Studies on Uricosuric Diuretics. V.[1] Convenient and Efficient Synthesis of 2,3-Dihydrobenzofuran Derivatives

Haruhiko SATO,* Kiyonori KUROMARU, Takenori ISHIZAWA, Bunya AOKI, and Hiroshi KOGA*

Exploratory Research Laboratories, Chugai Pharmaceutical Co., Ltd., 135 Komakado 1-chome, Gotemba-shi, Shizuoka 412, Japan.
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A practical procedure for synthesis of a new uricosuric agent, 5-chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-carboxylic acid (1, AA-193) is described, which starts from 2,5-dichlorophenol (3b) and involves 5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole (2) as the key intermediate. Successive treatment of 3b with benzoyl chloride–aluminum chloride ($AlCl_3$) and hot ethanolic sodium hydroxide gives 4-benzoyl-2,5-dichlorophenol (8, 61%), which is oximated with hydroxylamine hydrochloride and then transformed into the benzisoxazole 2 (88%) with potassium hydroxide in *N*,*N*-dimethylformamide (DMF) (method C). The reaction of 2 with aqueous formaldehyde and dimethylamine affords the Mannich base 11a (97%), which is treated with a sulfonium ylide 12, 14 or 15 followed by heating with sodium hydroxide (NaOH) in ethanol (EtOH) to give 1 in high yield (method E).

Keywords uricosuric agent; 5-chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-carboxylic acid; 5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole; AA-193

Since the discovery of tienilic acid {[2,3-dichloro-4-(2-thenoyl)phenoxy]acetic acid} as an uricosuric diuretic, a number of structurally related compounds have been synthesized.[2] In the course of our investigations on tienilic acid analogues, we have found that the 2,3-dihydrobenzofuran derivative (AA-193, **1**) possessed a potent uricosuric activity with little diuretic activity.[3] It is currently undergoing clinical evaluation as a new uricosuric agent.[4]

For the large-scale preparation of **1**, we investigated practical procedures for synthesis of **1**, particularly for construction of the 1,2-benzisoxazole moiety and the 2,3-dihydrobenzofuran ring.[3] Although there are a few reports on the preparation of the 1,2-benzisoxazole moiety and the 2,3-dihydrobenzofuran ring, none of them seems to be satisfactory for our purpose. Shutske *et al.*[2d] have reported the synthesis of the 1,2-benzisoxazole moiety from 2-(α-hydroxyiminobenzyl)chlorobenzene or 2-(α-hydroxyiminobenzyl)phenol. However, the former method resulted in a relatively low yield of benzisoxazole due to the unfavorable presence of the *E*-isomer of the oxime, and the latter method produced the benzoxazole derivative as a by-product, causing a marked decrease in the yield of the benzisoxazole derivative. Hoffman *et al.*[2c] have reported a preparation of 2,3-dihydrobenzofuran by the oxidative cyclization of *o*-allylphenol (Hoffman's method). We applied this to the synthesis of **1**,[3] but found that the method is not readily applicable to large-scale preparation. Yodo and Harada[5] have recently reported an improved Hoffman's method. Lehmann[6a] and Cadona and Croce[6b] have also reported that reaction of phenolic Mannich base methiodides with sulfonium methylides gave 2,3-dihydrobenzofurans.

In this paper, we describe some improved synthetic methods for AA-193 (**1**), including a practical preparative method.

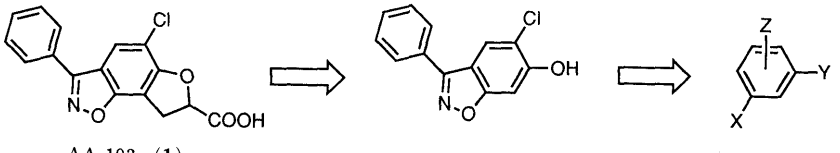
Results and Discussion

We chose 5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole (**2**) as the key intermediate. The retrosynthetic pathway of **1** is shown in Chart 1.

At first we investigated the construction of **2** from **3**. Resorcinol dimethyl ether (**3a**) was treated with sulfuryl chloride in chloroform followed by the action of benzoyl chloride and $AlCl_3$ in 1,2-dichloroethane to give 4-benzoyl-6-chlororesorcinol (**4**) in 81% yield. Heating of **4** with hydroxylamine hydrochloride in pyridine provided an oxime **5** which was cyclized according to the reported method,[2d] to afford the desired benzisoxazole **2**, but only in a low yield of 36%, along with the benzoxazole isomer **6** in 14% yield. The benzoxazole **6** apparently arose from the Beckmann rearrangement of the oxime intermediate with intramolecular capture by the phenol (method A in Chart 2).

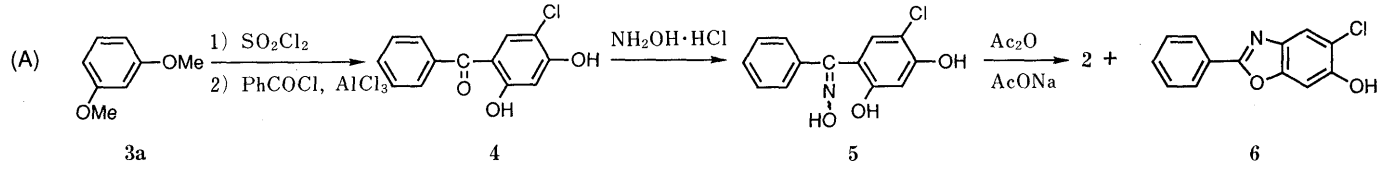
To prevent the undesirable Beckmann rearrangement, the phenol **4** was tosylated followed by addition of hydroxylamine hydrochloride to give the oxime **7** in 97% yield. This oxime **7** was smoothly cyclized upon treatment with potassium hydroxide in *N*-methyl-2-pyrrolidinone, possibly by an intramolecular nucleophilic attack of the oxime anion on the *o*-carbon atom, to afford **2** in 60% yield (method B).

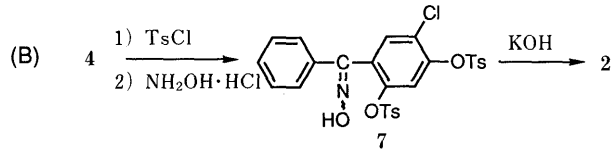
A chloro group as a leaving group was also used for the cyclization of the oxime to the isoxazole ring. The phenol **3b** was acylated with benzoyl chloride and $AlCl_3$ in 1,2-dichloroethane followed by heating with 2 N NaOH in EtOH to give 4-benzoyl-2,5-dichlorophenol (**8**) in 61% yield. Treatment of **8** with hydroxylamine hydrochloride followed by the action of potassium hydroxide in *N*,*N*-dimethylformamide (DMF) at refluxing temperature gave **2** in 88% yield (method C). This method was the best



AA-193 (**1**) **2** **3**

Chart 1





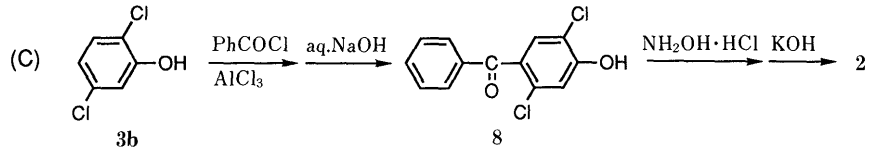
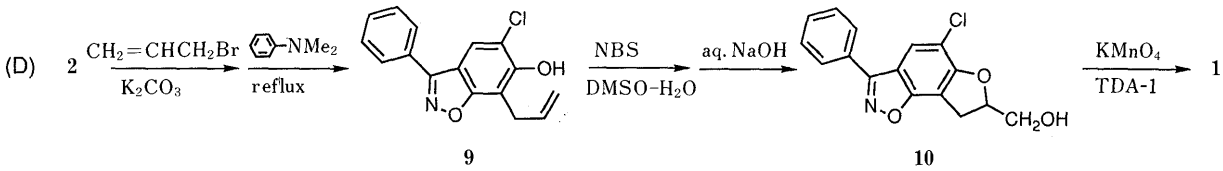


Chart 2



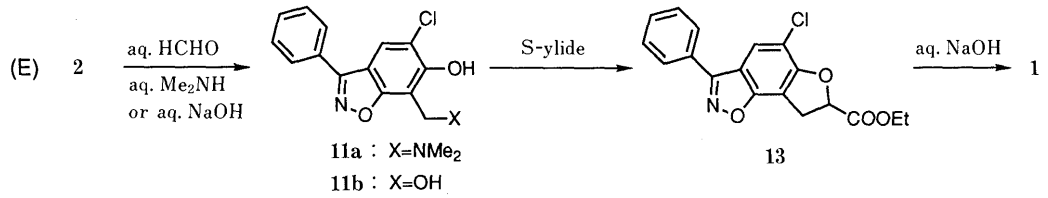


Chart 3

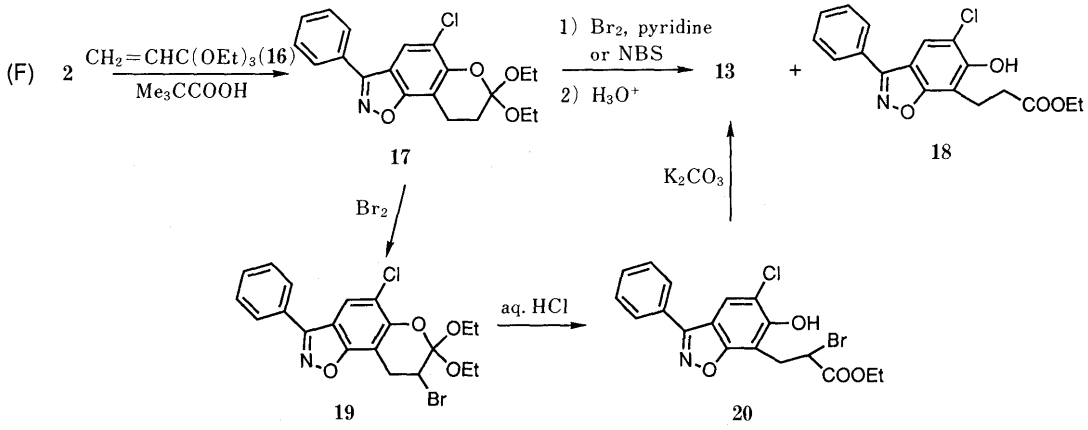


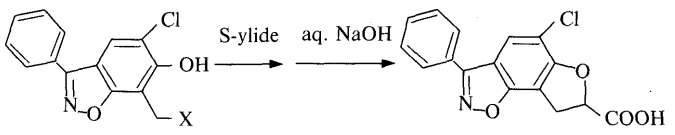
Chart 4

for large-scale preparation of **2**, and the total yield from **3b** was 54%.

Subsequently the conversion of **2** into the desired **1** was examined. Three synthetic methods studied are shown in Charts 3 and 4.

We have previously reported the synthesis of **1** through 7-allyl-5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole (**9**) and 5-chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-methanol (**10**),[3] according to Hoffman's method.[2c] In this method, a peracid was needed for the oxidative cyclization of **9** to **10**, and chromium(VI) oxide, which would produce a disposal problem if used on a large scale, was used for the oxidation of **10** to **1**. To overcome these problems, a method through a bromohydrin intermediate was investigated. Thus, treatment of the *o*-allylphenol **9** with *N*-bromosuccinimide (NBS) and H_2O in dimethyl sulfoxide (DMSO) gave the corresponding bromohydrin, which was cyclized to **10** upon treatment with 1 N NaOH in 85% yield. Oxidation of **10** with potassium permanganate ($KMnO_4$) in the presence of TDA-1 {tris[2-(2-methoxyethoxy)ethyl]amine} as a catalyst gave **1** in 43% yield (method D).

TABLE I



11 a: X=NMe_2
11 b: X=OH

1

Starting compd.	S-Ylide	Yield (%)
11a	$Me_2S^+C^-HCOOEt$ (**12**)	96
11a	$Me_2S^+(O)C^-HCOOEt$ (**14**)	80
11a	$(HOCH_2CH_2)_2S^+C^-HCOOEt$ (**15**)	80
11b	**12**	81
11b	**15**	51

In an alternative route, the phenol **2** was treated with aqueous formaldehyde and dimethylamine to give the Mannich base, 5-chloro-6-hydroxy-7-dimethylaminomethyl-3-phenyl-1,2-benzisoxazole (**11a**), in 97% yield. This compound **11a**, without being transformed to the Mannich base methiodide, was allowed to react with dimethylsulfonium carbethoxymethylide (**12**)[7] to afford an ester **13** in 97% yield. Hydrolysis of **13** with aqueous sodium hydroxide gave **1** in 99% yield (method E). This route was previously reported in reference 3.

Although this method is very useful for the preparation of **1**, dimethylsulfide, the precursor of the ylide **12**, which is also regenerated during the reaction of **11a** and **12**, is malodorous, and there is a problem in applying it to the large-scale preparation of **1**. Therefore, we sought an odorless ylide precursor and found that DMSO and bis(2-hydroxyethyl)sulfide were satisfactory for the purpose. The Mannich base **11a** was treated with dimethyloxosulfonium carbethoxymethylide (**14**)[8] or bis(2-hydroxyethyl)sulfonium carbethoxymethylide (**15**), followed by alkaline hydrolysis of the resulting ester **13**, to give **1** in high yield (Table I). The route using the ylide **15** is especially useful for the large-scale preparation of **1**. The 2-hydroxymethyl phenol **11b**, which was obtained by reaction of **2** with aqueous formaldehyde and sodium hydroxide in 98% yield, was also useful for the preparation of **1**, like the Mannich base **11a**, although the yields were slightly lower (Table I). We have already reported that method E was also very useful for the preparation of AA-193 derivatives.[3] Furthermore, it seemed to be very versatile as a general synthetic method for 2,3-dihydrobenzofurans compared to the reported method.[2c,5]

We further explored an alternate route to **1** from the phenol **2** (Chart 4). The phenol **2** was treated with triethyl orthoacrylate (**16**)[9] in refluxing toluene containing pivalic acid[10] for 5 h to afford a chroman **17** in 97% yield. A stirred mixture of **17** and pyridine in chloroform was treated with bromine at 0°C. The mixture was stirred at room temperature for 24 h, refluxed for 4 h, and treated with aqueous hydrochloric acid (HCl) at room temperature for 2 h to give **13** in 65% yield along with **18** in 29% yield. The reaction was found to proceed through intermediates **19** and **20**. Thus, when **17** was treated with bromine in the presence of pyridine, **19** was obtained in 33% yield together with **18**. The bromide **19** was susceptible to hydrolysis with aqueous HCl to give **20** in 98% yield, and this product was easily cyclized to **13** by treatment with K_2CO_3 in DMF at room temperature in 75% yield. The ester **18** was recovered when treated with bromine under the above conditions. It was found that NBS was also useful as the brominating agent in the place of bromine (the yield of **13** from **17** was 46%).

As a result, we have successfully developed practical synthetic methods for AA-193 (**1**), through the key intermediate **2** by a combination of methods C and E.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-24B spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are given in Hertz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, br=broad. For column chromatography, Wakogel C-200 (Wako, 0.074—0.149 mm) was used.

4-Benzoyl-6-chlororesorcinol (4). Method A Resorcinol dimethyl ether (50.4 g, 0.37 mol) was dissolved in $CHCl_3$ (500 ml) and the solution was cooled to 0—5 °C. SO_2Cl_2 (31 ml, 0.39 mol) was added portionwise to the solution and the resulting mixture was warmed to room temperature over a 5 h period, left to stand overnight, and evaporated to give crude 4-chloro-1,3-*O*,*O*-dimethylresorcinol. This crude resorcinol and benzoyl chloride (52.9 g, 0.38 mol) were dissolved in 1,2-dichloroethane (500 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (51.6 g, 0.39 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 3 h period. Further $AlCl_3$ (61.4 g, 0.46 mol) was added to the solution, and the resulting mixture was heated at 50 °C for 1 h, then cooled. Ice-water and concentrated (conc.) HCl were added to the reaction mixture, and the whole was stirred for 30 min. The slurry formed was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from toluene gave **4** (73.6 g, 81%) as crystals, mp 142—143.5 °C. *Anal.* Calcd for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65. Found: C, 62.87; H, 3.52. MS *m/z*: 248 (M^+), 247. IR (KBr) cm^{-1}: 3388 (OH), 1632 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 6.63 (1H, s, 2-H), 7.50 (1H, s, 5-H), 7.30—7.84 (5H, m, arom. H), 10.70 (1H, br s, OH), 12.37 (1H, br s, OH).

5-Chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole (2) and 5-Chloro-6-hydroxy-2-phenylbenzoxazole (6) A mixture of **4** (3.05 g, 0.012 mol) and $NH_2OH \cdot HCl$ (8.41 g, 0.12 mol) in pyridine (30 ml) was refluxed for 2 h, and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dired over Na_2SO_4, and evaporated to give 4-chloro-6-(α-hydroxyiminobenzyl)resorcinol (**5**). A mixture of this crude resorcinol, acetic anhydride (3.84 g, 0.038 mol), and sodium acetate (3.14 g, 0.038 mol) in DMF (40 ml) was refluxed for 2.5 h. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, evaporated, and chromatographed on silica gel with 1% MeOH–CH_2Cl_2 to give **2**[3] (1.10 g, 36%) and **6**[3] (0.42 g, 14%).

Compound 2. Method B A mixture of **4** (10.16 g, 0.041 mol) and tosyl chloride (16.33 g, 0.084 mol) in pyridine (100 ml) was refluxed for 2 h. After addition of $NH_2OH \cdot HCl$ (6.14 g, 0.084 mol), the solution was refluxed for a further 3 h and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 4-chloro-6-(α-hydroxyiminobenzyl)-1,3-*O*,*O*-ditosylresorcinol (**7**) (22.8 g, 97%). A mixture of this resorcinol (0.97 g, 1.7 mmol) and powdered KOH (1.12 g, 17 mmol) in *N*-methyl-2-pyrrolidinone (10 ml) was heated at 110 °C for 5 h. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with saturated (sat.) $NaHCO_3$ and sat. NaCl, dried over Na_2SO_4, evaporated, and chromatographed on silica gel with hexane–AcOEt to give **2** (0.25 g, 60%).

4-Benzoyl-2,5-dichlorophenol (8). Method C 2,5-Dichlorophenol (51 g, 0.31 mol) and benzoyl chloride (102.7 g, 0.73 mol) were dissolved in 1,2-dichloroethane (500 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (102.4 g, 0.77 mol) was added portionwise to the solution, and the resulting mixture was refluxed for 33 h, then cooled. Ice-water and conc. HCl were added to the reaction mixture, and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O–AcOEt. The extract

was washed with H_2O, dried over Na_2SO_4, and evaporated. A 4 N NaOH solution (500 ml) was added to a solution of the resulting residue in EtOH (50 ml) at room temperature. The mixture was refluxed for 30 min and then cooled. The mixture was neutralized with conc. HCl and then weakly basified with sat. $NaHCO_3$. The deposited crystals were collected by filtration, washed with H_2O, and dried. Recrystallization from toluene gave **8** (50.8 g, 61%) as a crystals, mp 161—163 °C. *Anal.* Calcd for $C_{13}H_8Cl_2O_2$: C, 58.46; H, 3.02. Found: C, 58.46; H, 2.92. MS *m/z*: 266 (M^+). IR (KBr) cm^{-1}: 1638 (C=O), 1590. NMR ($CDCl_3$–DMSO-d_6) δ: 7.08 (1H, s, 6-H), 7.30 (1H, s, 3-H), 7.20—7.90 (5H, m, arom. H), 10.55 (1H, br s, OH).

Compound 2 A mixture of **8** (50.8 g, 0.19 mol) and $NH_2OH \cdot HCl$ (21.2 g, 0.30 mol) in pyridine (400 ml) was refluxed for 2.5 h, and evaporated. Powdered KOH (69.4 g, 1.2 mol) was added to a stirred solution of this oxime in DMF (500 ml), and the mixture was refluxed for 12 h. After cooling, the mixture was acidified with aqueous HCl. The deposited crystals were collected by filtration, washed with H_2O, and dried. Recrystallization from AcOEt–hexane gave **2** (41.1 g, 88%).

5-Chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-methanol (10). Method D NBS (0.68 g, 3.8 mmol) and H_2O (0.34 ml, 19 mmol) were added to a stirred solution of 7-allyl-5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole (**9**)[3] (0.55 g, 1.9 mmol) in DMSO (9.5 ml), at 0—5 °C. The solution was stirred at room temperature for 22 h. Then H_2O (12 ml) was added to the reaction mixture, and the whole was stirred for 30 min. The solvent was decanted off and the residual oil was washed several times with H_2O by decantation. A 1 N NaOH solution (3.8 ml) was added to this crude bromohydrin and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **10**[3] (0.49 g, 85%).

5-Chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-carboxylic Acid (1) A mixture of **10** (0.18 g, 0.6 mmol), $KMnO_4$ (0.28 g, 1.8 mmol), and TDA-1 (0.19 ml, 0.6 mmol) in 1,2-dichloroethane (8 ml) was refluxed for 1.5 h, then cooled. A solution of Na_2SO_3 (0.19 g, 1.8 mmol) in H_2O (8 ml) was added and the mixture was stirred for 30 min. Then 4 N HCl (2 ml) and Et_2O were added and the whole was filtered. The filtrate was extracted with aqueous NaOH. The aqueous solution was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **1**[3] (80 mg, 43%).

Compound **1** was synthesized by method E starting from **2** through 5-chloro-6-hydroxy-7-dimethylaminomethyl-3-phenyl-1,2-benzisoxazole (**11a**) and ethyl 5-chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-carboxylate (**13**). This route using the ylide **12** was previously reported.[3]

The Synthesis of **1** Using the Ylide **14**[8]: Ethyl chloroformate (1.1 g, 0.01 mol) was added to a mixture of trimethylsulfoxonium iodide (2.2 g, 0.01 mol) and sodium hydride (60%) (0.8 g, 0.02 mol) in DMF (20 ml) at room temperature. Then **11a** (1.0 g, 0.0033 mol) was added to the solution and the mixture was heated at 90—100 °C for 9 h. Ice-water and conc. HCl were added to the solution and the mixture was extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give the crude ester. This ester was taken up in EtOH (10 ml), 1 N NaOH (10 ml) was added, and the mixture was heated at 80—90 °C for 30 min, then cooled. H_2O and Et_2O were added to the solution. The resulting mixture was extracted with H_2O and washed with Et_2O. The aqueous solution was acidified with HCl and extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **1** (0.83 g, 80%).

The Synthesis of **1** Using the Ylide **15**: A mixture of bis(2-hydroxyethyl)sulfide (1.22 g, 0.010 mol) and $BrCH_2COOEt$ (1.67 g, 0.010 mol) was left to stand overnight. The resulting gum was taken up inDMF (20 ml), and K_2CO_3 (1.4 g, 0.010 mol) was added at room temperature. Then **11a** (1.0 g, 0.0033 mol) was added to the solution and the mixture was heated at 60—70 °C for 8 h. After the solution had been cooled, 1 N NaOH (25 ml) was added and the mixture was heated at 60—70 °C for 30 min. Ice-water and conc. HCl were added to the solution and the mixture was extracted with Et_2O–AcOEt. The organic phase was extracted with aqueous $NaHCO_3$. The aqueous phase was acidified with HCl and extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **1** (0.83 g, 80%).

5-Chloro-6-hydroxy-7-hydroxymethyl-3-phenyl-1,2-benzisoxazole (11b) A mixture of **2** (6.0 g, 0.024 mol) and NaOH (2.0 g, 0.05 mol) in H_2O (100 ml) was treated with 35% HCHO (10.8 g, 0.13 mol) and the resulting mixture was heated at 70 °C for 3 h. Ice-water and conc. HCl were added to the solution and the mixture was extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **11b** (6.6 g, 98%) as crystals (acetone–H_2O), mp 155—157 °C (AcOEt). *Anal.* Calcd for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.66; N, 5.08. Found: C, 61.01; H, 3.60; N, 4.96. MS *m/z*: 275 (M^+). IR (KBr) cm^{-1}: 3352 (OH), 1618. NMR ($CDCl_3$–DMSO-d_6) δ: 5.05 (2H, s, CH_2OH), 7.25—7.57 (3H, m, arom. H), 7.64 (1H, s, 4-H), 7.57—7.95 (2H, m, arom. H), 9.50 (1H, br s, OH).

5-Chloro-7,7-diethoxy-3-phenylisoxazolo[5,4-*f*]chroman (17) A mixture of **2** (2.46 g, 0.01 mol), triethyl orthoacrylate (**16**)[9] (3.48 g, 0.02 mol), pivalic acid (2.04 g, 0.02 mol), and toluene (15 ml) was refluxed for 5 h. Ice-water and aqueous NaOH were added to the solution and the mixture was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from CH_2Cl_2–hexane gave **17** (3.6 g, 97%) as crystals, mp 121.5—123 °C. *Anal.* Calcd for $C_{20}H_{20}ClNO_4$: C, 64.26; H, 5.39; N, 3.75. Found: C, 64.24; H, 5.44; N, 3.89. MS *m/z*: 373 (M^+). IR (KBr) cm^{-1}: 2976, 1620. NMR ($CDCl_3$) δ: 1.20 (6H, t, J=7.6 Hz, CH_2CH_3), 2.18 (2H, t, J=6.4 Hz, Ph–CH_2–CH_2), 3.11 (2H, t, J=6.4 Hz, Ph–CH_2), 3.73 (4H, q, J=7.6 Hz, CH_2CH_3), 7.24—7.58 (3H, m, arom. H), 7.62 (1H, s, 4-H), 7.68—7.94 (2H, m, arom. H).

Ethyl 5-Chloro-7,8-dihydro-3-phenylfuro[2,3-*g*]-1,2-benzisoxazole-7-carboxylate (13) and Ethyl 3-5′-Chloro-6′-hydroxy-3′-phenyl-1′,2′-benziso-xazol-7′-ylpropionate (18) Compound **17** (1.5 g, 4 mmol) and pyridine (0.35 g, 4.4 mmol) were dissolved in $CHCl_3$ (20 ml) and the solution was cooled to 0—5 °C. Br_2 (0.70 g, 4.4 mmol) in $CHCl_3$ (5 ml) was added portionwise to the solution, and the resulting mixture was stirred at room temperature for 24 h, then refluxed for 4 h, and evaporated. The resulting residue was dissolved in Et_2O (30 ml), 10% HCl (50 ml) was added to this solution, and the resulting mixture was stirred at room temperature for 2 h. The mixture was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, evaporated, and chromatographed on silica gel with CH_2Cl_2 to give **13** (0.9 g, 65%) and **18** (0.4 g, 29%). Product **18**: mp 107—110 °C (Et_2O). *Anal.* Calcd for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.63; H, 4.52; N, 4.02. MS *m/z*: 345 (M^+). IR (KBr) cm^{-1}: 1728 (COOEt). NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.2 Hz, CH_3), 2.74 (1H, dd, J=6, 2 Hz, Ph–CH_2–CH_2), 2.86 (1H, d, J=6 Hz, Ph–CH_2–CH_2), 3.17 (1H, d, J=6 Hz, Ph–CH_2–CH_2), 3.28 (1H, dd, J=6, 2 Hz, Ph–CH_2), 4.10 (2H, q, J=7.2 Hz, CH_2CH_3), 7.34—7.68 (3H, m, arom. H), 7.74 (1H, s, 4′-H), 7.68—8.10 (2H, m, arom. H), 7.91 (1H, br s, OH).

8-Bromo-5-chloro-7,7-diethoxy-3-phenylisoxazolo[5,4-*f*]chroman (19) Compound **17** (2.00 g, 5.4 mmol) and pyridine (0.75 g, 9.5 mmol) were dissolved in $CHCl_3$ (20 ml) and the solution was cooled to 0—5 °C. Br_2 (0.93 g, 5.8 mmol) in $CHCl_3$ (10 ml) was added portionwise to the solution, and the resulting mixture was stirred at room temperature for 24 h, then refluxed for 13 h, and evaporated. H_2O was added to the residue, and the resulting mixture was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, evaporated, and chromatographed on silica gel with CH_2Cl_2–hexane to give **19** (0.80 g, 33%) and **18** (0.50 g, 27%). Product **19**: mp 135—136 °C (Et_2O). *Anal.* Calcd for $C_{20}H_{19}BrClNO_4$: C, 53.06; H, 4.23; N, 3.09. Found: C, 53.03; H, 4.08; N, 3.11. MS *m/z*: 451 (M^+). IR (KBr) cm^{-1}: 2980, 1624. NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.2 Hz, CH_3), 1.27 (3H, t, J=7.2 Hz, CH_3), 3.50—4.10 (6H, m, $CH_2CH_3 \times 2$, CH_2CHBr), 4.55 (1H, t, J=6 Hz, CHBr), 7.35—7.67 (3H, m, arom. H), 7.67—8.04 (2H, m, arom. H), 7.77 (1H, s, 4-H).

Ethyl 2-Bromo-3-5′-chloro-6′-hydroxy-3′-phenyl-1′,2′-benzisoxazol-7′-ylpropionate (20) A mixture of **19** (0.64 g, 1.4 mmol), 6 N HCl (60 ml), and Et_2O (60 ml) was stirred at room temperature for 16 h, then extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **20** (0.59 g, 98%) as crystals (CH_2Cl_2–Et_2O), mp 129.5—131.5 °C. *Anal.* Calcd for $C_{18}H_{15}BrClNO_4$: C, 50.91; H, 3.56; N, 3.30. Found: C, 50.89; H, 3.40; N, 3.33. MS *m/z*: 423 (M^+), 378. IR (KBr) cm^{-1}: 3320, 1736 (COOEt). NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.2 Hz, CH_3), 3.67 (2H, d, J=8 Hz, CH_2CHBr), 4.15 (2H, q, J=7.2 Hz, CH_2CH_3), 4.79 (1H, t, J=8 Hz, CHBr), 6.85 (1H, br s, OH), 7.27—7.57 (3H, m, arom. H), 7.69 (1H, s, 4′-H), 7.57—7.97 (2H, m, arom. H).

Compound 13 A mixture of **20** (0.46 g, 1.1 mmol), K_2CO_3 (0.32 g, 2.3 mmol), and DMF (10 ml) was stirred at room temperature for 6 h. H_2O was added, and the resulting mixture was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **13** (0.28 g, 75%).

The Synthesis of **13** Using NBS in Place of Bromine: Compound **17** (0.50 g, 1.3 mmol) was dissolved in $CHCl_3$ (5 ml) and the solution was cooled to 0—5 °C. NBS (0.26 g, 1.5 mmol) was added portionwise to the solution, and the resulting mixture was stirred at room temperature for 6 d. Conc. HCl (5 ml) was added to the solution, and the resulting mixture

was stirred at room temperature for 2 h. H_2O was added, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, evaporated, and chromatographed on silica gel with CH_2Cl_2–hexane to give **13** (0.21 g, 46%) and **18** (0.19 g, 41%).

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