using $CHCl_3$–EtOH (50:1) as solvent to give **8** (25 mg, 34%) and **9** (11 mg, 15%).

Compound **8**: Colorless cubes (from $CHCl_3$–EtOH), mp 221—221.5°. IR ν_{max}^{KBr} cm^{-1}: 1748 (C=O), 1684 (C=C), 1612, 1589 (arom.). Compound **8** was identical with authentic β-apopicrosikkimotoxin[6] on mixture melting point and IR spectral comparison.

Compound **9**: Colorless needles (from EtOH), mp 195.5—196°. IR ν_{max}^{KBr} cm^{-1}: 1748 (C=O), 1690 (C=C), 1591 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, OMe), 3.77 (9H, s, OMe), 3.84 (3H, s, OMe), *ca.* 3.8 (2H, m, C_4–H), 4.81 (2H, broad s, $-CH_2OCO-$), 5.22 (1H, m, C_1–H), 6.43 (2H, s, C_2'– and C_6'–H), 6.90 (1H, d, J=8 Hz, C_6–H), 6.99 (1H, d, J=8 Hz, C_5–H). MS *m/e*: 412 (M^+, 95%), 168 (100%). UV λ_{max}^{EtOH} nm (log ε): 276 sh (3.44). *Anal.* Calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.94; H, 5.86.

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