SYNTHESIS OF A NOVEL FURAN-CONTAINING TRICYCLIC PROSTACYCLIN ANALOGUE[1]

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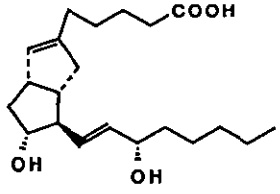
Abstract- Described herein is a synthesis of the new prostacyclin analogue (**2a**), which contains a highly strained tricyclic furan skeleton related to isocarbacyclin (**1**).

Since the enhanced chemical stability and potent biological activities of isocarbacyclin (**1**), a new carbon analog of prostacyclin, were found,[2] much attention has been focused on its structure-activity relationship. Apparently, the double bond located at the $C_{6\text{-}9\alpha}$ position of **1** plays a subtle role on the easy conformational change of α-chain, resulting in the enhancement of its biological activities. In connection with this important region, we have planned to make a synthetic entry into the new aromatic prostacyclin analogue (**2**), which contains a furan ring fused to this region of isocarbacyclin.



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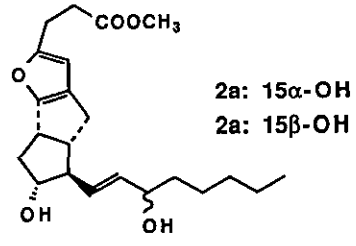
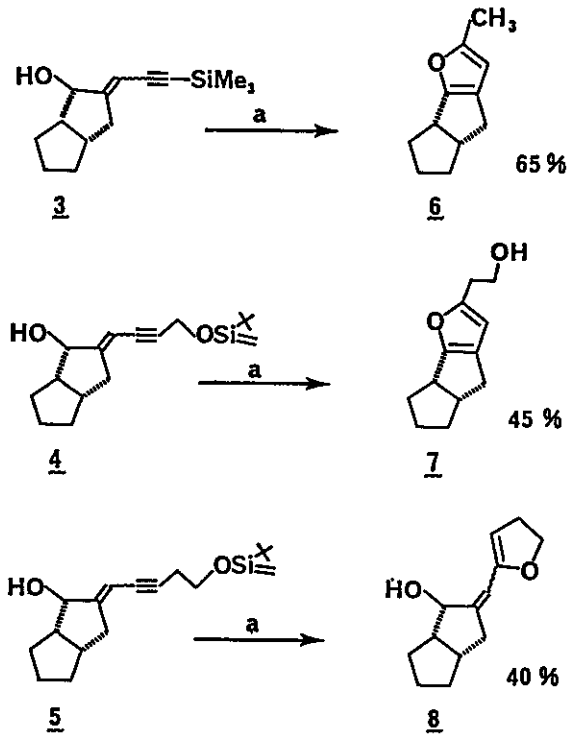


2

Our synthetic interests have also been directed to the construction of a highly strained fused furan system.[3] For this crucial construction of a cyclopenta[b]furan system,[3] we decided to investigate the suitability of the base-catalyzed cyclization of enyne alcohols.[4]

In the careful model study, we achieved that enyne alcohols (**3**) and (**4**) could be successfully transformed into tricyclic furans (**6**) and (**7**) in moderate yields (45-65%) when treated with 1 equiv. t-BuOK in dimethyl sulfoxide (DMSO)-tetrahydro-

furan (THF) at 100°C. Under these conditions, however, the cyclization of the enyne alcohol (5) gave the cyclic ether (8) without any formation of the desired fused furan ring (Scheme 1).

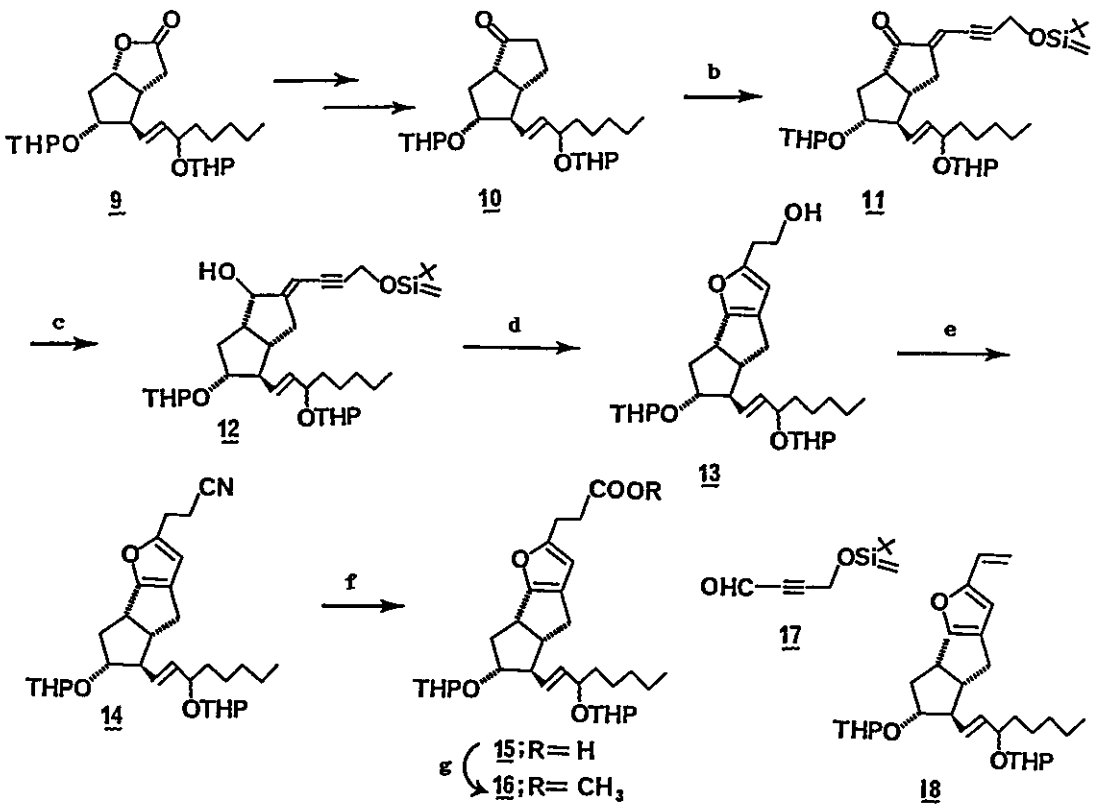


Scheme 1

Conditions: a) t-BuOK (1 equiv.), DMSO-THF (2:1), 100°C, 15-30 min

The preparation of the requisite prostanoid enyne alcohol (12) was next carried out according to the sequence shown in Scheme 2. The key synthetic intermediate (10) was prepared from the lactone (9)[5] in 45% overall yield through the sequence essentially same as before.[6] Generation of the enolate of 10 followed by trapping with aldehyde (17) afforded the corresponding aldol products, which was immediately dehydrated to furnish the enone (11). Reduction of 11 under Luche conditions gave the enyne alcohol (12).

Crucial furan-forming cyclization was now effected under milder conditions than those reported by Brandsma.[4] Thus, treatment of 12 with 1 equiv. t-BuOK in DMSO-THF at 70°C for 80 min gave the desired tricyclic furan (13) (40%) along with the eliminated product (18) (20%). For the elongation of the α-side chain, the mesylate of 13 was treated with excess NaCN in hexamethylphosphoric triamide (HMPA) to afford the nitrile (14) in 72% yield from 13. Owing to the relatively unstable character, 14 was carefully converted to the acid (15), which was found to be rather unstable, so that the direct deprotection of THP groups was



Scheme 2

Conditions: b) LDA, THF, -78°C, 30 min, then 17, -78°C, 10 min; $MeSO_2Cl$, Et_3N, CH_2Cl_2, -55°C, 20 min, then DBU; c) $NaBH_4$, $CeCl_3$, MeOH, 0°C; d) t-BuOK, DMSO-THF (2:1), 70°C, 80 min; e) $MeSO_2Cl$, Et_3N, CH_2Cl_2, -55°C; NaCN, HMPA, rt, 2 h; f) DIBAL-H, CH_2Cl_2, -25°C; NH_4Cl aq. -25°C; $AgNO_3$, KOH, EtOH, rt; g) CH_2N_2, ether; 16 - 2) AcOH-H_2O-THF(3:1:1), 60°C, 1 h

unsuccessful even under mild conditions. Therefore, further transformation was carried out by using the ester (16) which was more chemically stable and easily obtainable from 14 in 20% overall yield. The deprotection of THP groups of 16 afforded the desired diols (2a and 2b), which were easily separable by SiO_2 column chromatography (ether). More polar isomer (2a) [30%, ir (neat): 3380, 1735 cm^{-1}; pmr($CDCl_3$): δ5.88 (1H, s, furan), 5.70-5.65 (2H, m, olefins), 3.65 (3H, s, OCH_3); MS(EI): m/z 376 [M^+]] showed weak PGI_2-like activity in inhibition of platelet aggregation (IC_{50}; 0.4 μg/ml), while the less polar isomer (2b) was found to be less active than 2a.

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REFERENCES AND NOTES

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1. Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.
2. M. Shibasaki, Y. Torisawa, and S. Ikegami, Tetrahedron Lett., 1983, **24**, 3493; the latest efficient synthesis, see: S. Hashimoto, T. Shinoda, and S.Ikegami, J. Chem. Soc., Chem. Commun., 1988, 1137 and other references cited therein.
3. For the recent synthetic studies, see: E. J. Corey and A. K. Ghosh, Chem. Lett., 1987, 223; H. Nemoto, E. Shitara, K. Fukumoto, and T. Kametani, Heterocycles, 1987, **25**, 51; K. A. Richardson, J.Saunder, and R. J. K. Taylor, Tetrahedron Lett., 1985, **26**, 1171; K. C. Nikolson and H. Vorbruggen, ibid., 1983, **24**, 47.
4. P. H. M.Shreurs, W. G. Galeesloot, and L. Brandsma, Rec. trav. Chim. Pay-Bas, 1975, **94**, 70.
5. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, J. Am. Chem. Soc., 1970, **92**, 397.
6. Y. Torisawa, H. Okabe, and S. Ikegami, J. Chem. Soc., Chem. Commun., 1984, 1062.

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