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AZAPROSTANOIDS II. SYNTHESIS OF 12-AZACARBOPROSTACYCLIN ANALOGS[1]

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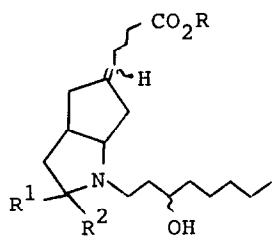
ABSTRACT: A total synthesis of 12-azacarboprostacyclin analogs 1 and 2 from 9 is described.

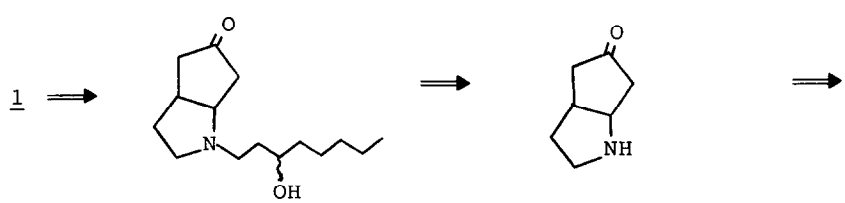
Synthetic orally active drugs based on prostacyclin[2] (PGI_2) could be potentially useful in the treatment of thrombotic disease, hypertension, platelet consumption and all forms of vascular disease.[3] Tremendous efforts have been focused upon carboprostacyclin[4] because of its PGI_2-like biological profile.[5] We have been interested in preparing azacarboprostacyclin analogs as potential anti-thrombotic agents for some time. A recent report[6] describing the synthesis of 12-azaprostacyclin analogs prompts us to disclose our efforts in this area. In this communication, we wish to report the synthesis of 12-azacarboprostacyclin analogs 1 and 2 from a common intermediate 9.



1, R = R^1 = R^2 = H

2, R = Me, R^1, R^2 = O

Retrosynthetically, 1 might be derived from 3 by a Wittig reaction. Compound 3 should be easily synthesized from 4 which, in turn, might be obtained by Dieckmann cyclization of 5 followed by decarboxylation. The readily available 6[7] could be a suitable starting material for compound 5. The synthesis of 2 was also realized via the common intermediate 9.



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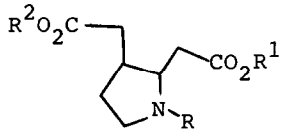

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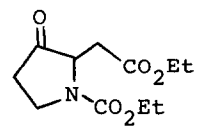

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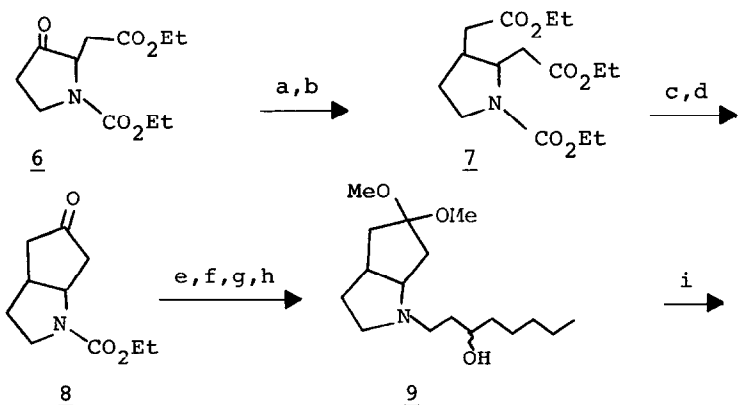
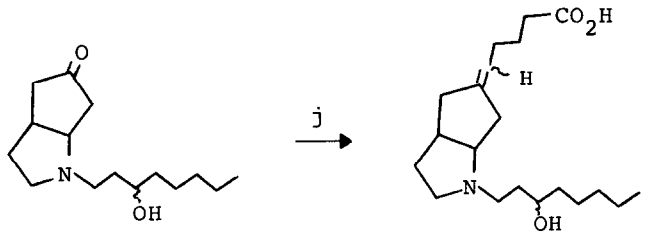
The actual synthetic route leading to 1 is shown in Scheme I. Compound 6 was reacted with the phosphonate derived from trimethyl phosphonoacetate to give the α,β-unsaturated ester which was smoothly hydrogenated to the diester 7 as an oil in 70% yield after HPLC purification [IR (neat) 1740, 1700 cm^{-1}; NMR ($CDCl_3$) δ 4.17 (q, J=7Hz, $2CO_2\underline{CH_2}CH_3$), 3.70 (S, $CO_2\underline{CH_3}$), 1.27 (t, J=7Hz, $2CO_2CH_2\underline{CH_3}$)]. Dieckmann cyclization of 7 followed by decarboxylation[8] gave rise to the oily ketone 8 in 51% yield after purification by HPLC [IR(CH_2Cl_2) 1750, 1700 cm^{-1}; NMR ($CDCl_3$) δ 4.11 (q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 1.23 (t, J=7Hz, $CO_2CH_2\underline{CH_3}$)] Ketone 8 was then converted to 9 in 57% yield by the following transformations: 1. protection of the ketone as dimethyl ketal; 2. cleavage of the carbamate by methyl lithium; 3. conjugate addition of the resulting amine to 3-keto-1-heptene and finally, reduction of the ketone. The protected ketone in 9 was unmasked to give 3 as an oil after HPLC purification [IR (CH_2Cl_2) 3250, 1740 cm^{-1}]. Compound 3 was allowed to react with the phosphorane derived from (4-carboxybutyl)-triphenylphosphonium bromide to yield 1[9] in 85% yield after purification by flash column chromatography using methanol-methylene chloride as an eluent.

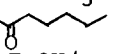
Scheme I



6 7 8 9

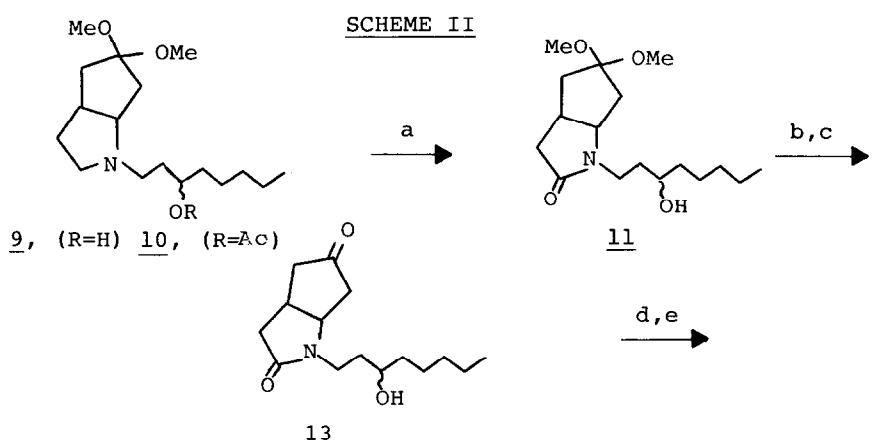


3 1

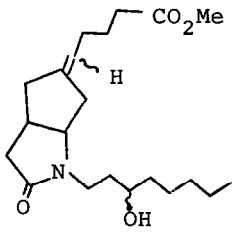
Conditions: a. $(MeO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Me$/NaH/THF; b. H_2/10%Pd on C/EtOAc; c. NaH/DMF; d. NaCl/DMSO-H_2O/150°; e. $CH(OMe)_3$/p-TsOH/MeOH-CH_2Cl_2; f. MeLi/THF/0°; g.  /glyme; h. $NaBH_4$/EtOH/-20°; i. p-TsOH/acetone; j. $Ph_3\overset{+}{P}(CH_2)_4\ CO_2H\bar{B}r$/$KOBu^t$/PhH/80°

In order to synthesize 2 by using an intermediate in Scheme I, it requires conversion of the pyrrolidine ring to a five-membered lactam. After several unsuccessful attempts on 3 and 1, we turned our attention to compound 9 (Scheme II). The hydroxy group in 9 was protected as an acetate to afford 10 [mp 82-84°C; IR(CH_2Cl_2) 1730 cm^{-1}; NMR ($CDCl_3$) δ 3.24 (s, OCH_3), 3.16 (s, OCH_3), 2.00 (s, $O\overset{O}{\overset{\|}{C}}CH_3$)]. Oxidation of 10 to lactam 11 was realized by employing N-bromosuccinimide (NBS).[10] Compound 11 was easily isolated from the other unidentified products, albeit in 30% yield [IR (CH_2Cl_2) 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (s, 2 OCH_3), 2.00 (s, $O\overset{O}{\overset{\|}{C}}CH_3$)]. In a small scale (0.15 mM) NBS oxidation, only desired 11, which showed normal five-membered lactam absorption[1] in IR, was observed. However, the other regioisomer 12 [IR (CH_2Cl_2) 1730 and 1635 cm^{-1}] appeared when attempting to scale-up the reaction. With 11 in hand, the remaining steps were straightforward. Deprotection of the acetate and dimethyl ketal afforded the hydroxyketone 13 [IR(CH_2Cl_2) 3460, 1750, 1670 cm^{-1}] Compound 13, upon treatment with the phosphorane described previously, gave an acid[12] which was converted to 2[9]. The overall yield from 11 to 2 was ca 30%.

SCHEME II



9, (R=H) 10, (R=Ac) 11 13



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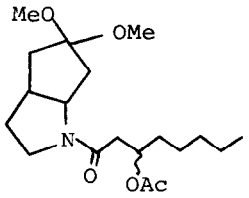

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Conditions: a. NBS/$NaHCO_3$/THF-H_2O; b. K_2CO_3/MeOH; c. p-TsOH/acetone; d. $Ph_3\overset{+}{P}(CH_2)_4CO_2H\bar{B}r$/$KOBu^t$/PhH/80°; e. CH_2N_2

While compound 1 did not inhibit cat platelet aggregation induced by arachidonic acid[13], compound 2 gave 25% inhibition of ADP-induced rat platelet aggregation at $2.5x10^{-4}$M.[14]

References and Notes

1. Contribution No. 3136 from Central Research and Development Department. For Azaprostanoids I. see C.-L. J. Wang, Tetrahedron Lett., 23, 1067 (1982).
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7. (a) T.A. Geissman and A.C. Waiss, Jr., J. Org. Chem., 27, 139 (1962); (b) G. Stork and A. G. Schultz, J. Am. Chem. Soc., 93, 4074 (1971).
8. A.P. Krapcho and A.J. Lovey, Tetrahedron Lett., 957 (1973).
9. 1: oil, IR (CH_2Cl_2) 3400-2600 (br), 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (bs, 2H, $-CO_2H$ & - OH), 5.11(m,1H), 4.20-1.00 (m, 29H), 0.83 (t,3H); HRMS m/z 337.2611 (M+), calcd. for $C_{20}H_{35}NO_3$: 337.2617.
   2: oil, consisting of four racemic diastereomers, IR (CH_2Cl_2) 3610-3300 (br), 1740, 1665 cm^{-1}; NMR ($CDCl_3$) δ 5.20 (m, 1H), 3.63 (S, 3H), 4.10-1.00 (m, 27H), 0.90 (t,3H); HRMS m/z 365.2559 (M^+), calcd. for $C_{21}H_{35}NO_4$: 365.2566.
10. A. Picot and X. Lusinchi, Synthesis, 109 (1975).
11. In Ref. 6, a closely related five-membered lactam has shown IR absorption at 1670 cm^{-1}.
12. This acid could not be separated from the Wittig reagent.

13. The author thanks Professor A. M. Lefer of Thomas Jefferson University for conducting the tests.
14. I am indebted to Dr. W. Galbraith (Biochemicals Department) for obtaining the data. Technical assistance from Ms. T.L. Taylor is greatly appreciated.

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