SYNTHESIS OF BENZOXOLANE PROSTACYCLIN ANALOGUE

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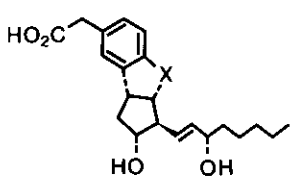
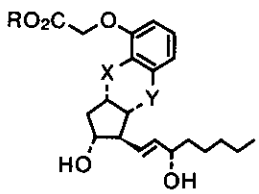
Abstract — Benzoxolane prostacyclin analogue ((±)-**1**) was synthesized with key steps involving regio- and stereocontrolled carbon-carbon bond formation using allylic phosphate (**17**) and stabilized copper reagent derived from **15**, followed by intramolecular selenoetherification leading to cyclopentanobenzoxolane (**19**).

The preceding paper reported the synthesis of benzodioxane prostacyclin analogue ((±)-**3**),[1] which showed a different profile in terms of biological activities compared with its isosters, benzopyran- **4** and benzindene prostacyclin mimic **5**.[2] This suggested that transformation of the central ring might be an attractive method for modulating biological activities, and we carried out another study along this line. Here we report the synthesis of structurally more rigid benzoxolane prostacyclin analogue ((±)-**1**), an isoster of benzcarbacyclin derivative (**2**).[3]

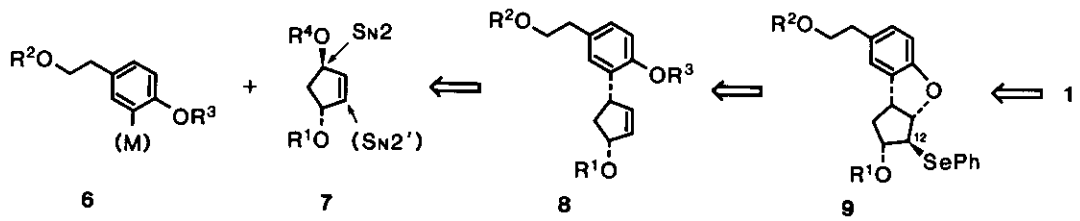


1 X=O
2 X=CH_2



3 X=Y=O **a** : R=H, **b** : R=Me
4 X=O, Y=CH_2, R=H
5 X=Y=CH_2, R=H

Our synthetic plan shown in Scheme 1, involves the preparation of 4-phenyl-2-cyclopenten-1-ol derivative (**8**), and its conversion into cyclopentanobenzoxolane (**9**) by selenoetherification. We assumed that **8** could

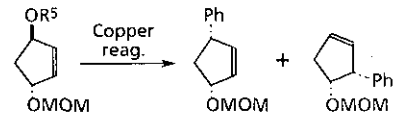


Scheme 1

be prepared favorably by a regio- and stereocontrolled carbon-carbon bond formation between o-metallated phenyl ether (**6**) and allylic ester (7), while introduction of the propenyl group to C_{12} (PG numbering) of **9**, and subsequent extension of α- and ω-side chains were expected to afford target compound (±)-**1**.

We first concentrated on model study of carbon-carbon bond formation using organocopper and allylic ester[4] for obtaining **8** (Table 1). Homocuprate (**13a**) was found to react with allylic acetate (**10a**) preferentially in an S_N2 manner to give the desired product (**11**) in 49% yield based on **10a**, but the yield based on **13a** was only 24%. Therefore we examined various phenylcopper reagents and allylic esters, in order to increase the yield and minimize reagent loss. Trials with phenylcopper itself (Entry 2) or its $BF_3{\cdot}OEt_2$ complex (Entry 3) did not work, but combinations of stabilized phenylcoppers[5] and active allylic esters (Entries 6-12) led to greatly improved results, although a small amount of S_N2' product (**12**) (Entries 8, 11) was sometimes obtained. The best result was achieved by the combination of allylic phosphate (**10e**)[6] and $PhCu{\cdot}2.5P(NMe_2)_3$ **13f** to give **11** in 73% and 61% yield based on **10e** and **13f**, respectively, with excellent S_N2/S_N2' selectivity (Entry 12).

Table 1. Reaction of organocopper reagents with allylic esters



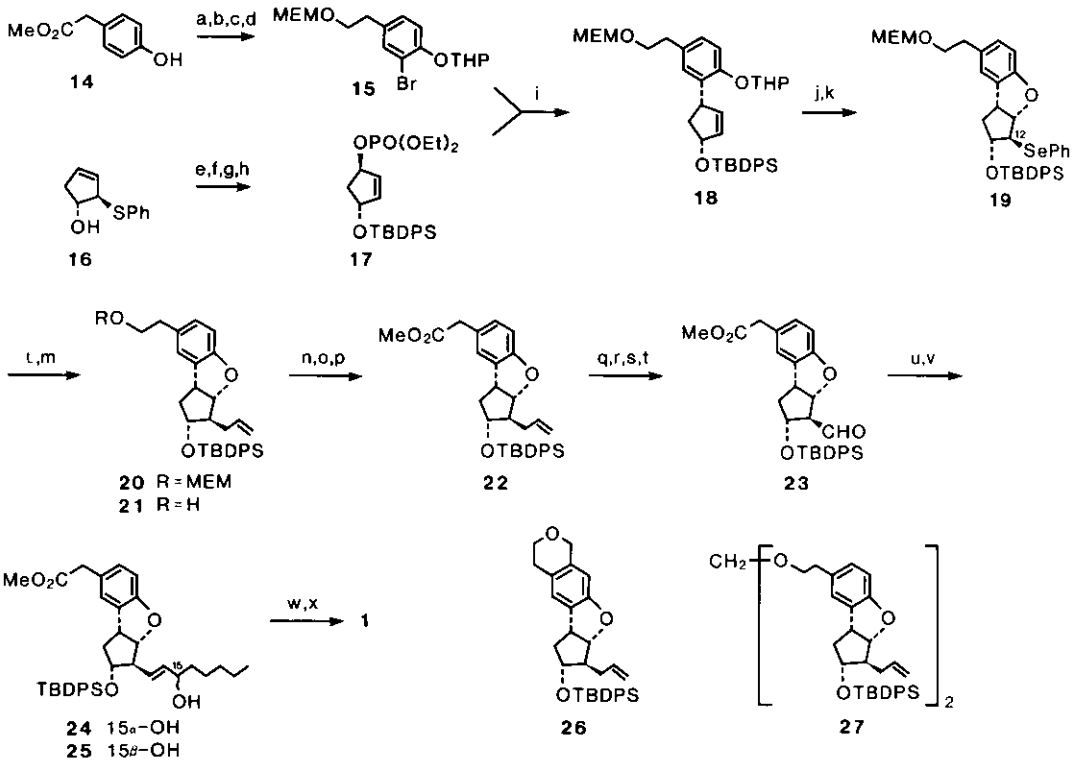
R5
a: MeCO
b: 2,4-Cl_2-PhCO
c: C_6F_5CO
d: CF_3CO
e: $(EtO)_2PO$

Copper reagents **13**
a: Ph_2CuLi
b: PhCu
c: $PhCu{\cdot}BF_3{\cdot}OEt_2$ (1 : 2)
d: $PhCu{\cdot}P(n\text{-}Bu)_3$ (1 : 1.2)
e: $PhCu{\cdot}P(n\text{-}Bu)_3$ (1 : 2.4)
f: $PhCu{\cdot}P(NMe_2)_3$ (1 : 2.5)
g: Ph(CN)CuLi

Entry	Subst. **10**	Reag. **13**	Temp. (°C)	Time[a] (h)	Reag./ Subst.	Yield[b] (%)	**11** / **12**[c]
1	a	a	-40 ↗ 0	1.5	2	49 (12)	>20 : 1
2	a	b	-70 ↗ -20	1	2	0 (0)	--
3	a	c	-70 ↗ -20	1	2	0 (0)	--
4	a	d	-70 ↗ rt	o.n.[d]	2	trace	--
5	b	d	-20 ↗ 0	o.n.	2	39 (20)	>20 : 1
6	c	d	-20 ↗ -10	3	2	67 (34)	>20 : 1
7	d	d	-20 ↗ -10	3	2	67 (34)	>20 : 1
8	e	d	-20 ↗ -10	3	2	87 (44)	7 : 1
9	d	d	-20 ↗ -10	o.n.	1.2	34 (28)	>20 : 1
10	d	e	-20 ↗ -10	2	1.2	59 (49)	>20 : 1
11	e	e	-20 ↗ -10	2	1.2	69 (58)	13 : 1
12	e	f	-20	1.5	1.2	73 (61)	>20 : 1
13	d	g	-15 ↗ rt	o.n.	3	47 (16)	2 : 3

[a] After reaching the final temperature.
[b] Yields in parentheses are based on phenyl group(s) in reagents.
[c] The ratio was determined by ^1H-nmr analysis.
[d] Overnight

Having reached a practical solution for the carbon-carbon bond formation, we embarked on the synthesis of (±)-**1**, with the results given in Scheme 2. Beginning with methyl 4-hydroxyphenylacetate (**14**), four-step conversion, namely, bromination, protection of the hydroxy group as THP ether, reduction of the ester to the alcohol, and its protection with the MEM group, afforded o-bromophenyl ether (**15**), one of the components of the key intermediate (**18**). The other component, the allylic phosphate (**17**), was prepared from the known allylic sulfide (**16**) via silylation, oxidation to the sulfoxide, rearrangement to the allylic alcohol, and esterification. We chose **17** bearing a bulkier *t*-butyldiphenylsilyloxy group at δ-position instead of **10e**, which we expected would induce further improvement in S_N2 / S_N2' ratio. As expected, the reaction between **17** and the hexamethyl phosphorous triamide-stabilized organocopper



a) NBS (1 eq.)/DMF (66%). b) DHP, PPTS/CH_2Cl_2. c) $LiAlH_4/Et_2O$. d) MEMCl, *i*-Pr_2NEt/CH_2Cl_2 (b, c, d 88%). e) *t*-$BuPh_2SiCl$, DMAP/DMF. f) mCPBA (1 eq.)/CH_2Cl_2, -70°C. g) Ph_3P (1.47 eq.)/MeOH-PhMe, 65°C, overnight (e, f, g 88%). h) *n*-BuLi (1 eq.)/HMPA-THF, -20°C; $(EtO)_2POCl$ (1.5 eq.) (63%). i) i. **15** (2 eq.), *n*-BuLi (2 eq.)/THF, -70°C, 15 min; ii. CuBr·SMe_2 (2 eq.), $(Me_2N)_3P$ (5 eq.)/THF, -70°C, add. over 20 min, additional 15 min, and then -30°C, 40 min; iii. **17** (1 eq.)/THF, -20 - -30°C, add. over 40 min, and then -20°C, 50 min (86% based on **17**). j) PPTS/MeOH (72%). k) PhSeBr (1.3 eq.), propylene oxide (5 eq.)/CH_2Cl_2, 0°C, and then room temperature, overnight (95%). l) *n*-$Bu_3SnCH_2CH=CH_2$ (3 eq.)/PhH, hν, 5 h (60%). m) TMSCl (4 eq.), NaI (4 eq.)/MeCN, add. in equal two portions at 0 and 20 min; -15°C, total 50 min, aq. NH_4Cl quench (85%). n) i. $(COCl)_2$ (2 eq.), DMSO (4 eq.)/CH_2Cl_2, -78°C; ii. **21** (1 eq.); iii. Et_3N (4 eq.), -78°C↗-20°C. o) $NaClO_2$ (5 eq.), $Me_2C=CHMe$ (28 eq.), $NaH_2PO_4·2H_2O$ (3.75 eq.)/*t*-BuOH-H_2O, room temperature, 10 min. p) CH_2N_2/Et_2O (n, o, p 73%). q) PhSeCl (1.1 eq.)/CCl_4, 0°C, 10 min; Py, 30% H_2O_2, 0°C, and then room temperature, 1 h (77%). r) CsOAc (3 eq.), 18-Crown-6 (1 eq.)/PhMe, reflux, 19 h (86%). s) OsO_4 (0.1 eq.), Me_3NO (2 eq.)/MeCOMe-THF-H_2O, 4 h, room temperature. t) $NaIO_4$ (2 eq.)/DME-H_2O, room temperature, overnight (s, t 61%). u) $(MeO)_2POCH_2COC_5H_{11}{}^n$ (1.5 eq.), NaH (1.3 eq.)/THF, room temperature, 20 min; **23**, room temperature, 40 min (95%). v) $CeCl_3·7H_2O$ (1 eq.), $NaBH_4$ (1 eq.)/THF-MeOH, 0°C, 5 min (**24** 61%, **25** 36%). w) *n*-Bu_4NF/THF (67%). x) aq. NaOH-MeOH (72%).

Scheme 2

prepared from **15** went satisfactorily and exclusively gave **18** in 86% yield based on **17** (i. **15** 2 eq., *n*-BuLi 2 eq./THF, -70°C; ii. CuBr·SMe_2 2 eq., $(Me_2N)_3P$ 5 eq./THF, -70°C and then -30°C; iii. **17** 1 eq./THF, add. at -20 - -30°C and then -20°C).

In the next key step, the phenol obtained by deprotection of the THP group in **18** was subjected to seleno-etherification.[7] We found that a combination of phenylselenenyl bromide and propylene oxide[8] worked

nicely to give the desired cyclopentanobenzoxolane (**19**) in excellent yield (95%). The propenyl group was introduced by trapping the radical formed from **19** with allyltin,[1] which was followed by deprotection of the MEM group to afford the alcohol (**21**). The latter process was problematic at the beginning. Thus treatment of **20** with $ZnBr_2/CH_2Cl_2$[9] led to formation of tetracyclic compound (**26**,[10] 69%) with only a small amount of **21** (12%), while another procedure, namely, TMSCl, NaI/MeCN treatment and subsequent quenching with aq. NaCl gave the dimeric compound (**27**) as the major product (72%). Eventually, we were able to solve the problem by replacing the quenching medium of aq. NaCl with weakly acidic aq. NH_4Cl to obtain **21** in good yield (85%).

Further conversion of alcohol (**21**) to ester (**22**) by stepwise oxidation to the acid, and its esterification completed the formation of the α-side chain, leaving construction of the ω-side chain as the final task. The propenyl group in **22** was transformed into a formyl group to obtain the versatile intermediate (**23**) by sequential procedures including addition of phenylselenenyl chloride and oxidative elimination to the allylic chloride in one pot, its conversion into the allylic acetate, and cleavage of the double bond. Extension of the ω-side chain was performed by the Horner-Emmons reaction to obtain the (E)-enone, which was reduced to a mixture of allylic alcohols (**24**,15α-OH, less polar, 61%) and (**25**, 15β-OH, more polar, 36%).[11] Finally, deprotection via the methyl ester furnished benzoxolane prostacyclin analogue ((±)-**1**).[12]

Compound (±)-**1** was found to be far less active in inhibiting platelet aggregation (IC_{50} = 189 μM, ADP, rabbit PRP) than benzodioxane prostacyclin analogue ((±)-**3a**) and non-cytoprotective.

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8. Usage of phenylselenenyl chloride itself led to a modest yield (43%) partly because of deblocking of the hydroxy-protecting group(s) by the generating acid, which was very severe in the case of selenenyl bromide, while a combination of propylene oxide and selenenyl chloride failed to improve the yield.
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10. The same type of isochroman formation assisted by $TiCl_4$ has been reported by D. L. Mohler and W. Thompson, Tetrahedron Lett., 1987, **28**, 2567.
11. The 11-hydroxy-protecting group in **24** and **25** was removed separately to give the methyl ester of (±)-**1** (15α-OH, more polar) and its 15β-OH isomer (less polar) respectively. The stereochemistry at C_{15} was assigned tentatively according to the general rule.
12. 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 final compound and selected intermediates are as follows: **18**: oil; ir ($CHCl_3$) 1610, 1497, 1428, 1367, 1112, 820, 612 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (9H, s), 1.40-2.13 (7H, m), 2.40-2.73 (1H, m), 2.73 (2H, t, J = 7 Hz), 3.36 (3H, s), 3.33-4.19 (9H, m), 4.69 (2H, s), 4.93 (1H, t, J = 7 Hz), 5.27-5.43 (1H, m), 5.70-5.94 (2H, m), 7.02 (2H, s), 7.13 (1H, s), 7.27-7.50 (6H, m), 7.60-7.86 (4H, m) ppm. **19**: oil; ir ($CHCl_3$) 1489, 1428, 1113, 820, 612 cm^{-1}; nmr ($CDCl_3$) δ 0.74 (9H, s), 2.02 (1H, dq, J = 14 and 2 Hz), 2.35 (1H, ddd, J = 14, 9 and 4.5 Hz), 2.85 (2H, t, J = 7 Hz), 3.38 (3H, s), 3.50-3.77 (6H, m), 3.86-3.99 (2H, m), 4.25-4.32 (1H, m), 4.72 (2H, s), 5.21 (2H, d, J = 9 Hz), 6.66 (1H, d, J = 8 Hz), 6.94 (1H, dd, J = 8 and 2 Hz), 7.01 (1H, br s), 7.12-7.57 (15H, m) ppm. **21**: oil; ir ($CHCl_3$) 3624, 1490, 1429, 1113, 919, 819, 612 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (9H, s), 1.40 (1H, br s, O*H*), 1.78-2.20 (4H, m), 2.28-2.42 (1H, m), 2.79 (2H, t, J = 7 Hz), 3.72 (1H, td, J = 9 and 4 Hz), 3.79 (2H, t, J = 7 Hz), 3.92 (1H, q, J = 5 Hz), 4.82 (1H, dd, J = 9 and 3 Hz), 4.93 (1H, d, J = 12 Hz), 4.94 (1H, d, J = 16 Hz), 5.46-5.68 (1H, m), 6.71 (1H, d, J = 8 Hz), 6.94 (1H, d, J = 8 Hz), 6.98 (1H, s), 7.28-7.65 (10H, m) ppm. **1**: mp 122-123°C (EtOAc-n-hexane); ir (KBr) 3412, 3264, 2932, 2864, 1707, 1616, 1490, 1248, 1202, 970 cm^{-1}; nmr (CD_3OD) δ 0.92 (3H, t, J = 7 Hz), 1.20-1.75 (9H, m), 2.42-2.66 (2H, m), 3.50 (2H, s), 3.73 (1H, q, J = 9 Hz), 3.88 (1H, td, J = 9 and 6 Hz), 4.00-4.10 (1H, m), 4.85 (1H, dd, J = 9 and 7 Hz), 5.58-5.79 (2H, m) 6.66 (1H, d, J = 8 Hz), 7.00 (1H, dd, J = 8 and 2 Hz), 7.09 (1H, s) ppm.

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