CHEMISTRY LETTERS, pp. 1683-1686, 1993.

Synthesis of (±)-Arthrographol (Asperfuran)

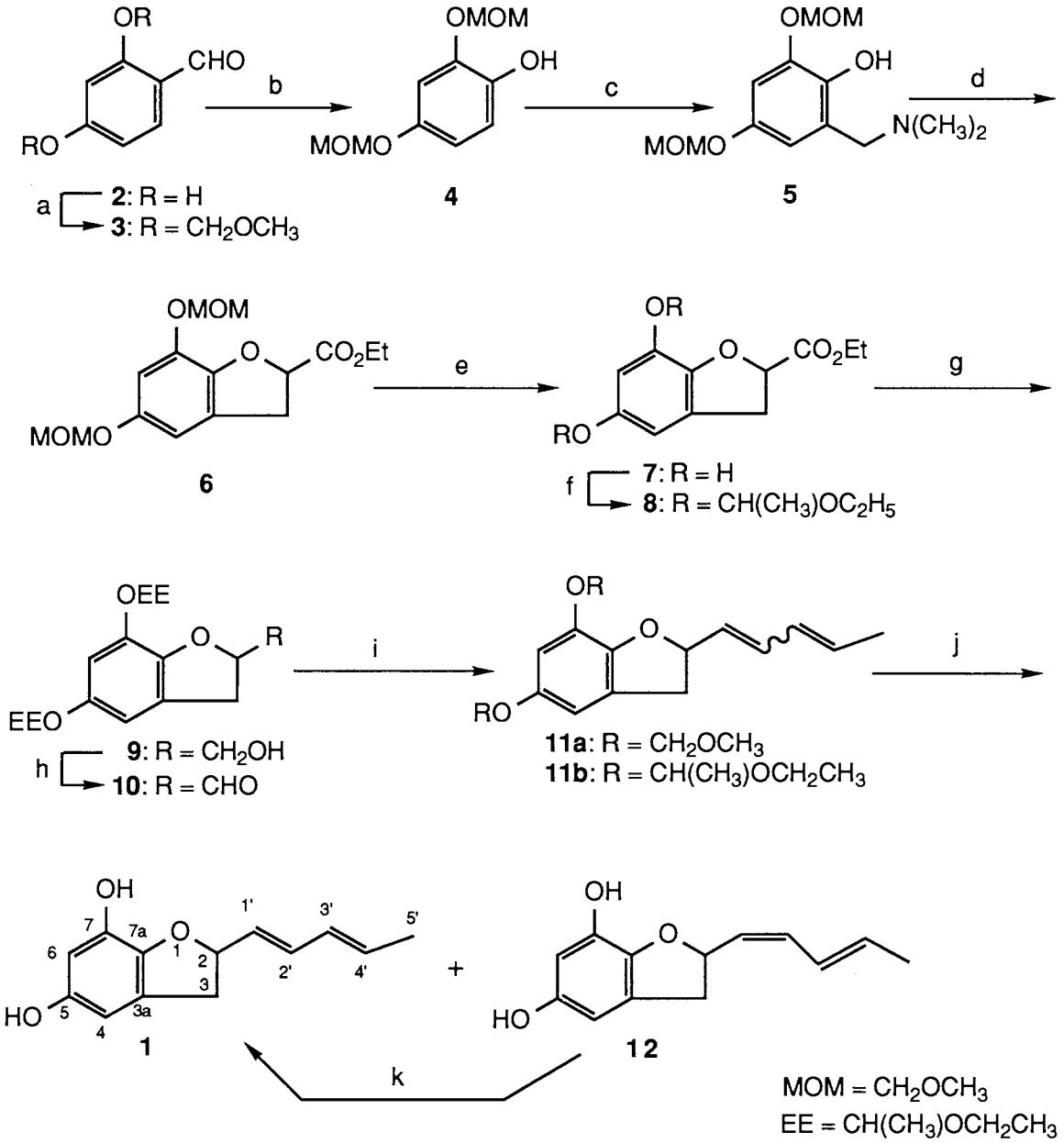
Muneharu MIYAKE and Yasuo FUJIMOTO*

Nihon University, College of Pharmacy, 7-7-1 Narashnodai, Funabashi, Chiba 274

Arthrographol, antifungal dihydrobenzofuran, have been synthesized starting from 2,4-dihydroxybenzaldehyde in 10 steps.

Arthrographol(=Asperfuran)(**1**) was a dihydrobenzofuran isolated from the metabolites of *Arthrographis pinicola* [1] and *Aspergillus oryzae* [2] by two groups, W. A. Ayer and K. Nozawa[1] and W. Pfefferle et al.[2], independently. Arthrographol (**1**) showed antifungal activity against *Ophiostoma clavigerum* (= *Ceratocystis clavigera*) which associated with pine tree mortality and inhibited chitin synthase. We have interested in these remarkable biological activities because pine tree wilting disease is serious problem in Japan and planned to investigate the structure-activity relationship on arthrographol and related dihydrobenzofuran derivatives. We report herein total synthesis[3] of (±)-arthrographol starting from 2,4-dihydroxybenzaldehyde.

Treatment of 2,4-dihydroxybenzaldehyde (**2**) with methoxymethyl chloride-N,N-diisopropylethylamine in THF gave 2,4-dimethoxymethyloxybenzaldehyde (**3**, 92.4%).[4] Baeyer-Villiger oxidation of **3** with *m*-chloroperbenzoic acid in AcOEt at room temperature overnight afforded 2,4-dimethoxymethyloxyphenol (**4**, 79.2%) which was subjected to a Mannich reaction in THF-H_2O at room temperature to produce 2-dimethylaminomethylphenol derivative (**5**, 91.1%). Reaction of a Mannich base (**5**) with ethoxycarbonylmethyl dimethylsufonium bromide in the presence of potassium carbonate in DMF at 60-70 °C for 4 h gave a dihydrofuran derivative (**6**, 57.5%).[5] Removal (**7**, 57.7%) of methoxymethyl groups of **6** followed by reprotection of the resulting hydroxyl groups with ethyl vinyl ether-pyridinium *p*-toluenesulfonate in THF-CH_2Cl_2 at room temperature for 30 min yielded an ethoxyethyl derivative (**8**, 93.5%).[6] Lithium aluminum hydride reduction of **8** and Swern's oxidation (-78 °C for 2 h, then at room temperture for 1 h) of the resulting alcohol (**9**) afforded an aldehyde (**10**, 62.4%). Wittig reaction of **10** with triphenylphosphonium *E*-buteneylide in THF at room temperature for 2 h led to the formation of a mixture of 1'(*E*),3'(*E*)- and 1'(*Z*),3'(*E*)-diene (**11b**, 49.4%)[7] in a ratio of 1 : 9. Deprotection of the mixture with MeOH-H_2O-AcOH (50 : 50 : 1) and isomerization of the double bond with



Scheme 1. (a) CH_3OCH_2Cl-diisopropylethylamine; (b) m-CPBA; (c) 50%Me_2NH-37%HCHO; (d) $Me_2\overset{+}{S}CH_2CO_2Et\ \overset{-}{Br}$ K_2CO_3; (e) MeOH-HCl; (f) PPTS-$C_2H_5OCH{=}CH_2$; (g) $LiAlH_4$; (h) DMSO-$(COCl)_2$; (i) $CH_3CH{=}CHCH_2\overset{+}{P}Ph_3\overset{-}{Br}$-NaH; (j) AcOH-MeOH-$H_2O$ (1 : 50 : 50); (k) Ph_2S_2-THF, reflux

diphenyl disulfide in refluxing THF for 16 h[8] gave (±)-arthrographol (**1**, 94.0%). The ^{1}H-NMR (400 MHz) and MS spectra of synthetic arthrographol were identical with those of natural arthrographol. Studies on the biological activities of (±)-arthrographol and of its relatives will be published elsewhere.

References

1) W. A. Ayer and K. Nozawa, *Can. J. Microbiol.*, **36**, 83 (1990).

2) W. Pfefferle, H. Anke, M. Bross, B. Steffan, R. Vianden, and W. Steglich, *J. Antibiotics,* **43** (6), 648 (1990).

3) A total synthesis of (±)-arthrographol has been reported by W. A. Ayer, and P. A. Craw, *Can. J. Chem.*, **69**, 1909 (1991).

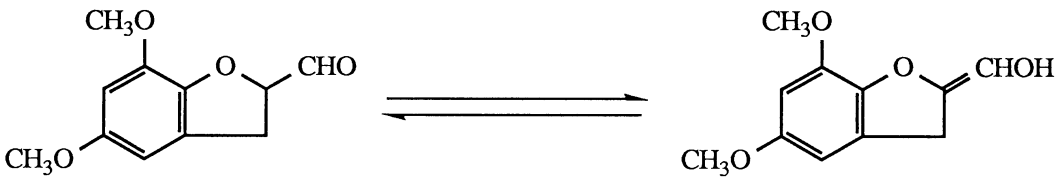
4) All new compounds described in the text gave satisfactory spectral data consistent with the assigned structures. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$ containing TMS as an internal standard unless otherwise stated. Selected physical properties for 2,4-dimethoxymethyloxybezaldehyde (**3**): EI-MS (*m/z*): 226 $(M)^+$(100), 181 $(M\text{-}C_2H_5O)^+$(52); ^{1}H NMR (δ): 3.49, 3.53 (3H each, s), 5.22, 5.29 (2H each, s), 6.75 (1H, dd, J=2.2, 8.8 Hz), 6.83 (1H, d, J=2.2 Hz), 7.81 (1H, d, J=8.8 Hz), 10.35 (1H, s, CHO); 2,4-dimethoxymethyloxyphenol (**4**): EI-MS (*m/z*): 214 $(M)^+$ (70), 45 $(C_2H_5O)^+$(100); ^{1}H NMR (δ): 3.48, 3.52 (3H each, s), 5.09, 5.18 (2H each, s), 5.64 (1H, brs, OH), 6.65 (1H, dd, J=2.9, 8.8 Hz), 6.83 (1H, d, J=2.9 Hz), 6.8 (1H, d, J=8.8 Hz); 2-dimethylaminomethyl-4,6-dimethoxymethyloxyphenol (**5**): EI-MS (*m/z*): 271 $(M)^+$(95), 226 $(M\text{-}C_2H_5O)^+$(99); ^{1}H NMR (δ): 2.33 (6H, s, $(CH_3)_2N$), 3.60 (2H, s, CH_2N); 2-ethoxycarbonyl- 5,7-dimethoxymethyloxy-2,3-dihydrobezofuran (**6**): EI-MS (*m/z*): 312 $(M)^+$(88); ^{1}H NMR (δ): 3.34 (1H, dd, J=6.2, 16.1 Hz, H-3), 3.52 (1H, dd, J=10.6, 16.1 Hz, H-3), 5.20 (1H, dd, J=6.2, 10.6 Hz, H-2); 2-ethoxycarbonyl-5,7-dihydroxy-2,3-dihydrobenzofuran (**7**): EI-MS (*m/z*): 224 $(M)^+$(83), 151 $(M\text{-}CO_2Et)^+$(100); ^{1}H NMR (acetone-d_6, δ): 3.25 (1H, dd, J=6.7, 15.7 Hz, H-3), 3.48 (1H, dd, J=10.3, 15.7 Hz, H-3), 5.14 (1H, dd, J=6.7, 10.3 Hz, H-2); 2-ethoxycarbonyl-5,7-diethoxyethyloxy-2,3-dihydrobenzofuran (**8**): EI-MS (*m/z*): 368 $(M)^+$(0.9), 224 $(M\text{-}C_4H_8O \times 2)^+$(100), ^{1}H NMR (δ): 1.15-1.58 (m, CH_3 x 5), 3.32 (1H, dd, J=6.2, 16.1 Hz, H-3), 5.49 (1H, m, H-2); 2-hydroxymethyl-5,7-diethoxyethyloxy-2,3-dihydrobenzofuran (**9**): EI-MS (*m/z*) : 326 $(M)^+$(1.4), 182 $(M\text{-}C_4H_8O \times 2)^+$(73), ^{1}H NMR (δ): 1.17-1.24 (m, CH_3 x 2), 1.44-1.51 (m, CH_3 x 2), 3.01 (1H, m, H-3), 3.21 (1H, m, H-3), 3.51-3.85 (6H, m); 2-formyl-5,7-diethoxyethyl-2,3-dihydrobenzofuran (**10**): ^{1}H NMR (δ): 1.17-1.48 (m, CH_3 x 4), 2.98 (1H, m, H-3), 3.24 (1H, m, H-3), 9.86 (1H, brs, CHO); 2-(1',3'-pentadienyl)-5,7-diethoxyethyloxy-2,3-dihydrobezofuran

(**11b**): EI-MS (*m/z*): 362 $(M)^+$(2.5), 218 $(M-C_4H_8O_2)^+$(100); 2-[1'(*Z*),3'(*E*)-pentadienyl]-5,7-dihydroxy-2,3-dihydrobenzofuran (**12**): EI-MS (*m/z*): 218 $(M)^+$ (100), 163 $(M-C_4H_7)^+$(67), 138 $(M-C_6H_8)^+$(74); ^1H NMR (δ): 1.82 (3H, brd, J=6.6 Hz, H-5'), 2.95 (1H, dd, J=7.8, 15.4 Hz, H-3), 3.32 (1H, dd, J=8.8, 15.4 Hz, H-3), 4.72, 5.16 (1H each, brs, OH), 5.52 (1H, dd, J=9.5, 10.3 Hz, H-1'), 5.65 (1H, ddd, J=8.1, 8.8, 9.5 Hz, H-2), 5.86 (1H, dq, J=6.6, 14.7 Hz, H-4'), 6.26 (1H, d, J=2.2 Hz, H-4), 6.27 (1H, d, J=2.2 Hz, H-6), 6.39 (1H, d, J=11.0, 14.7 Hz, H-3'); ^{13}C NMR (δ): 18.4 (C-5'), 37.8 (C-3), 79.8 (C-2), 102.6 (C-6), 103.6 (C-4), 126.1 (C-3'), 126.8 (C-1'), 128.1 (C-3a), 132.4 (C-2'), 133.3 (C-4'), 140.1 (C-7a or C-7), 140.3 (C-7 or C-7a), 150.4 (C-5).

5) H. Sato, T. Dan, E. Onuma, H. Tanaka, B. Aoki, and H. Koga, *Chem. Pharm. Bull.*, **39** (7), 1760 (1991).

6) Elimination of the methoxymethyl group of the compound (**11a**) under various conditions did not give satisfying results (~30% yield). Thus we replaced the protecting group by ethoxyethyl group at this sage.

7) The low yield of this reaction might be due to the enolization of 2-formyldihydrobenzofuran (**10**) under reaction conditions. W. A. Ayer and P. A. Craw reported that 5,7-dimethoxy-2-formyldihydrobenzofuran was a mixture of the aldehyde form and its enol tautomer, see Ref. 3.



8) M. A. Ali, and Y. Tsuda, *Chem. Pharm. Bull.*, **40** (10), 2842 (1992).

(Received June 30, 1993)