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SYNTHESIS OF DIMERIC CARBACYCLIN STRUCTURES: ILOPROST-11-ILOPROST-ESTER AND ILOPROST-15-ILOPROSTESTER

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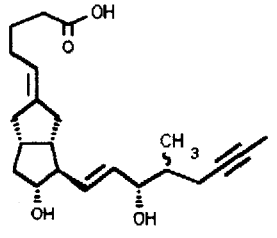
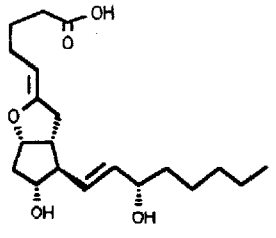
Summary: The syntheses of dimeric carbacyclins **3** and **4** were accomplished by coupling of suitably protected precursors with DCCI in the presence of DMAP starting from the carbacyclin iloprost.

Iloprost (**1**) is a stable analogue of the natural prostacyclin **2** . It has the same biological profile and potency as prostacyclin and shows promise in the treatment of arterial occlusive disease.[1,2]

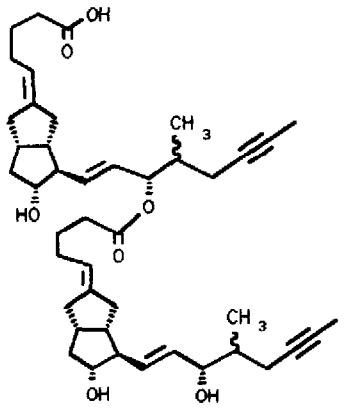


1

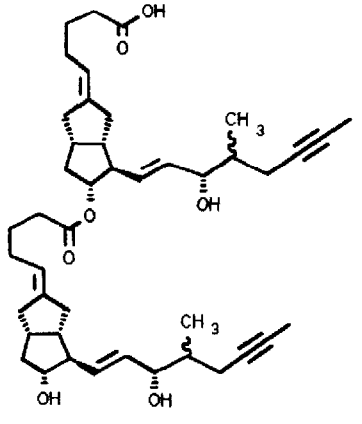


2

For pharmaceutical applications the purification of the material is very important. Because of regulatory requirements the byproducts of a new drug must be known down to the 0.1% scale. We observed during the evaporation process of purified material the formation of two new decomposition products.
Chromatographic isolation of minute amounts of these impurities followed by spectroscopic structure elucidation suggested the formation of the dimeric esters **3** and **4** of iloprost.



3

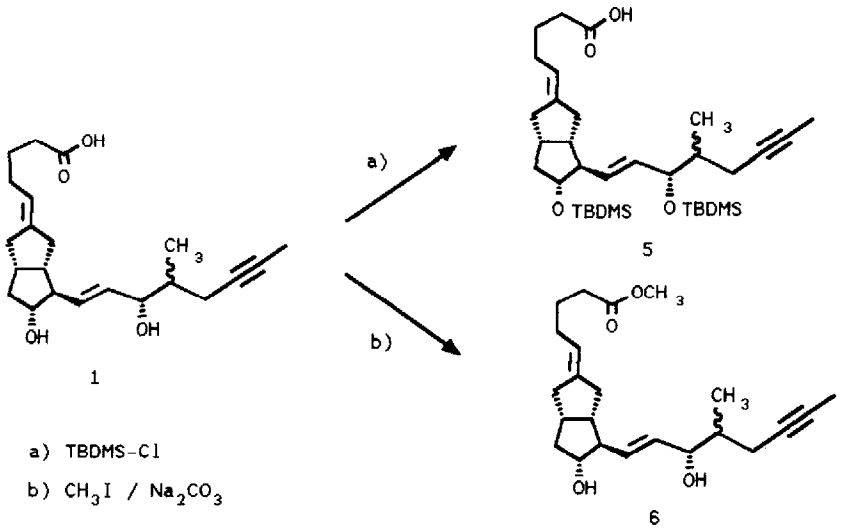


4

To confirm structures 3 and 4 and for comparison it was necessary to prepare the compounds on a gram scale. Initial attempts to condense unprotected iloprost (1) gave intractable mixtures.

Therefore our strategy for synthesis was to condense the 11- or 15-monosilylated Iloprost-trimethylsilyl-ethylester 11 or 12 with 11,15-disilylated iloprost 5 to dimeric structures 13 and 14 .

To prepare the proper protected materials we started syntheses from 1 , which was silylated with tert.butyl-dimethylsilylchloride[3] (TBDMS-Cl) to give 11,15-disilylated iloprost 5 .
For synthesis of the other required building block, iloprost (1) was esterified to give 6 with methyl iodide/Na_2CO_3 in acetone.

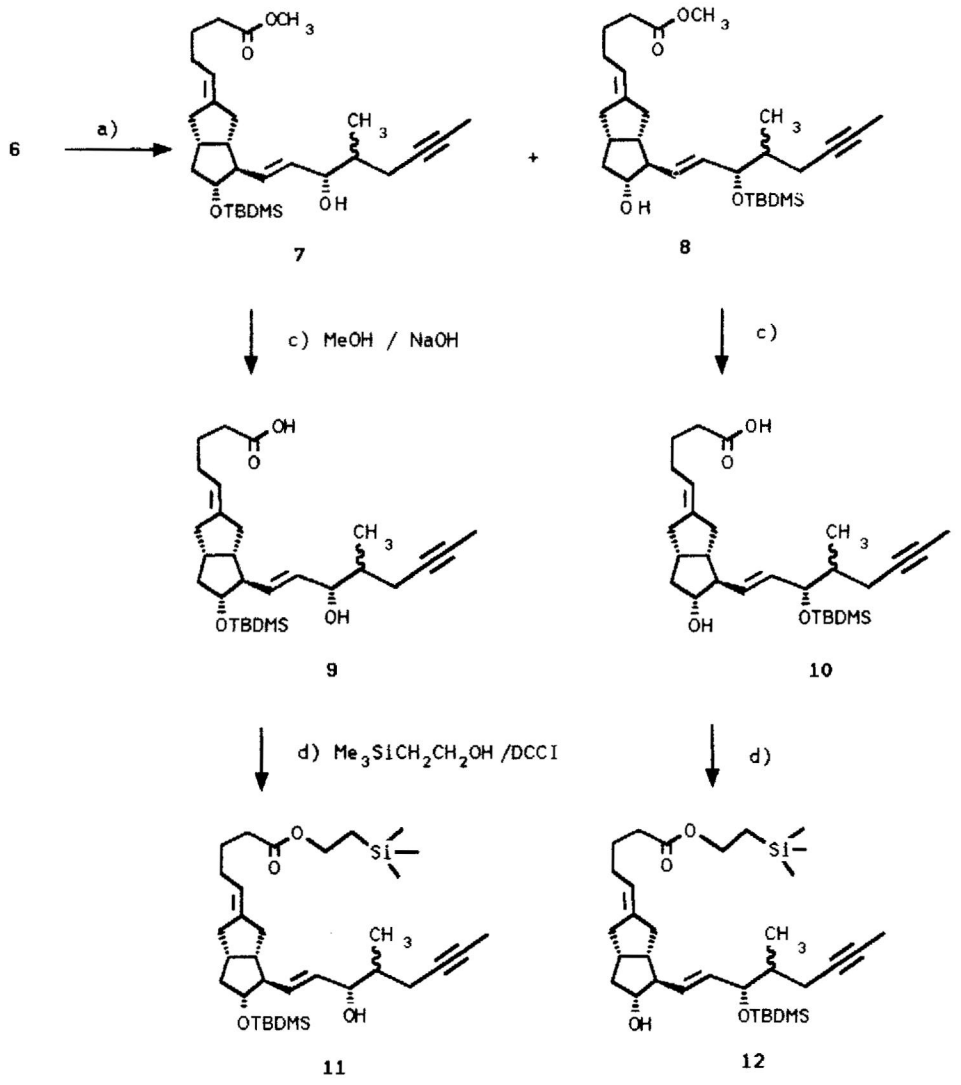


6 was silylated with tert.butyl-dimethylsilyl-chloride[3] to give the 11-tert.-butyldimethylsilyl isomer 7 and the less polar 15-tert.butyldimethylsilyl isomer 8 in a 2:1 ratio, which were separated by chromatogra-phy on silica gel.

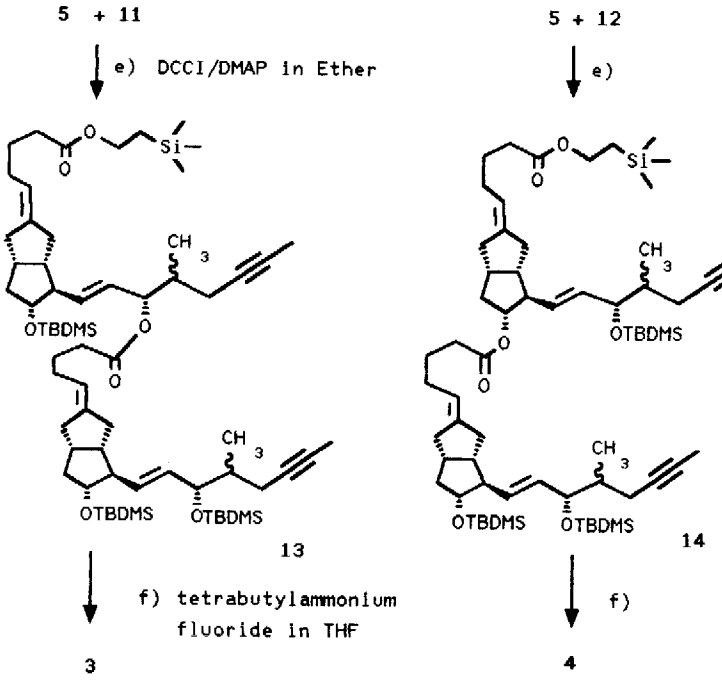
After saponification of the methylesters 7 and 8 (10% NaOH, MeOH,3h,20°C) to 9 and 10 in a smooth reaction, these compounds were converted to the trimethyl-silylethyl-esters 11 and 12 with an excess of trimethylsilylethanol (10 eq to reduce selfcondensation) in ether in the presence of 4-dimethyl-aminopyridine (DMAP) and dicyclohexylcarbodiimide (DCCI) in 80% yield.

Condensing 5 and 11 in ether in the presence of DCCI and DMAP gave the hydroxyl and carboxyl protected dimeric structure 13 in 85 % isolated yield after chromatography. The trimethylsilyl-ethylester and TBDMS-ethers were cleaved simultaneously by tetrabutylammonium fluoride in THF.[4]

The crude product 3 was purified by chromatography on Uetikon R-Sil-18 silica gel with acetonitrile/water 75:25 as eluent in 95% yield.



In an analogous way the dimeric isomer **4** was prepared by esterification of **5** and **12** to compound **14**, which was deprotected and worked up to **4** in 85% yield after purification by reversed phase chromatography on silylated silicagel with actonitrile/water 75:25 as eluent.



The dimeric carbacyclins 3 and 4 both gave iloprost (1) after saponification. Spectroscopic data of 3 and 4 are in agreement with the given structures.[5]

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References and Notes:

1. R.C.Nickolson, M.H.Town, H.Vorbrüggen, Med. Res. Rev. **1985**, 5, 1.
2. (a) W.Skuballa, H.Vorbrüggen, Angew. Chem. **1981**, 93, 1080; Angew. Chem. Int. Ed. Engl. **1981**, 20, 1046.
(b) B.Bennua, H.Dahl, H.Vorbrüggen, Synthesis **1986**, 41.
3. E. J. Corey and A. Venkateswarlu, J.Am.Chem.Soc., **1972**, 94, 6190.
4. (a) P.Sieber, Helv. Chim. Acta 1977, 60, 2711. (b) H.Gerlach, Helv. Chim.Acta **1977**, 60, 3039. (c) J.D.White, S.Ohira; J. Org. Chem. **1986**, 51, 5492.
5. **3**: colorless oil; FAB-MS: m/e 703 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$/300 MHz):δ 0.93/0.95/0.96/1.02 (d each, 6 Hz, 6H, 16- and 16'-CH_3), 1.79 (m, 6H, H-20 and H-20'), 3.76 (dt, 1H), 3.93-4.01 (m, 1H), 4.09 (m, 1H), 4,81 (q, 1H, J=8Hz), 5.18-5.28 (m, 2H), 5.43-5.57 (m, 4H); IR (neat): 1727 cm^{-1} (COOR), 1713 cm^{-1}(COOH).
4 : colorless oil; FAB-MS: m/e 703 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$/300 MHz): δ 0.92/0.97/01.05/1.06 (d each, 6H, J=6.8 Hz, 16- and 16'-CH_3), 1.78 (m, 6H, H-20 and H-20'), 3.61 (dt, 1H, J=7Hz), 3.72 (dt, 1H, J=8.3 Hz), 3.95 (t, 1H, J= 7.45 Hz), 4.95-5.04 (m, 1H), 5.13-5.59 (m, 6H); IR(neat): 1726 cm^{-1}(COOR), 1713 cm^{-1}(COOH).

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