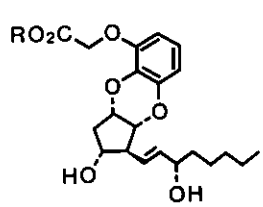
SYNTHESIS OF BENZODIOXANE PROSTACYCLIN ANALOGUE

Sachio Mori* and Shozo Takechi
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku,
Osaka 553, Japan

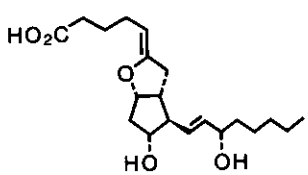
Abstract — Benzodioxane prostacyclin analogue ((±)-**1**) was synthesized via stereocontrolled construction of cyclopentanobenzodioxane (**17**) (**7**, R^2 = MOM) utilizing the Mitsunobu reaction, and subsequent introduction of the propenyl group into **17** by radical C-C coupling leading to **19** (**8**, R^2 = MOM).

Much effort has been devoted to the syntheses of stable prostacyclin analogues[1] to overcome the instability of natural prostacyclin (**2**) caused by the inherent labile enol ether-linkage and get better therapeutic efficacy.

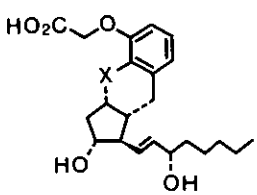
In the course of these studies, it has been shown that, in spite of their noticeable structural deviations from natural **2**, benzopyran- and benzindene prostaglandins (**3**[2a] and **4**[2]) are strong prostacyclin-like inhibitors of platelet aggregation, and that **4** is cytoprotective as well. In these compounds, the central ring systems, together with the benzene ring, seemed to play an important role for the spatial arrangement required for the biological activities, and we were interested in modulating this part. In this paper, we report the synthesis of a new stable benzodioxane prostacyclin analogue ((±)-**1**).



1a R=H
b R=Me



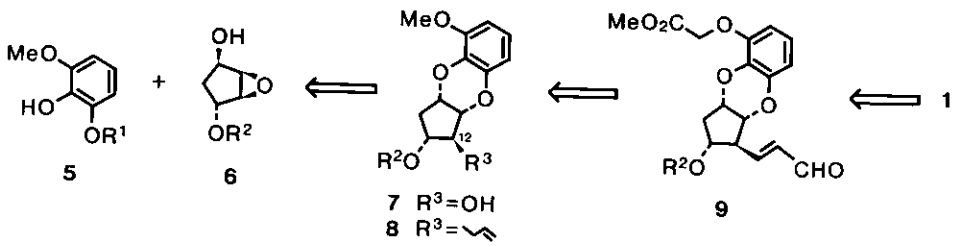
2



3 X=O
4 X=CH_2

The outline of our synthetic plan is shown in Scheme 1. The construction of the functionalized cis-fused cyclopentanobenzodioxane (**7**) and introduction of a carbon synthon to C_{12} (PG numbering) of **7**, both in a completely stereocontrolled manner, constitute the core of our synthesis.

We envisioned that the configuration in epoxy alcohol (**6**) carrying four contiguous stereogenic centers, could be securely transferred into **7** by a series of reactions, namely, condensation with differentially



Scheme 1

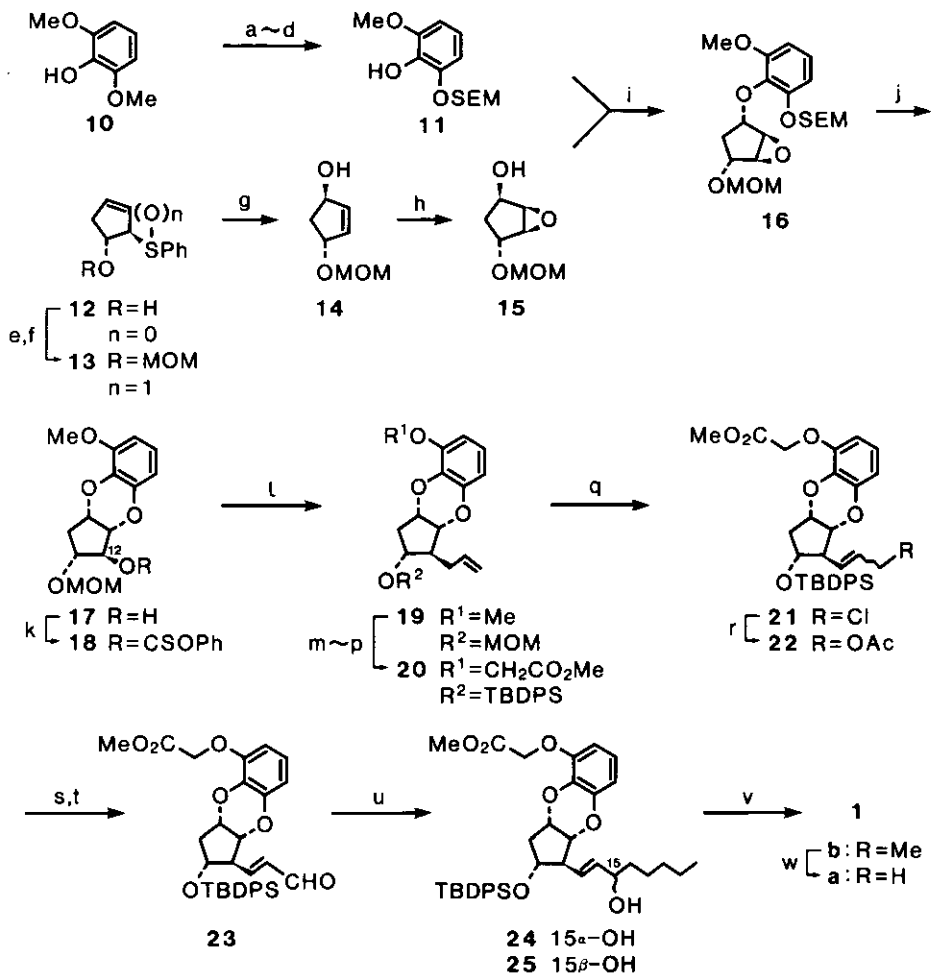
protected pyrogallol (**5**) using the Mitsunobu reaction,[3a] removal of the protecting group R^1 and dioxane-ring formation with concomitant epoxide-ring opening. For introduction of a carbon synthon to C_{12}, we relied on an approach of trapping the radical derived from the thionocarbonate of alcohol (**7**) with allyltributyltin.[4] Finally, further extension of α- and ω-side chains via α,β-unsaturated aldehyde (**9**) was expected to afford the desired benzodioxane prostacyclin analogue ((±)-**1**) (Scheme 1). The feasibility of our plan was established as follows (Scheme 2).

1) Synthesis of the functionalized cis-fused cyclopentanobenzodioxane (**17**) (**7**, R^2 = MOM)

One of the components of **17**, 1,3-di-O-protected pyrogallol (**11**), was obtained in 63% overall yield from 2,6-dimethoxyphenol (**10**) by a sequence of protection-deprotection procedures consisting of mesylation, selective monodemethylation with BBr_3, protection with SEM group and demesylation with *n*-BuLi, while the other component, 2,3-epoxy alcohol (**15**), was prepared in 67% overall yield from the known allylic sulfide (**12**)[5] in a stereochemically unambiguous way. Thus, the sulfoxide (**13**) obtained from **12** was subjected to sulfoxide-sulfenate rearrangement[5] to give allylic alcohol (**14**), which was further oxidized to **15**. The most crucial condensation of these two bulky components was effected by the Mitsunobu reaction[3b] (**11** 1 eq., **15** 1.2 eq., DEAD 1.5 eq., Ph_3P 1.7 eq./THF, room temperature, 3 days, 87% from **11**) to give seco-compound (**16**) with inversion. To our satisfaction, treatment of **16** with *n*-Bu_4NF in THF at 55°C brought about not only removal of the SEM group, but also cyclization to the desired **17** (93%).

2) Introduction of the propenyl group to C_{12} of cyclopentanobenzodioxane (**17**)

Thionocarbonate (**18**) prepared from alcohol (**17**) was irradiated with a high-pressure mercury lamp in the presence of allyltributyltin to obtain 12β-propenyl-substituted compound (**19**, 75%) as a single isomer, indicating that the approach of allyltin to the intermediary radical occurred exclusively from the less hindered convex side.



a) NaH, MsCl/DMF. b) BBr_3 (1.05 eq.)/CH_2Cl_2, -40°C, 2 h (a, b 68%). c) SEMCl, *i*-Pr_2NEt/CH_2Cl_2. d) *n*-BuLi (1.53 eq.)/Et_2O, -78°C (c, d 92%). e) MOMCl, *i*-Pr_2NEt/CH_2Cl_2 (91%). f) mCPBA (1.23 eq.)/CH_2Cl_2, -78°C. g) Ph_3P (1.69 eq.)/MeOH-PhH, 50°C, 64 h (f, g 83%). h) mCPBA (1.3 eq.)/CH_2Cl_2, room temperature, overnight (89%). i) **11** (1 eq.), **15** (1.2 eq.), DEAD (1.5 eq.), Ph_3P (1.7 eq.)/THF, room temperature, 3 days (87% from **11**). j) *n*-Bu_4NF (3 eq.)/THF, 55°C, 17 h (93%). k) *n*-BuLi (1.1 eq.)/THF, -78°C; PhOCSCl (1.2 eq.), -78°C→0°C (92%). l) *n*-$Bu_3SnCH_2CH=CH_2$ (3 eq.)/PhH, hν, 10 h (75%). m) *n*-BuSLi/HMPA, 100°C, 30 min (99%). n) NaH/DME; $BrCH_2CO_2Me$ (90%). o) $BF_3{\cdot}OEt_2$, Me_2S/CH_2Cl_2, 0°C, 2 h (94%). p) *t*-$BuPh_2SiCl$, DMAP/DMF (97%). q) PhSeCl (1.1 eq.)/CCl_4, 0°C; Py, 30% H_2O_2, 0°C and then room temperature, 1.5 h (77%). r) CsOAc (3.0 eq.), 18-Crown-6 (1.0 eq.)/PhMe, reflux, 24 h (E-**22**, 80%). s) K_2CO_3/MeOH-CH_2Cl_2, room temperature, 2 h; CH_2N_2-Et_2O (94%). t) PCC/CH_2Cl_2 (96%). u) *n*-$C_5H_{11}MgBr$ (1.2 eq.)/THF, -78°C (total 71%). v) *n*-Bu_4NF/THF; CH_2N_2-Et_2O/MeOH (80%). w) aq. NaOH-MeOH-THF (70%).

Scheme 2

3) Extension of side chains

Starting from **19**, the α-side chain was built up by demethylation and subsequent alkylation using methyl bromoacetate, which was followed by exchange of the MOM protecting group for TBDPS group to give **20** in 81% overall yield. Elaboration of the ω-side chain commenced with conversion of **20** into allylic chloride (**21**) (E/Z = 13/1, 77%) by consecutive treatment with phenylselenenyl chloride and hydrogen peroxide in *one pot*. In the next step, by reaction with cesium acetate,[6] **21** was transformed into allylic acetate (**22**), which was then purified, by single recrystallization to obtain the pure E-isomer in 80% yield. Further conversion of E-**22** to α,β-unsaturated aldehyde (**23**, 90%) was done by methanolysis and subsequent PCC oxidation. In the last stage of extension, treatment of aldehyde (**23**) with *n*-pentylmagnesium bromide (1.2 eq., -78°C) gave a mixture of alcohols, 15α-OH (**24**[7a], less polar, 48%) and 15β-OH (**25**[7b], more polar, 23%), together with recovered **23** (21%). Finally, stepwise deprotection by desilylation and hydrolysis completed the synthesis of benzodioxane prostacyclin analogue ((±)-**1a**),[8] along with its methyl ester ((±)-**1b**).

Compound (±)-**1a** and its methyl ester (±)-**1b** showed very weak platelet aggregation inhibitory activity (IC_{50} = 1.35 μM and 4.58 μM, respectively, ADP, rabbit PRP), while the latter was cytoprotective against HCl·EtOH-induced ulcer in rats (ED_{50} = 52 μg/kg). Thus compound (±)-**1b** has turned out to be a new lead substance after which selective antiulcer prostacyclin analogues can be modeled. Further studies in modification of ω-side chains and structure-activity relationship will be reported in the future.

ACKNOWLEDGEMENT

We thank Drs. K. Uchida and M. Doteuchi for testing the biological activities.

REFERENCES AND NOTES

1. a) R. C. Nickolson, M. H. Town, and H. Vorbrüggen, Med. Res. Rev., 1985, **5**, 1. b) P. A. Aristoff, 'Advances in Prostaglandin, Thromboxane and Leukotriene Research,' Vol. 14, ed. by J. E. Pike and D. R. Morton, Jr., Raven Press, New York, 1985, p. 309.
2. a) P. A. Aristoff, A. W. Harrison, and A. M. Huber, Tetrahedron Lett., 1984, **25**, 3955. b) P. A. Aristoff and A. W. Harrison, ibid., 1982, **23**, 2067; P. A. Aristoff, A. W. Harrison, J. W. Aiken, R. R. Gorman, and J. E. Pike, 'Advances in Prostaglandin, Thromboxane and Leukotriene Research,' Vol. 11, ed. by B. Samuelsson, R. Paoletti, and P. W. Ramwell, Raven Press, New York, 1983, p. 267; P. A. Aristoff, A. W. Harrison, P. D. Johnson and A. Robert, ibid., Vol. 15, ed. by O. Hayaishi and S. Yamamoto, 1985, p. 275.
3. a) O. Mitsunobu, Synthesis, 1981, 1. b) To the best of our knowledge, no example of the intermolecular Mitsunobu reaction between 2,6-disubstituted phenol and alicyclic alcohol has been reported.

4. G. E. Keck, E. J. Enholm, J. B. Yates, and M. R. Wiley, Tetrahedron, 1985, **41**, 4079.
5. D. A. Evans, T. C. Crawford, T. T. Fujimoto, and R. C. Thomas, J. Org. Chem., 1974, **39**, 3176.
6. Y. Torisawa, H. Okabe, and S. Ikegami, Chemistry Lett., 1984, 1555.
7. a) After removal of the 11-hydroxy-protecting group, 15α-OH **1b** is more polar than the corresponding 15β-OH isomer in accordance with the generally accepted rule. b) The structure of **25** was established unambiguously on the basis of X-ray crystal analysis. Details will be reported in Acta Crystallogr. by Dr. M. Shiro of our laboratories.
8. All new compounds were characterized by ^{1}H-nmr and ir spectra and gave satisfactory elemental analyses and mass spectra. The spectral data and melting points (not corrected) of the target compounds and selected intermediates are as follows: **17**: mp 69-70°C (Et_2O-n-hexane); ir ($CHCl_3$) 3604, 3476, 1603, 1499, 1475, 1280, 1110, 954, cm^{-1}; nmr ($CDCl_3$) δ 2.13 (1H, ddd, J = 2.5, 6 and 15 Hz), 2.62 (1H, ddd, J = 6, 10 and 15 Hz), 3.37 (3H, s), 3.83 (3H, s), 3.50-3.95 (2H, m, containing O*H*), 4.05-4.41 (3H, m), 4.67 (2H, s), 6.47 (1H, dd, J = 2 and 8 Hz), 6.57 (1H, dd, J = 2 and 8 Hz), 6.80 (1H, t, J = 8 Hz) ppm. **19**: mp 48.5-49.5°C (n-pentane); ir ($CHCl_3$) 1642, 1603, 1499, 1477, 1107, 918 cm^{-1}; nmr ($CDCl_3$) δ 1.93-2.57 (5H, m), 3.33 (3H, s), 3.85 (3H, s), 3.72-4.23 (2H, m), 4.26-4.45 (1H, m), 4.59 (2H, m), 4.98-5.30 (2H, m), 5.60-6.13 (1H, m), 6.40-6.65 (2H, m), 6.78 (1H, t, J = 8 Hz) ppm. **23**: mp 103.5-104.5°C (EtOAc-n-hexane); ir ($CHCl_3$) 1764, 1743, 1692, 1601, 1499, 1476, 1113, 974, 823 cm^{-1}; nmr ($CDCl_3$) δ 1.03 (9H, s), 2.20-2.37 (2H, m), 2.98-3.36 (1H, m), 3.78 (3H, s), 4.00-4.30 (3H, m), 4.71 (2H, s), 6.05 (1H, dd, J = 7 and 16 Hz), 6.33 (1H, dd, J = 7 and 16 Hz), 6.40-6.85 (3H, m), 7.28-7.47 (6H, m), 7.53-7.72 (4H, m), 9.23 (1H, d, J = 7 Hz) ppm. **24**: oil; ir ($CHCl_3$) 3608, 1763, 1743, 1600, 1498, 1475, 1114, 970, 821, cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3H, deformed t, J = 6 Hz), 1.03 (9H, s), 1.00-1.90 (9H, m containing O*H*), 2.05-2.25 (2H, m), 2.76-3.03 (1H, m), 3.79 (3H, s), 3.80-4.30 (4H, m), 4.72 (2H, s), 5.22-5.70 (2H, m), 6.40-6.87 (3H, m), 7.30-7.50 (6H, m), 7.60-7.80 (4H, m) ppm. **25**: mp 83-84°C (Et_2O-n-pentane); ir ($CHCl_3$) 3608, 1764, 1742, 1600, 1498, 1476, 1113, 969, 821 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3H, deformed t, J = 6 Hz), 1.03 (9H, s), 1.00-1.90 (9H, m containing O*H*), 2.05-2.25 (2H, m), 2.76-3.03 (1H, m), 3.79 (3H, s), 3.80-4.30 (4H, m), 4.72 (2H, s), 5.22-5.70 (2H, m), 6.40-6.87 (3H, m), 7.30-7.50 (6H, m), 7.60-7.80 (4H, m) ppm. **1b**: mp 121-123°C (EtOAc-n-hexane); ir ($CHCl_3$) 3608, 3008, 2960, 2940, 2864, 1762, 1744, 1600, 1498, 1476, 1125, 970 cm^{-1}; nmr ($CDCl_3$ + CD_3OD) δ 0.88 (3H, deformed t, J = 6 Hz), 1.10-1.80 (8H, m), 1.90-2.20 (1H, m), 2.35-2.81 (2H, m), 3.82 (3H, s), 3.80-4.40 (4H, m), 4.70 (2H, s), 5.43-5.86 (2H, m), 6.39-6.87 (3H, m) ppm. **1a**: mp 156-158°C (EtOAc-n-hexane); ir (KBr) 3404, 2960, 2940, 2864, 1745, 1709, 1615, 1596, 1501, 1477, 1434, 1131, 984, 968, 904, 760, 712 cm^{-1}; nmr (CD_3OD) δ 0.89 (3H, deformed t, J = 6 Hz), 1.10-1.80 (8H, m), 1.82-2.10 (1H, m), 2.33-2.75 (2H, m), 3.86-4.35 (4H, m), 4.63 (2H, s), 5.41-5.87 (2H, m), 6.42-6.83 (3H, m) ppm.

Received, 7th March, 1990