Communications to the Editor

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SYNTHESIS OF A HIGHLY POTENT ANALOGUE OF PROSTACYCLIN, (-)-5-METHYLENEISOCARBACYCLIN

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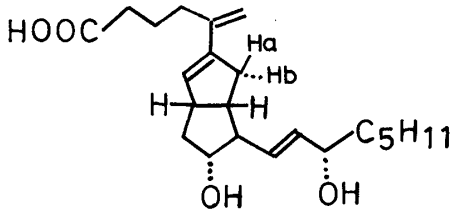
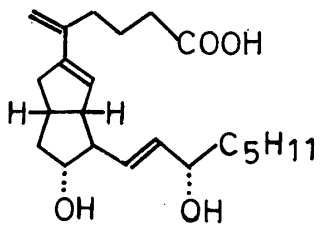
Synthesis of (-)-5-methyleneisocarbacyclin (1a) is described. The compound (1a) was found to be a platelet aggregation inhibitor as potent as prostacyclin.

KEYWORDS——methyleneisocarbacyclin; isocarbacyclin; carbacyclin; prostacyclin; platelet aggregation inhibitor

Since the discovery of prostacyclin, a large number of its analogues have been synthesized to improve the instability.[1] We[2] and others[3] reported the synthesis of isocarbacyclin, a stable carbon analogue of prostacyclin, which has platelet antiaggregating activity more potent than carbacyclin (9(O)-methano-prostacyclin) but less potent than prostacyclin.[3a] Having to find a more potent analogue, we planned to synthesize an analogue of isocarbacyclin having an exo-methylene group at the C-5 position. This would have structural features more similar to prostacyclin: Such an analogue (1a) has the π-electron system from the C-5 through the C-6(9α) position which is approximately similar to the system in prostacyclin with its oxygen lonepair electrons from C-5 through 9α-oxygen. Moreover the α-carboxy side chain is oriented in a favourable position just as it is in prostacyclin (Z-configuration), because the trans-dienic structure is considered to be more stable than the cis-dienic structure. Here, We describe the synthesis of 5-methyleneisocarbacyclin (5-methylene-9(O)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1) (1a).



1a

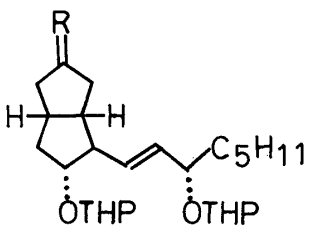


1b

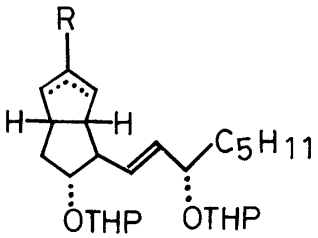
The ketone (2)[4] was used as the starting material. Firstly, the carbon-frame-work of carboxylic side chain and the double bond at C-6(9α) position were introduced by the following two step operation. Horner reaction of 2 with trimethyl phosphonoacetate and NaH in THF and DMF (1:1) gave the unsaturated ester (3). Treatment of 3 with lithium dicyclohexylamide in THF containing HMPA, followed by the addition of 4-benzyloxy-1-bromobutane, afforded the ester (4) as an inseparable mixture of the double bond isomers in 77% yield from 2 (vide infra).

Secondly, the dienic structure was introduced by the following sequence of reactions. $LiAlH_4$ reduction of 4 yielded the alcohol (5), which was treated with dimethyl-t-butylchlorosilane in DMF in the presence of imidazol to afford the silyl ether (6). Debenzylation of 6 with Na in liquid NH_3 and THF gave the alcohol (7) in 85% yield from 4. The hydroxy group in 7 was protected as acetate with acetic anhydride in pyridine to afford the compound (8). Deprotection of 8 with tetrabutylammonium fluoride in THF gave 9 in 95% yield from 7. In order to introduce the double bond, the hydroxy group in 9 was converted to mesylate by treatment with MsCl in pyridine to afford 10. Treatment of 10 with DBU in HMPA in the presence of NaI yielded the diene (11) in 89% yield from 9.

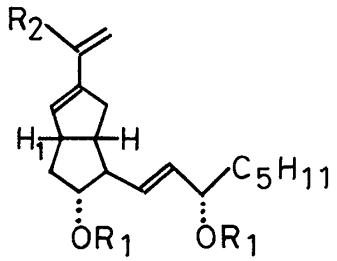
The compound (11) was then converted to 1a by the following sequence of reactions. Treatment of 11 with K_2CO_3 in methanol, followed by chromatographic separation, afforded the more polar alcohol (12a) and the less polar alcohol (12b) in 56% and 42% yield, respectively. The structures of 12a and 12b were assigned on the basis of nuclear magnetic resonance spectra: 12a has a signal due to an H_1 proton at 3.10 (δ), a characteristic of isocarbacyclin.[3b] On the other hand, the compound (12b) does not have such a signal in the nuclear magnetic resonance spectrum. Oxidation of 12a with CrO_3 in aqueous pyridine,[5] followed by the



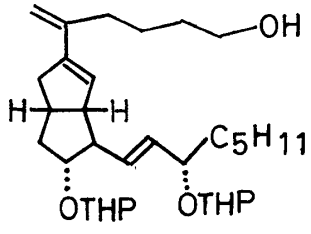
2; R= O
3; R= CHCOOMe



4; R=CH(COOMe)$CH_2CH_2CH_2OCH_2Ph$
5; R=CH(CH_2OH)$CH_2CH_2CH_2OCH_2Ph$
6; R=CH($CH_2CH_2CH_2OCH_2Ph$)($CH_2OSi(t\text{-}Bu)Me_2$)
7; R=CH($CH_2CH_2CH_2CH_2OH$)($CH_2OSi(t\text{-}Bu)Me_2$)
8; R=CH($CH_2CH_2CH_2CH_2OAc$)($CH_2OSi(t\text{-}Bu)Me_2$)
9; R=CH($CH_2CH_2CH_2CH_2OAc$)(CH_2OH)
10; R=CH($CH_2CH_2CH_2CH_2OAc$)(CH_2OMs)
11; R= C($CH_2CH_2CH_2CH_2OAc$)=CH_2



12a; R_1= THP, R_2= $CH_2CH_2CH_2CH_2OH$
13; R_1= THP, R_2= $CH_2CH_2CH_2COOMe$
14; R_1= H, R_2= $CH_2CH_2CH_2COOMe$



12b

esterification with diazomethane, afforded the compound (13). Treatment of 13 with aqueous acetic acid and THF gave the alcohol (14), mp 69-70°C. Finally, hydrolysis of 14 with sodium hydroxide in aqueous methanol yielded (-)-5-methylene-isocarbacyclin (1a),[6] mp 78-80°C, in 45% yield from 12a.

Following a sequence of reactions similar to that described for 1a, the alcohol (12b) afforded (+)-5-methylene-6,9α-methano-Δ^6-prostaglandin I_1 (1b),[7] mp 88-90°C.

The structures of 1a and 1b were further confirmed by careful analysis of their nuclear magnetic resonance spectra (400 MHz), including decoupling and nuclear Overhauser effect experiments. Especially, the trans dienic structure in 1a was determined by the nuclear Overhauser effect experiment: The nuclear Overhauser effects occurred between the exo-methylene protons at the C-5 position and the Ha or Hb proton.[8]

The compound (1a) exhibited platelet antiaggregating activity (IC_{50}=1.0 ng/ml) using human platelet-rich plasma (ADP). In contrast, the compound (1b) was inactive in the same test.[9]

REFERENCES AND NOTES

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6) IR ($CHCl_3$); 3400, 1710, 1630, 1595, 1090, 975 cm^{-1}. NMR ($CDCl_3$) δ: 0.90 (3H, t), 3.07 (1H, m), 3.6-4.2 (2H, m), 4.94 (2H, br s), 5.55 (2H, m), 5.74 (1H, br s). $(\alpha)_D^{24}$ = -33.4° (C=1.0, $CHCl_3$). monohydrate: mp 86-88°C.
7) IR ($CHCl_3$); 3400, 1710, 1630, 1600, 1085, 975 cm^{-1}. NMR ($CDCl_3$) δ: 0.88 (3H, t), 3.5-4.2 (2H, m), 4.93 (2H, br s), 5.58 (2H, m), 5.75 (1H, br s). $(\alpha)_D^{24}$ = + 137.4° (C=1.0, $CHCl_3$).
8) We thank Dr. H. Haruyama for analysis of the NMR spectra.
9) The compound (1a) was as potent as prostacyclin in the same test. Using rabbit platelet-rich plasma the compound (1a) was found approximately five times as potent as prostacyclin in the same test. We thank Dr. T. Oshima for testing biological activities.

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