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A DIRECT TOTAL SYNTHESIS OF THROMBOXANE B_2 (±)

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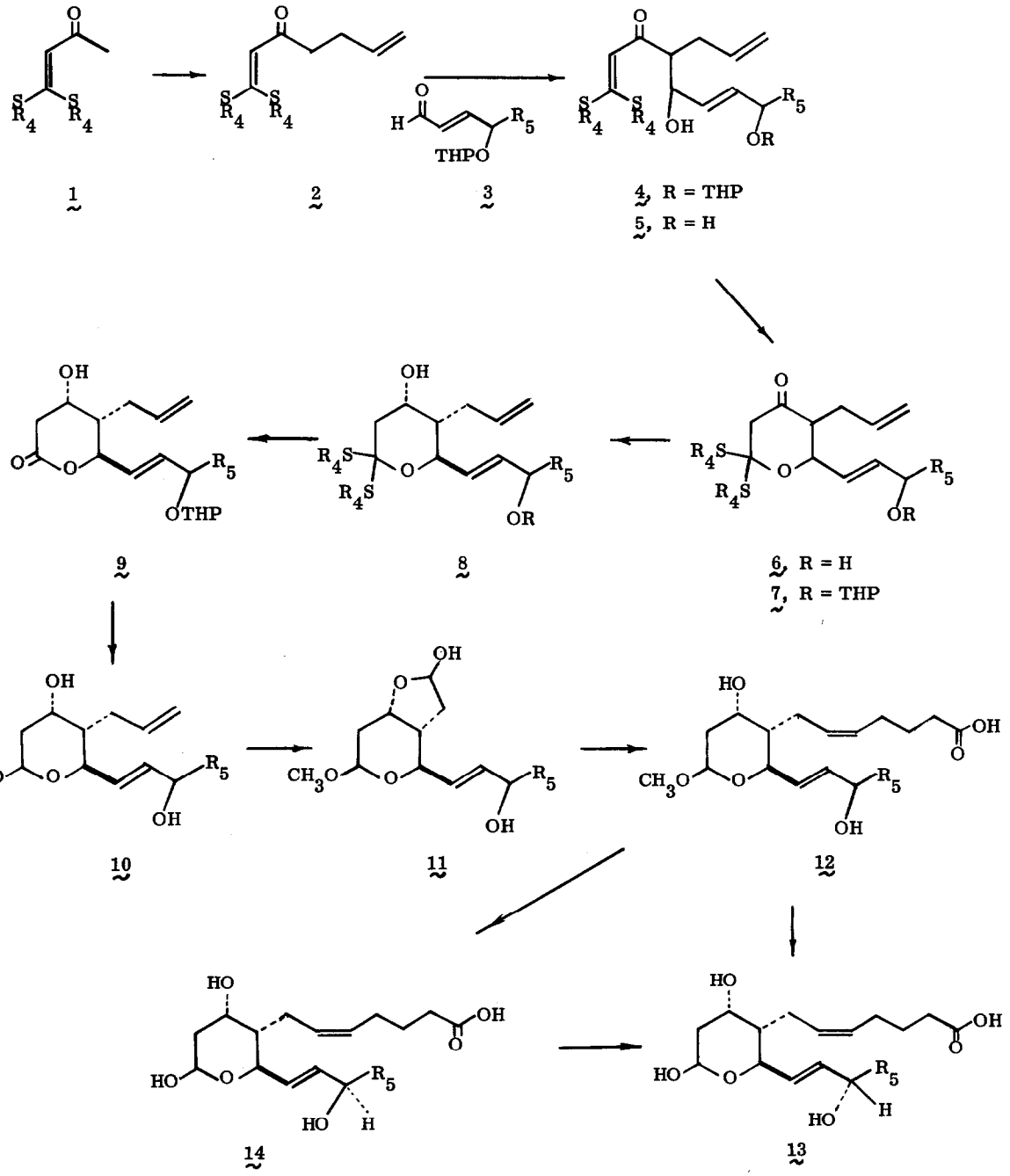
The prostaglandin 9,11-endoperoxide PGG_2[1] serves as a precursor not only of the prostaglandins (PG's) but also of another biologically interesting family designated as the thromboxanes.[2] This note describes a direct chemical synthesis of thromboxane B_2 (13) (racemic form) which does not require the intermediacy of a prostanoid. Three groups at the Upjohn company have recently disclosed routes to thromboxane B_2 from prostaglandins or prostaglandin precursors.[3]

The readily available enone 1[4] was converted to the lithium enolate (1 equiv lithium diisopropylamide in tetrahydrofuran-hexamethylphosphoricamide (THF-HMPA) (10:1) at -25° for 5 hr) which underwent alkylation to 2 (75% yield)[5] when treated with allyl bromide (2 equiv, first at -25° and then gradual warming to 25° over 2 hrs). Similar lithiation of 2 (1.1 equiv of lithium diisopropylamide in THF at -25° for 5 hr) and subsequent reaction with the aldehyde 3[6] gave the 1,2-adduct 4 (75% yield) as a non-separable mixture of diasteromers which was used as such (carbonyl max 1640 cm^{-1}). Depyranylation of 4 (acetic acid-water-THF, 3:1:1, at 45° for 3 hr) gave the diol 5 which was cyclized directly to 6 (carbonyl max 1723 cm^{-1}) by stirring in methylene chloride solution at 0° for ca. 0.5 hr with a catalytic amount of insoluble acid (e.g., p-toluenesulfonic acid). The cyclization product 6 could be separated from any remaining 5 by rapid chromatography on Florisil (cold room).[7] The THP derivative 7 was then formed from 6 in the usual way.

The mixture of isomeric ketones 7 was reduced by sodium borohydride (excess in ethanol at 0° for 0.5 hr) to afford an easily separable mixture of diastereomeric alcohols showing two spots of R_f 0.52 and 0.22 on silica gel plates using pet ether-ether 2:1. The product of R_f 0.52, which corresponds to 8 (mixture of 15α- and 15β-epimers) as shown by subsequent conversion to thromboxane B_2 as described below, (ca. 45% yield overall from 5)[7] was further transformed as follows. Exposure of 8 to silver nitrate (2 equiv)-silver oxide (4 equiv) in acetonitrile-water (4:1) at 0° for 2 hr afforded the hydroxy lactone 9 (85% yield) which was treated successively with (a) diisobutylaluminum hydride (4 equiv) in toluene at -78° for 0.5 hr and (b) methanol containing 1 equiv of boron trifluoride etherate at 25° for 2.5 hr to furnish the hydroxy acetal 10 in 95% yield. Hydroxylation of 10 with osmium tetroxide-pyridine in ether and cleavage of the resulting diol with sodium periodate in dioxane-water (3:1) at 25° for 0.5 hr gave the lactol-acetal 11 (70% yield).


1
2
3
4, R = THP
5, R = H
6, R = H
7, R = THP
8
9
10
11
12
13
14
$R_4 = \underline{n}\text{-}C_4H_9$; $R_5 = \underline{n}\text{-}C_5H_{11}$

Reaction of 11 with the ylide prepared from 4-carboxybutyl-triphenylphosphonium bromide and sodium methylsulfinyl carbanide in DMSO in the usual way[8] afforded 85% of 12 which was hydrolyzed to a mixture of (±)-thromboxane B_2 (13) and the C-15 epimer 14 by treatment with 85% phosphoric acid-water-THF (1:10:10) at 40° for 6 hr. After chromatographic separation on silica gel using ethyl acetate-acetic acid (99:1) pure 13 (R_f 0.24) and 14 (R_f 0.33) were obtained (approx. equal amounts and > 90% total yield). The infrared and proton magnetic resonance spectra of 13 were identical to those of an authentic sample of thromboxane B_2,[9] and the thin layer chromatographic behaviour of the two was identical in several different solvent systems. In addition the mass spectra of the tris-trimethylsilyl ether-methyl ester of 13 and that of the same derivative of thromboxane B_2 were indistinguishable. The 15-epimer 14 could also be converted to 13 using the superoxide displacement method.[10,11] Treatment of 14 with diazomethane and then methanol containing a catalytic amount of boron trifluoride etherate yielded the corresponding methyl ester-methyl acetal which could be transformed selectively to the 15-mesylate by reaction with 1.3 equiv of methanesulfonyl chloride and 1.3 equiv of triethylamine in methylene chloride at -25°. The unstable mesylate was subjected (without purification or delay) to displacement using potassium superoxide (6 equiv) in dimethyl sulfoxide-dimethylformamide-dimethoxyethane (1:1:1) at 0° for 20 min and 25° for 40 min to give the methyl acetal of thromboxane B_2, acid-catalyzed hydrolysis of which yielded thromboxane B_2 itself (13).

The most suitable conditions found thus far for the reaction of the lithio derivative of 2 with the aldehyde 3 involve reaction of the two components at 0° for 10 min, under which conditions the predominating product is that leading to the cyclization product 6 with the carbon sidechains trans to one another. The The cyclization of 5 to 6 is rapidly reversible but no appreciable cis → trans side chain isomerization seems to occur under mild cyclization conditions. A convenient reagent for the conversion of 5 to 6 on larger scale is silica gel-polyphosphoric acid 3:1 by weight.

A subsequent publication from these laboratories will deal with a direct synthetic route to thromboxane B_2 which leads to the natural (optically active form).[12]

References and Notes

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3. (a) N. A. Nelson and R. W. Jackson, Tetrahedron Lett., 3275 (1976); (b) R. C. Kelly, I. Schletter and S. J. Stein, ibid., 3279 (1976); (c) W. P. Schneider and R. A. Morge, ibid., 3283 (1976).
4. A Thullier and J. Vialle, Bull. Chem. Soc. France, 2182 (1962).
5. The assignment of structure to the various synthetic intermediates was confirmed by infrared and proton magnetic resonance data and, in the case of thermally stable intermediates, mass spectra of chromatographically homogeneous samples.

6. The aldehyde 3 was prepared from n-hexanal and 1,3-bis(methylthio) allyllithium using a previously described method; see, E. J. Corey, B. W. Erickson and R. Noyori, J. Am. Chem. Soc., 93, 1724 (1971).
7. Studies are currently underway to find optimal conditions for the conversion of 2 to 6.
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9. Kindly provided by Dr. John Pike of the Upjohn Company.
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