SYNTHESIS OF CIS-BICYCLO[4.3.0]NON-2-ENE DERIVATIVES. THE POTENT HOMOISOCARBACYCLIN ANALOGS

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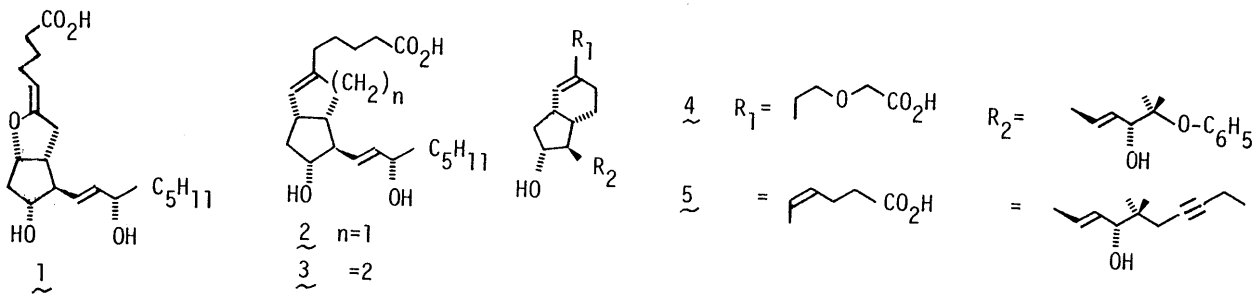
Synthesis of homoisocarbacyclin has been achieved efficiently by a general strategy with stereo- and regiochemical control. One of homoisocarbacyclin derivatives, 3-oxa homoisocarbacyclin analog (4), was shown to be potently active in inhibiting gastric ulcer. Another analog, conjugated diene derivative (5), was found to have a biological profile similar to prostacyclin.

KEYWORDS homoisocarbacyclin analog; cis-bicyclo[4.3.0]non-2-ene derivative; isocarbacyclin; stereoselective reduction of enone; antiulcer activity; platelet aggregation inhibitory activity

The potent biological activity of natural prostacyclin (PGI_2, 1)[1] coupled with inherent instability have led to many efforts to prepare chemically stable prostacyclin mimics. The most attractive one of those reported is isocarbacyclin (2)[2] which has been shown to have a profile nearly identical to prostacyclin (1). In the course of our synthesis studies of stable and biologically potent prostacyclin mimics, we became interested in a novel analog with a cis-bicyclo[4.3.0]nonane nucleus, homoisocarbacyclin analog (3), whose functional groups might be allowed stereochemically to take suitable positions as in isocarbacyclin (2) (MM2). So our attention was concentrated on a synthesis of many homoisocarbacyclin analogs with various upper and lower chains in attempts to improve potency and duration of activity. Here we wish to report the practical synthesis of two promising analogs (4 and 5) and the preliminary determination of their biological activities.



The synthesis of both 4 and 5 started with the Corey lactone (6) via the key intermediate (11).[3] The Corey lactone (6) was efficiently converted to the ester (7) in five steps (63% overal yield). Hydroboration of 7 followed by oxidative workup afforded the alcohol (8) in a stereocontrolled manner (100%). Reduction of 8 and subsequent oxidation furnished dialdehyde (10). Successive intramolecular cyclization of 10 by an aldol condensation gave the versatile key intermediate (11) in a fully regiocontrolled manner (69% yield from 8) (Chart 1).

With the important α,β-unsaturated aldehyde (11) in hand, we next tried the conversion of 11 to the 3-oxa analog (4) and the conjugated diene analog (5). Wittig reaction of 11 and subsequent hydroboration furnished the homoallylalcohol (12) (92% yield). O-Alkylation of 12 followed by desilylation provided the versatile alcohol (13)[4] (89% yield). Oxidation of 13 gave the corresponding aldehyde (14) which reacted with the β-keto phosphonate anion derived from 15[5] to afford the enone (16) (90% yield). Reduction of 16 with $NaBH_4$ followed by the removal of the tetrahydropyranyl moiety gave the diastereomer[6] 19a and 19b in the ratio of 57:43 (90% yield).[7] While, it should be noted that the desired diastereomer (19a) was predominantly obtained by the reduction of 17[6] with diisobutylalminum 2,6-di-t-butyl-4-methylphenoxide in toluene

(Yamamoto-Ono reagent)[8] (19a:19b 89:11, 89% yield). Hydrolysis of 19a with 7% aq. KOH in methanol afforded the 3-oxa analog (4)[9] (90% yield) (Chart 2).

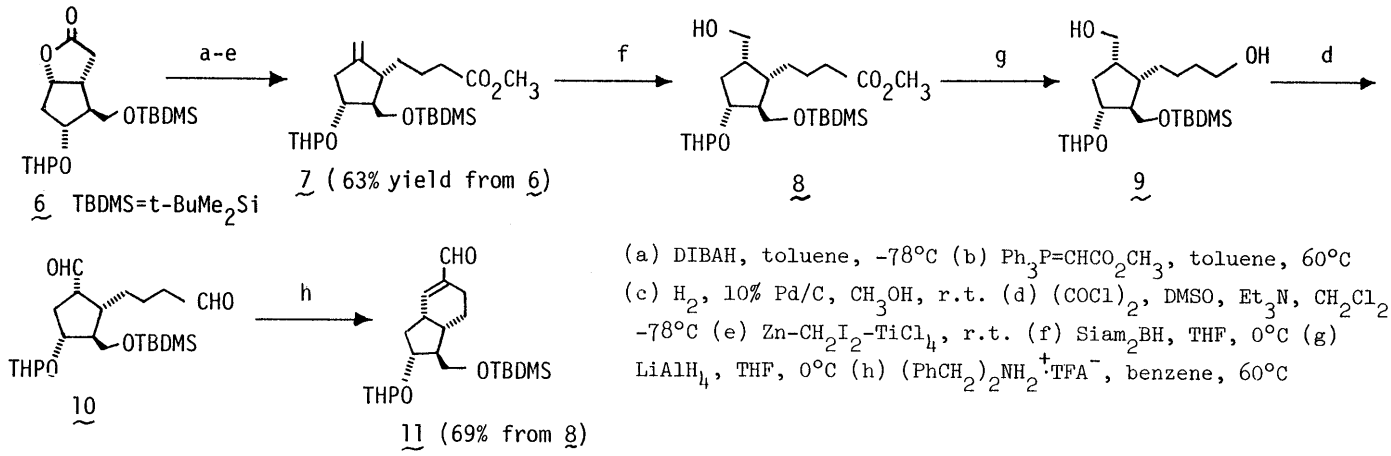


Chart 1

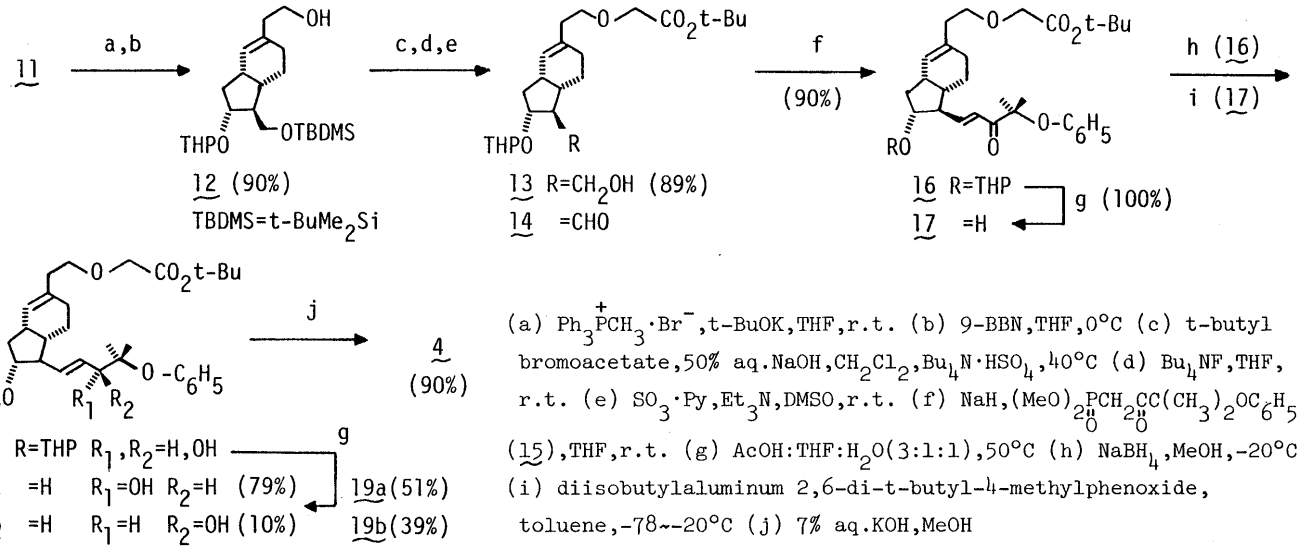


Chart 2

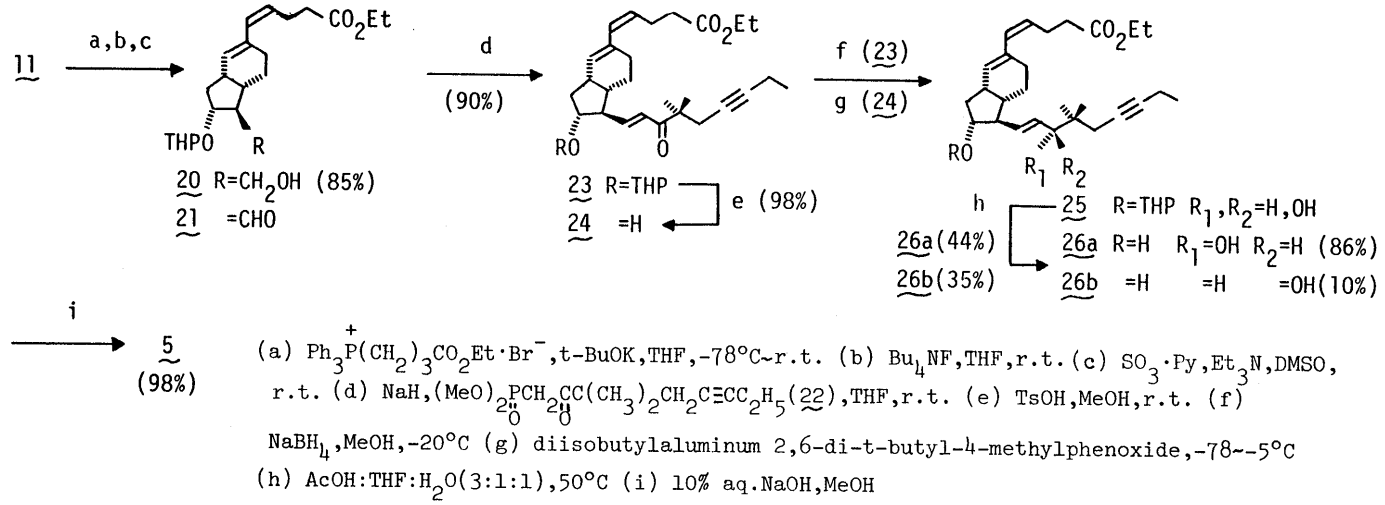
The synthesis of conjugated diene analog (5) is described below. Treatment of 11 with Wittig reagent derived from 3-ethoxycarbonylpropyltriphenylphosphonium bromide and potassium t-butoxide in THF and a subsequent desilylation reaction provided the versatile conjugated diene intermediate (20)[10] exclusively in Z geometry (85% yield from 11).[10] Transformation of 20 into the conjugated diene analog (5)[12] was accomplished in the same way as descrived for the synthesis of 4 (66% yield from 21) (Chart 3). It was noteworthy that the diastereomeric ratio of 26a:26b[7] on the reduction of 24[6] was similarly increased from 56:44 (79% yield) to 89.6:10.4 (96% yield) with Yamamoto-Ono reagent.[8]

This synthesis of homoisocarbacyclin analogs (4 and 5) has proven feasible on a large scale and, furthermore, it allows the preparation of various analogs of 4 and 5.

Preliminary biological examinations indicated that the 3-oxa analog (4) had potent and long-lasting antiulcer activities. Inhibitory ratios (ED_{50}) in ethanol-induced gastric lesions at 1.5 and 5 h after oral administration of 4 were 1.1 μg/kg and 25 μg/kg, respectively.[14] However, 4 did not inhibit platelet aggregation of rabbit PRP at a concentration of 3×10^{-6} M. Thus, the analog (4) was shown to have a good separation of antiulcer activity from inhibitory activity in platelet aggregation.

On the other hand, the conjugated diene analog (5) appeared to have a biological profile similar to prostacyclin. Compound 5 inhibited ADP- and collagen-induced platelet aggregation of rabbit PRP, with ED_{50}

of 5.2 x 10^{-9} M and 6.7 x 10^{-9} M, respectively, as well as ethanol-induced gastric lesion [ED_{50} 6.3 μg/kg (1.5 h), 47 μg/kg (5 h), p.o. in rats].[14]



(a) $Ph_3\overset{+}{P}(CH_2)_3CO_2Et\cdot Br^-$,t-BuOK,THF,-78°C~r.t. (b) Bu_4NF,THF,r.t. (c) $SO_3\cdot Py$,Et_3N,DMSO, r.t. (d) NaH,$(MeO)_2\overset{O}{\overset{\|}{P}}CH_2\overset{O}{\overset{\|}{C}}C(CH_3)_2CH_2C{\equiv}CC_2H_5$(22),THF,r.t. (e) TsOH,MeOH,r.t. (f) $NaBH_4$,MeOH,-20°C (g) diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide,-78~-5°C (h) AcOH:THF:H_2O(3:1:1),50°C (i) 10% aq.NaOH,MeOH

Chart 3

Further studies are now in progress on various biological properties of both homoisocarbacyclin analogs 4 and 5.

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2) M.Shibasaki, Y.Torisawa, and S.Ikegami, Tetrahedron Lett., 24, 3493(1983); M.Shibasaki, H.Fukasawa, and S.Ikegami, Tetrahedron Lett., 24, 2497(1983).

3) A.Takahashi and M.Shibasaki, Tetrahedron Lett., 28, 1893(1987). 11:pale yellow oil. IR(neat)cm^{-1}:1685 (CHO). ^{1}H-NMR($CDCl_3$) δ:0.05(6H,s), 0.85(9H,s), 4.50-4.70(1H,bs), 6.60-6.78(1H,m), 9.40(1H,s). MS m/z: 319(M^+-THP).

4) 13:pale yellow oil. IR(neat)cm^{-1}:3450(OH), 1745(ester). ^{1}H-NMR($CDCl_3$) δ:1.48(9H,s), 3.95(2H,s), 4.55-4.77(1H,m), 5.42(1H,bs). MS m/z:326(M^+-THP).

5) The synthesis of 15 was described as follows; Methylation of methyl (±)-2-phenoxypropionate with LDA and CH_3I in THF at -78 °C to r.t. gave methyl 2-methyl-2-phenoxypropionate(91%), which was transformed into the phosphonate 15 (98%) by the method of Corey and Kwiatkowski: see E.J.Corey and G.T.Kwiatkowski, J. Am. Chem. Soc., 88, 5654(1966).

6) All structural assignments were confirmed by proton magnetic resonance, infrared and mass spectral data.

7) The diastereomeric mixture of the allylic alcohol was easily separated by column chromatography on silica gel (ether:n-hexane 5:1): see N.H.Andersen, J. Lipid. Res., 40, 316(1969).

8) S.Iguchi, H.Nakai, M.Hayashi, H.Yamamoto, and K.Maruoka, Bull. Chem. Soc. Jpn., 54, 3033(1981).

9) 4:colorless crystalline, mp:90-91 °C. IR(KBr)cm^{-1}:3400(COOH and OH), 1730(CO). ^{1}H-NMR($CDCl_3$) δ:1.23 (6H,s), 3.46(2H,t,J=6Hz), 4.07(2H,s), 5.43(1H,bs), 5.50-5.76(2H,m), 6.60-7.43(5H,m). MS m/z 431(M^++H).

10) 20:pale yellow oil. IR(neat)cm^{-1}:3450(OH), 1735(ester). ^{1}H-NMR($CDCl_3$) δ:1.25(3H,t,J=7.5Hz), 4.13(2H,q, J=7.5Hz), 5.05-5.41(1H,m), 5.58(1H,bs), 5.80(1H,d,J=12.5Hz). MS m/z:378(M^+).

11) K.Iseki, M.Shinoda, C.Ishiyama, Y.Hayashi, S.Yamada, and M.Shibasaki, Chem. Lett., 1986, 559.

12) 5:pale yellow oil. IR(neat)cm^{-1}:3400(COOH and OH), 1705(CO). ^{1}H-NMR δ:0.98(6H,s), 5.10-5.75(4H,m), 5.84(1H,d,J=12.5Hz). MS m/z:400(M^+).

13) The synthesis of 22 was as follows; Methylation of ethyl (±)-2-methyl-4-heptynoate with LDA and CH_3I in THF at -78 °C to r.t. yielded ethyl 2,2-dimethyl-4-heptynoate(80%), which was transformed into the phosphonate 22 by Corey's method: see ref.5. Preparation of ethyl (±)-2-methyl-4-heptynoate: see W.Skuballa, E.Schillinger, C.-St.Strurzebecher, and H.Vorbruggen, J. Med. Chem., 29, 315(1986).

14) Fasted male rats were given the test substance orally 0.5 or 4.0 h prior to receiving 1 ml of intragastric ethanol(99.5%). Then, 1 h later, the rats were sacrificed and evaluated for their gastric lesion according to Robert's method: see A.Rovert, J.E.Nezamis, C.Lancaster, and A.J.Hanchar, Gastroenterology, 77, 433(1979).

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