Furan Derivatives. II. The Cyclization of 3-(Benzofuran-3-yl)-propionic Acid Derivatives

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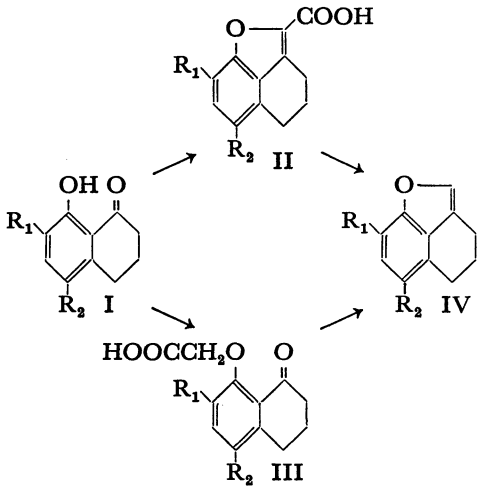
A compound, 6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-one (XX), was prepared in a 72% yield by heating 3-(5-methoxy-2,3-dihydrobenzofuran-3-yl)propionic acid (XIX) with polyphosphoric acid. However, when 3-(5-methoxybenzofuran-3-yl)propionic acid (IX) or 3-(2-benzoyl-5-methoxybenzofuran-3-yl)-propionic acid (XIII) were treated with polyphosphoric acid, the product was 7-methoxy-2,3-dihydro-1*H*-cyclopenta[*b*]benzofuran-3-one (XI) rather than the corresponding naphtho[1,8-*bc*]furan derivatives, Also, neither naphtho[1,8-*bc*]furan nor cyclopenta[*b*]benzofuran derivatives were obtained from 3-(2-benzyl-5-methoxybenzofuran-3-yl)propionic acid (XIV) or 3-(2-ethyl-5-methoxybenzofuran-3-yl)propionic acid (XVII).

Naphtho[1,8-*bc*]furans (IV) have been prepared[1] by the two methods shown in Scheme 1. The yields of carboxylic acids (II) based on tetralones (I) were almost the same as one another (40—50%), regardless of the kind of the substituents (R_1 and R_2) on the benzene ring. The yields of naphtho[1,8-*bc*]furans (IV) based on carboxylic acids (III) were found in the region of 40—70%, according to kind of substituent (R_1 and R_2). We attempted to devise a novel method to synthesize naphtho[1,8-*bc*]furans from 3-(5-methoxybenzofuran-3-yl)propionic acid (IX), as the yields of II or IV (based on I or III respectively) were not very good.

Results and Discussion

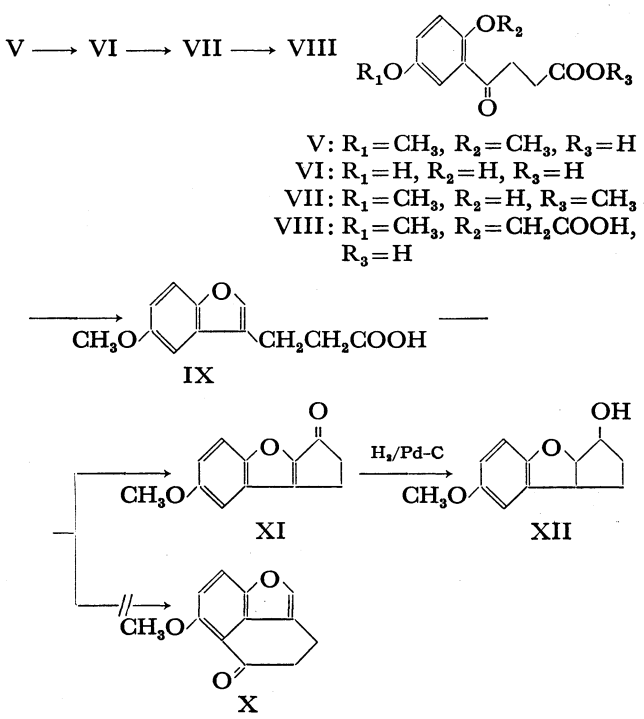
The important intermediate compound 3-(5-methoxybenzofuran-3-yl)propionic acid (IX) was obtained, as is shown in Scheme 2, according to the method of Hallmann *et al.*[2] It was expected that the naphtho-[1,8-*bc*]furan derivative (X) would be produced from IX by intramolecular cyclization. When IX was treated with polyphosphoric acid, cyclization took place[3] to give a crystalline product. However, the product was 7-methoxy-2,3-dihydro-1*H*-cyclopenta[*b*]-benzofuran-3-one (XI) rather than X. This result suggests that the furan ring is more reactive than the benzene ring. The structure of XI was determined from the spectral properties. The IR and UV spectra showed absorptions due to a conjugated-carbonyl group at 1698 cm^{-1} and at 284 (ε 24600) and 289 nm (24000) respectively. The NMR spectrum exhibited no peak corresponding to a hydrogen atom on the furan ring. The structure of XI was also supported by the catalytic hydrogenation of XI with 5% palladium–charcoal to give 7-methoxy-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-3-ol (XII).

The formation of XI rather than X in the cyclization mentioned above required us to make further attempts to prepare such benzofuran derivatives as XIII, XIV, and XVII, all of which have substituents on the 2-position of the furan ring. For this reason, the XIII compound 3-(2-benzoyl-5-methoxybenzofuran-3-yl)-propionic acid was prepared from VII and phenacyl bromide.[1] When XIII was treated with polyphos-

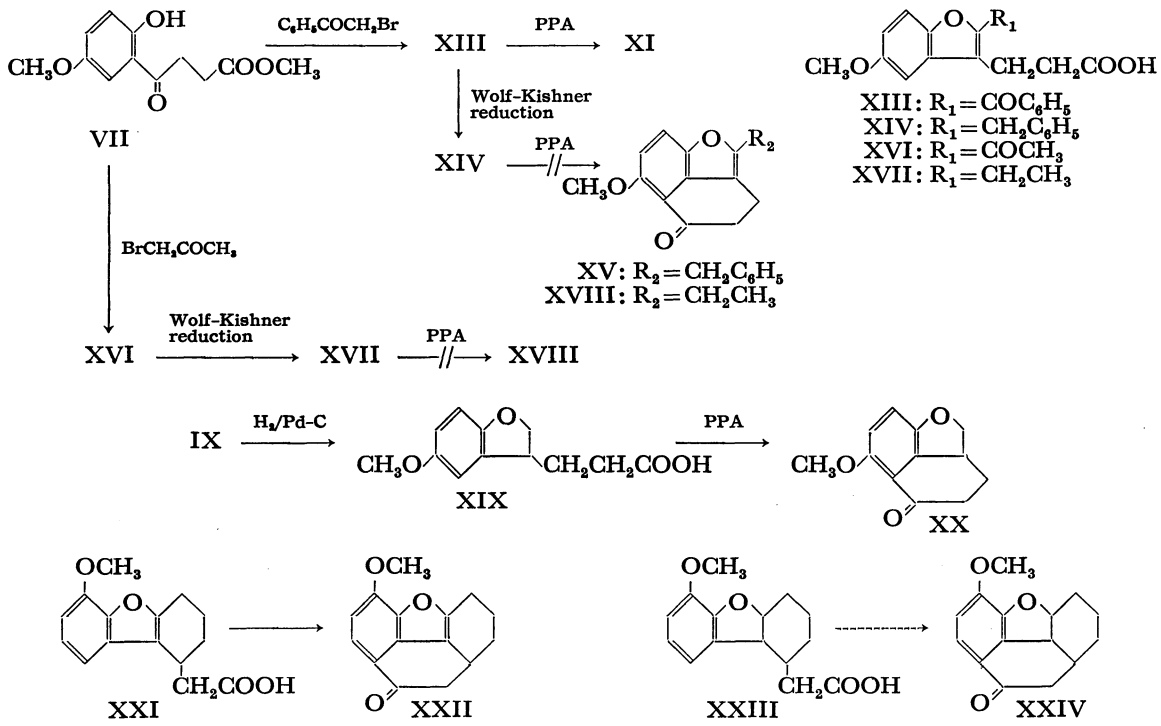


a) R_1=H, R_2=H b) R_1=H, R_2=OCH_3
c) R_1=OCH_3, R_2=H d) R_1=OCH_3, R_2=Cl

Scheme 1.



Scheme 2.



Scheme 3.

phoric acid, a carbonyl compound was produced along with benzoic acid. The carbonyl compound was identical in its IR spectra with the product (XI) obtained from the reaction between IX and polyphosphoric acid. Therefore, XIII was converted to 3-(2-benzyl-5-methoxybenzofuran-3-yl)propionic acid(XIV) by a Wolf-Kishner reduction,[4] as the benzoyl group tended to be eliminated under acidic reaction conditions and so XIV was treated with polyphosphoric acid. Nevertheless, only a tarry material was produced; the desired naphtho[1,8-*bc*]furan derivative (XV) was not obtained. Similarly, 3-(2-acetyl-5-methoxybenzofuran-3-yl)propionic acid (XVI) was prepared by the reaction between VII and bromoacetone and was reduced to 3-(2-ethyl-5-methoxybenzofuran-3-yl)propionic acid (XVII). Also, the corresponding naphtho[1,8-*bc*]furan derivative (XVIII) was not obtained by the treatment of XVII with polyphosphoric acid.

From these results, it appears difficult to convert benzofuran derivatives (IX, XIII, XIV, and XVII) where furan rings remained fully unsaturated to naphtho[1,8-*bc*]furan derivatives by intramolecular cyclization. We made a further examination of a partially saturated benzofuran derivative. The IX compound was reduced to 3-(5-methoxy-2,3-dihydrobenzofuran-3-yl)propionic acid (XIX) by catalytic hydrogenation with 10% palladium–charcoal. When XIX was treated with polyphosphoric acid,[5] the desired 6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-one (XX) was obtained in a 72% yield. Compound XX showed an absorption corresponding to the carbonyl group at 1670 cm^{-1} in the IR spectrum and peaks corresponding to two adjacent aromatic hydrogen atoms on the benzene ring at δ 6.90 (d, 1H, J=8 Hz) and 6.68 (d, 1H, J=8 Hz) in the NMR spectrum.

These results suggest that the presence of the carbon–carbon double bond of the furan ring hinders intramolecular cyclization because of the formation of by-products, but partially saturated benzofuran derivatives readily undergo cyclization to the corresponding naphtho[1,8-*bc*]furan derivatives. Dendy *et al.*[6] obtained a phenanthro[4,5-*bcd*]furan derivative (XXII) in a very poor yield from a benzofuran derivative (XXI). They ascribed this difficulty of cyclization to a strain in the fused-ring system. However, the above results suggest that the dihydrobenzofuran derivative (XXIII) may be converted to a phenanthro[4,5-*bcd*]furan derivative (XXIV) in a good yield. The reactivities of naphtho[1,8-*bc*]furans will be further investigated.

Experimental

All the melting points are uncorrected. The column chromatography was performed on silica gel (WAKOGEL C-200). The polyphosphoric acid (PPA) was prepared from 85% phosphoric acid (100 ml) and phosphorus pentoxide (125 g) by heating them at 160—165 °C for 5 h. Unless otherwise stated, anhydrous sodium sulfate was employed as the drying agent. The infrared absorption spectra were determined with a JASCO Model DS 402 G infrared spectrophotometer. The ultraviolet absorption spectra were determined with a Shimadzu Model UV-200 spectrophotometer. The nuclear magnetic resonance spectra were determined at 100 MHz with a JEOL Model 4H-100 NMR spectrometer, using tetramethylsilane as the internal standard.

3-(2,5-Dihydroxybenzoyl)propionic Acid (VI). A mixture of 3-(2,5-dimethoxybenzoyl)propionic acid (V, 20 g)[7] and pyridinium chloride (100 g) was heated for 40 min at 200 °C.[8] After cooling, the mixture was poured into dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with 1M hydrochloric acid and water, dried, and then evaporated. The residue was recrystallized from 35% aqueous

methanol to give 11.1 g (63%) of VI as orange prisms; mp 181—182 °C. IR(KBr): 3200 (OH), 1700 (COOH), 1635 (C=O), 1175 (OH), and 830 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 57.03; H, 4.80%. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%.

Methyl 3-(2-Hydroxy-5-methoxybenzoyl)propionate (VII). A mixture of VI (15.0 g), dimethyl sulfate (13.0 g), potassium carbonate (17.0 g), and acetone (50 ml) was refluxed for 2.5 hr at 62 °C.[9] After the decomposition of the dimethyl sulfate with water, the reaction mixture was extracted with ether. The ethereal layer was washed with a 1M potassium carbonate solution and water, dried, and then evaporated. The residue was chromatographed over silica gel and eluted with benzene (95)–ether (5); the first fraction gave 16.5 g (48%) of crystals. Recrystallization from ether–hexane gave yellow plates of VII; mp 41—42 °C. IR (KBr): 1726 ($COOCH_3$), 1642 (C=O), 1042 cm^{-1} (OCH_3). NMR ($CDCl_3$): δ 2.75 (t, 2H, J=7 Hz, $-CH_2-$), 3.35 (t, 2H, J=7 Hz, $-CH_2-$), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.90 (d, 1H, J=9 Hz, Ar–H), 7.10 (d, d, 1H, J=3 Hz and 9 Hz, Ar–H), 7.20 (d, 1H, J=3 Hz, Ar–H), 11.60 (s, 1H, OH). Found: C, 60.66; H, 6.06%. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%.

The yield of VII was not good because of the formation of methyl 3-(2,5-dimethoxybenzoyl)propionate and methyl 3-(2,5-dihydroxybenzoyl)propionate.

3-(2-Carboxymethoxy-5-methoxybenzoyl)propionic Acid (VIII). Compound VIII was prepared (84%) according to the method of Hallmann *et al.* Colorless prisms (from tetrahydrofuran–benzene); mp 188—189 °C. (lit,[2] mp 189—190 °C)

3-(5-Methoxybenzofuran-3-yl)propionic Acid (IX). Compound IX was also prepared (67%) according to the method of Hallmann *et al.* Colorless plates (from benzene–hexane); mp 124—125 °C. (lit,[2] mp 126—127 °C) IR (KBr): 1681 (COOH), 1620 (C=C), 792 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR (CD_3COCD_3): δ 2.73 (t, 2H, J=7 Hz, $-CH_2-$), 2.98 (t, 2H, J=7 Hz, $-CH_2-$), 3.85 (s, 3H, OCH_3), 6.90 (d, d, 1H, J=3 Hz and 8 Hz, Ar–H), 7.19 (d, 1H, J=3 Hz, Ar–H), 7.35 (d, 1H, J=8 Hz, Ar–H), 7.60 (s, 1H, furan H). UV (EtOH): λ_{max} 210 (ε 23800), 252 (8300), 304 (4100), 302 nm (3700). Though a mixture of VIII (200 mg), sodium acetate (500 mg), and acetic anhydride (7 ml) was heated for 1 h at 145 °C and for 10 min at 160 °C, only a tarry material was produced.

7-Methoxy-2,3-dihydro-1H-cyclopenta[b]benzofuran-3-one (XI). A mixture of IX (0.5 g) and polyphosphoric acid (70 g) was heated for 4 h at 80 °C with stirring. The reaction mixture was decomposed with ice–water, and the resulting precipitates were extracted with ether. The ethereal layer was washed with a 1M potassium carbonate solution and water, dried, and then evaporated. The residue was chromatographed over silica gel and eluted with benzene(92)–ether(8) to give 0.2 g (43%) of crystals; mp 136—138 °C. Recrystallization from benzene–hexane gave colorless needles of XI; mp 138—139 °C. IR (KBr): 1695 (C=O), 810 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR (CD_3COCD_3): δ 3.87 (s, 3H, OCH_3), 7.12 (d, d, 1H, J=2 Hz and 9 Hz, Ar–H), 7.28 (d, 1H, J=2 Hz, Ar–H), 7.52 (d, 1H, J=9 Hz, Ar–H). UV (EtOH): λ_{max} 219 (ε 14400), 284 (24600), 289 (24000), 325 nm (5600). Found: C, 71.09; H, 4.92%. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99%.

7-Methoxy-2, 3, 3a, 8b-tetrahydro-1H-cyclopenta [b] benzofuran-3-ol (XII). A mixture of XI (200 mg), palladium chloride (50 mg) in 0.1 M hydrochloric acid (5 ml), charcoal (100 mg), and ethanol (60 ml) was shaken under a hydrogen atmosphere for 1.5 h at room temperature. After the removal of the catalyst, the ethanol was evaporated. The residue was chromatographed over silica gel and eluted with benzene (9)–ether (1) to give 150 mg (74%) of crystals; mp 66—67 °C. Recrystallization from methanol gave XII as colorless plates; mp 68—69 °C. IR (KBr): 3530 (OH), 1100 (C–OH), 1030 cm^{-1} (OCH_3). NMR (CCl_4): δ 1.20—1.95 (m, 4H, $-CH_2-$+ $-CH_2-$), 2.35 (s, 1H, OH), 3.67 (s, 3H, OCH_3), 3.70 (m, 1H, =CH–), 4.87 (d, d, 1H, J=5 Hz and 7 Hz, a hydrogen atom on the 3a carbon atom), 6.53 (s, 3H, Ar–H). UV (EtOH): λ_{max} 204 (ε 14300), 230 (4200), 300 nm (2900). Found: C, 69.73; H, 6.74%. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%.

3-(2-Benzoyl-5-methoxybenzofuran-3-yl)propionic Acid (XIII). A mixture of VII (1.5 g), phenacyl bromide (6.1 g), and potassium carbonate (4.4 g) was heated for 3 h at 140 °C. The reaction mixture was then extracted with acetone, and the acetone was evaporated. The residue was dissolved in a small amount of ethanol and hydrolyzed with a 3M potassium hydroxide solution. The alkaline solution was acidified with 6M hydrochloric acid, and the resulting precipitates were extracted with ether. The ethereal layer was then extracted with a 1M potassium carbonate solution, and the alkaline solution was acidified with 6M hydrochloric acid. The resulting precipitates were extracted with ether, and the ethereal layer was washed with water, and then evaporated. The residue was triturated with benzene to give 0.8 g (57%) of crystals; mp 169—170 °C. Recrystallization from methanol gave colorless needles of XIII; mp 171—172 °C. IR (KBr): 1720 (COOH), 1637 (C=O), 1027 (OCH_3), 810 cm^{-1} (two adjacent aromatic hydrogen atoms). UV(EtOH): λ_{max} 207 (ε 33000), 257 (9300), 317 nm (20900). Found: C, 70.39; H, 5.13%. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98%.

The Formation of XI from XIII. A mixture of XIII (100 mg) and polyphosphoric acid (10 g) was heated with stirring for 4 hr at 90 °C. The reaction mixture was then decomposed with ice–water and extracted with ether. The ethereal layer was washed with a 1M potassium carbonate solution and water, dried, and then evaporated. The residue was chromatographed over silica gel and eluted with benzene (92)–ether (8) to give 20 mg (33%) of crystals; mp 135—136 °C. Recrystallization from benzene–hexane gave colorless needles of XI; mp 138—139 °C. The compound was identical in its IR spectra with the sample prepared from IX and polyphosphoric acid.

3-(2-Benzyl-5-methoxybenzofuran-3-yl)propionic Acid (XIV). A mixture of XIII (500 mg), 80% hydrazine hydrate (2.5 g), potassium hydroxide (7.0 g), and triethylene glycol (25 ml) was heated for 1 h at 140 °C; the temperature was thereafter gradually raised to 190 °C, after which the mixture was kept for 4 h at that temperature. The reaction mixture was poured into ice–water, acidified with 6M hydrochloric acid, and then extracted with ether. The ethereal layer was washed with water, dried, and then evaporated. The residue was chromatographed on silica gel and eluted with benzene (9)–ether (1) to give 220 mg (46%) of crystals; mp 116—117 °C. Recrystallization from ether–hexane gave colorless needles of XIV; mp 117—118 °C. IR (KBr): 1700 (COOH), 1624 (C=C), 803cm^{-1} (two adjacent aromatic hydrogen atoms). NMR ($CDCl_3$): δ 2.66 (d, 2H, J=7 Hz, $-CH_2-$), 2.92 (d, 2H, J=7 Hz, $-CH_2-$), 3.80 (s, 3H, OCH_3), 4.06 (s, 2H, $-CH_2-$), 6.79 (d, d, 1H, J=2 Hz and 8 Hz, Ar–H), 6.93 (d, 1H, J=2 Hz, Ar–H), 7.22 (s, 5H, Ar–H), 7.25 (d, d, 1H, J=1 Hz and 8 Hz, Ar–H), 9.66 (broad s, 1H, COOH). UV (EtOH): λ_{max} 210 (ε 31400), 255 (14000), 292 (5600), 302 nm (5000). Found: C, 73.51; H, 5.85%. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85%. Though a mixture of XIV (100 mg) and polyphosphoric acid (14 g) was heated with stirring for 4 h at 90 °C, XV was not obtained.

3-(2-Acetyl-5-methoxybenzofuran-3-yl)propionic Acid (XVI).

A mixture of VII (2.0 g), bromoacetone (7.0 g), and potassium carbonate (7.0 g) was refluxed for 4 h at 120 °C. The reaction mixture was then extracted with acetone, and the acetone was evaporated. The residue was dissolved in a small amount of ethanol and hydrolyzed with a 3M potassium hydroxide solution. The alkaline solution was acidified with 6M hydrochloric acid, and the resulting precipitates were extracted with ether. The ethereal layer was washed with water, dried, and then evaporated. The residue was chromatographed on silica gel and eluted with benzene (8)–ether (2) to give 1.0 g (44%) of crystals; mp 124—126 °C. Recrystallization from aqueous methanol gave colorless needles of XVI; mp 124—126 °C. IR (KBr): 1710 (COOH), 1675 (C=O), 800 cm^{-1} (two adjacent aromatic hydrogen atoms). UV (EtOH): λ_{max} 205 (ε 21500), 296 nm (17800). Found: C, 63.90; H, 5.31%. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38%.

3-(2-Ethyl-5-methoxybenzofuran-3-yl)propionic Acid (XVII). Compound XVII was obtained (54%) by a method similar to the preparation of XIV from XIII. Recrystallization from ether–hexane gave colorless prisms; mp 86—87 °C. IR (KBr): 1713 (COOH) and 813 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR ($CDCl_3$): δ 1.25 (t, 3H, J=7 Hz, CH_3), 2.50—3.00 (m, 6H, $-CH_2-$), 3.82 (s, 3H, OCH_3), 6.80 (d, d, 1H, J=2 Hz and 8 Hz, Ar–H), 6.92 (d, 1H, J=2 Hz, Ar–H), 7.26 (d, d, 1H, J=1 Hz and 8 Hz, Ar–H), 9.91 (broad s, 1H, COOH). Found: C, 67.79; H, 6.50%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. Though a mixture of XVII (100 mg) and polyphosphoric acid (8 g) was heated with stirring for 6 h at 90 °C, XVIII was not obtained.

3-(5-Methoxy-2,3-dihydrobenzofuran-3-yl)propionic Acid (XIX). A mixture of IX (300 mg), 10% palladium–charcoal (200 mg), and ethanol (70 ml) was shaken under a hydrogen atmosphere for 20 h at room temperature. After the subsequent removal of the catalyst, the ethanol was evaporated to give 280 mg (92%) of crystals; mp 94—96 °C. Recrystallization from benzene–hexane gave colorless plates of XIX; mp 96—97 °C. IR (KBr): 1692 (COOH), 1033 (OCH_3), 800 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR ($CDCl_3$): δ 2.00 (m, 2H, $-CH_2-$), 2.42 (t, 2H, J=6 Hz, $-CH_2-$), 3.47 (m, 1H, =CH–), 3.77 (s, 3H, OCH_3), 4.20 (d, d, 1H, J=5 Hz and 9 Hz, $-CH_2-$), 4.60 (t, 1H, J=9 Hz, –OCH–), 6.70 (s, 2H, Ar–H), 6.76 (s, 1H, Ar–H), 10.90 (broad s, 1H, COOH). UV (EtOH): λ_{max} 204 (ε 16400), 230 (6300), 299 nm (4800). Found: C, 64.66; H, 6.22%. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%.

6-Methoxy-2a,3,4,5-tetrahydro-2H-naphtho[1,8-bc]furan-5-one (XX). A mixture of XIX (300 mg) and polyphosphoric acid (30 g) was heated with stirring for 4 h at 80 °C. The reaction mixture was then decomposed with ice–water, and the resulting precipitates were extracted with ether. The ethereal layer was washed with a 1M potassium carbonate solution and water, dried, and then evaporated to give 200 mg (72%) of crystals; mp 102—103 °C. Recrystallization from benzene–hexane gave colorless prisms of XX; mp 104—105 °C. IR (KBr): 1670 (C=O), 832 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR ($CDCl_3$): δ 3.72 (m, 1H, =CH–), 3.88 (s, 3H, OCH_3), 4.10 (d, d, 1H, J=9 Hz and 10 Hz, –OCH–), 4.84 (t, 1H, J=9 Hz, –OCH–), 6.80 (d, 1H, J=8 Hz, Ar–H), 6.91 (d, 1H, J=8 Hz, Ar–H). Found: C, 70.37; H, 6.05%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

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