A stereospecific, total synthesis of thromboxane B_2

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A stereospecific, total synthesis of crystalline thromboxane B_2 from D-glucose is described.

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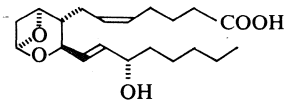
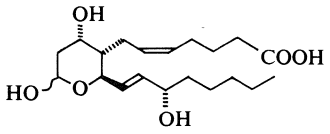
La synthèse stéréospécifique et totale de la thromboxane B_2 cristalline à partir du D-glucose est décrite.

The pioneering recent studies of Hamberg *et al.* (1) on the biosynthesis of prostaglandins has led to the discovery of a new class of compounds called the thromboxanes. It appears that in many cells, the normal transformation of endoperoxide intermediates into prostaglandins is altered in favor of the formation of thromboxane A_2, which, in turn, is rapidly transformed into thromboxane B_2 (2).



Thromboxane A_2



Thromboxane B_2

While the remarkable biological properties of the relatively unstable A_2 component (half-life in aqueous solution ~30 s) have been recognized, much less is known of the more stable B_2 component. In this paper, we describe a stereospecific total synthesis of crystalline thromboxane B_2, from D-glucose, based on the systematic and stereocontrolled introduction of functional groups.[2] Thromboxane B_2 can be considered as a 2,4,6-trideoxy-D-*ribo*-hexose, in which positions 4 and 6 are the sites of *C*-branching and chain extension, respectively. The plan for a practical synthesis of this substance was therefore based on the stereospecific introduction of the acid side chain at C-4, and appropriate chain extension at C-6 in a suitable carbohydrate derivative. Scheme 1 outlines the synthetic sequence leading to thromboxane B_2, and its C-15 epimer.[3]

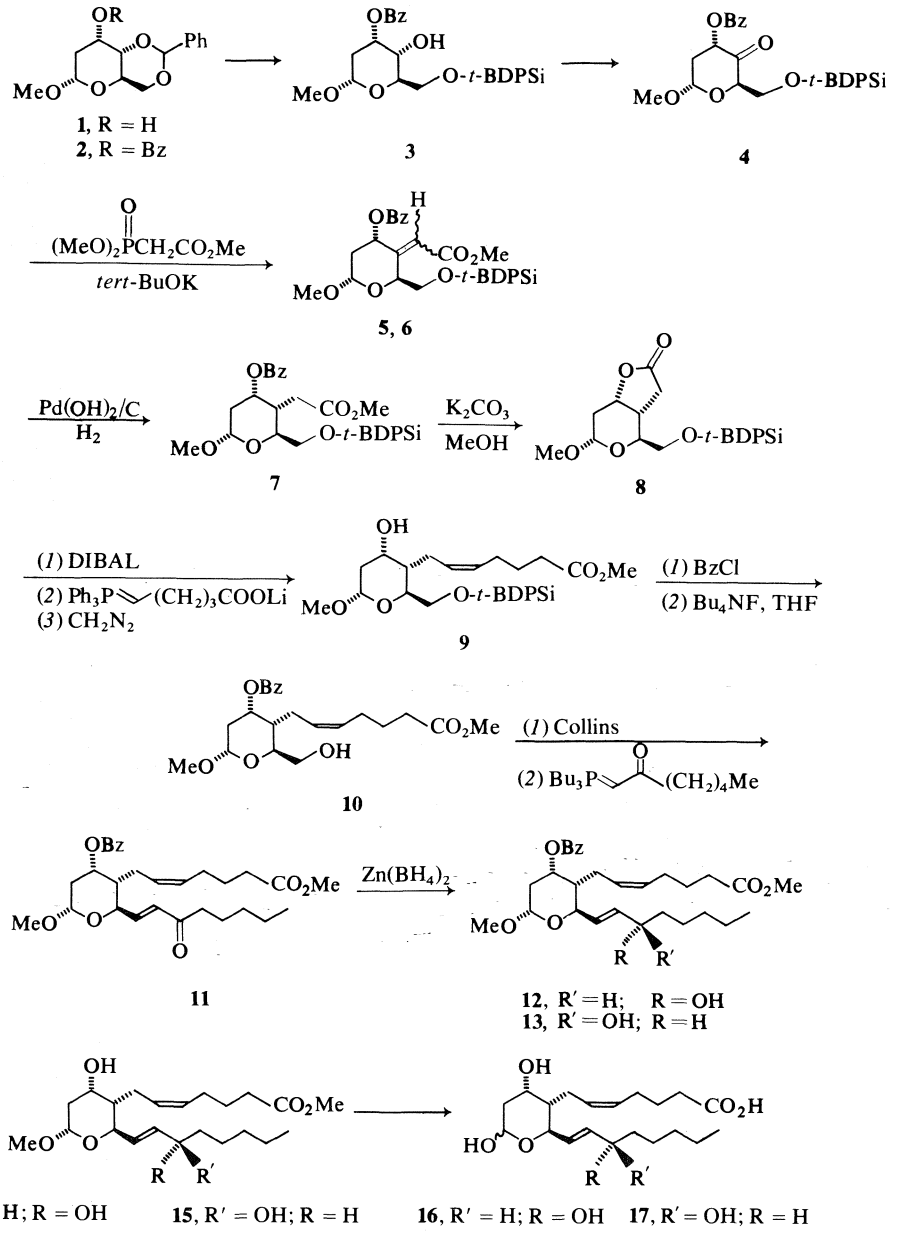
The readily available methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside **1** (4) was transformed into the corresponding 3-benzoate **2**, mp 100–101 °C, $[\alpha]_D^{25}$ +183° (*c* 1.18)[4] (89%), and the latter was sequentially hydrogenolyzed (20% $Pd(OH)_2/C$, H_2, quantitative), and silylated with *tert*-butyldiphenylsilyl chloride (5), to give the crystalline compound **3** (90%), mp 116–117 °C, $[\alpha]_D^{25}$ +90.2° (*c* 1.1). Oxidation of **3** in dimethyl sulfoxide and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDAC·HCl) (6) in the presence of pyridinium trifluoroacetate (25 °C, overnight), gave the highly crystalline 4-uloside derivative **4** (85%), mp 86–88 °C, $[\alpha]_D^{25}$ +148° (*c* 1.22). Lack of any detectable epimerization at C-3 was ascertained by nmr spectral data, and by subsequent transformation. Treatment of **4** with trimethylphosphonoacetate in the presence of potassium *tert*-butoxide gave a mixture of two compounds **5** and **6** that were

[1]NRCC predoctoral fellow, 1972–1976.

[2]While this manuscript was in preparation, a series of papers was published on the synthesis of thromboxane B_2 from prostaglandin $F_{2\alpha}$ and from a prostaglandin intermediate, see ref. 3).

[3]Prostaglandin numbering.

[4]Optical rotations were recorded in chloroform. Melting points are uncorrected. Crystalline compounds gave correct microanalyses. All compounds exhibited nmr spectra (60, 100 MHz) that were in accord with their structures.



SCHEME 1

separated by chromatography and isolated as syrups (95%) in a ratio of 3:2.[5] For the more polar component, $[\alpha]_D$ +162.5° (*c* 1.0); for the less polar component, $[\alpha]_D$ +199.3° (*c* 1.2). Hydrogenation (20% $Pd(OH)_2/C$, H_2, overnight) of **5** and **6** individually, or as a mixture resulting from the above reaction, gave **7**, isolated as a syrup (95%); $[\alpha]_D^{25}$ +100° (*c* 1.1). Treatment of **7** with potassium carbonate in methanol (25 °C, 60 h, N_2) gave the highly crystalline lactone **8** (85%); mp 80.5–81.5 °C; $[\alpha]_D^{25}$ +41.8° (*c* 1.05); *m/e* 409 (*M* − 31), *m/e* 383 (*M* − 57). Reduction of **8** with diisobutylaluminium hydride (DIBAL) in

[5]Ozonolysis of **5** and **6** individually gave the crystalline 4-uloside derivative **4**.

toluene (quantitative), followed by treatment with 4-carboxybutyltriphenylphosphonium bromide in HMPT, in the presence of lithium bis(trimethylsilyl)amide 7, gave, after esterification with diazomethane and chromatography, the branched-chain derivative **9** as a syrup (67–71%); $[\alpha]_D^{25}$ +62° (*c* 1); *m/e* 483 (*M* − 57), *m/e* 465 (*M* − 57 − 18). Since hydrogenation of **5** and **6** was expected to occur by *cis*-addition, it was possible that the resulting products **7** and **8** could also have alternative configurations, *i.e.* epimeric at C-4. This possibility was dismissed by detailed nmr analysis of the products **7** and **8**, and by chemical means. Thus, oxidation of **9** with EDAC·HCl in DMSO, followed by attempted equilibration with K_2CO_3–MeOH, and finally reduction with sodium borohydride gave the starting compound **9**, in which the configurations at C-3 and C-4 were preserved. It is well known from work done in this laboratory and elsewhere, that axial substituents that are vicinal to carbonyl groups are prone to epimerization, leading to the thermodynamically more stable equatorial isomer. Thus, had the catalytic reduction led to a lactone of opposite configuration at C-4 (*i.e.* D-*xylo* configuration), the axially disposed C-branched unit at C-4 would have most assuredly undergone epimerization during the treatment of the corresponding 3-uloside with base, in contrast to experimental results.

Benzoylation of **9**, followed by treatment of the product with tetra *n*-butylammonium fluoride in THF (8), gave, after chromatographic purification, compound **10** as a syrup (90%); $[\alpha]_D^{25}$ +130° (*c* 1.02); *m/e* 374 (*M* − 32). Collins oxidation (quantitative), followed by a Wittig reaction in the usual manner (9), gave the expected product **11**, isolated as a syrup in 76–80% yield; $[\alpha]_D^{25}$ +153° (*c* 1.14); M^+ 500; *m/e* 468 (*M* − 32). Reduction of **11** with zinc borohydride in a mixture of DME and ether (25 °C, 4 h) gave a mixture of the epimeric products **12** and **13** (1:1) (73%). Chromatographic separation gave the 15 *S* isomer **12**, $[\alpha]_D^{25}$ +137.8° (*c* 1.19); M^+ 502, *m/e* 484 (*M* − 18), and the 15 *R* isomer **13**, $[\alpha]_D^{25}$ +132.0° (*c* 0.91), M^+ 502, etc., as colorless syrups. Treatment of **12** and **13** individually with potassium carbonate in methanol, effected smooth debenzoylation to give the respective epimeric alcohols, **14** (15 *S* isomer), $[\alpha]_D^{25}$ +95.8° (*c* 1.09); *Exact Mass* calcd. for a fragment, *M* − H_2O: 348.2249; measured: 348.2246, and **15** (15 *R* isomer), $[\alpha]_D^{25}$ +93.2° (*c* 1.1). The chromatographic properties of **14**, and the mass spectral fragmentation of the corresponding *O*-trimethylsilyl derivative were in accord with data recorded for the natural thromboxane B_2 derivatives (1). For the bis *O*-trimethylsilyl derivative, *Exact Mass* calcd. for a fragment, *M* − 32: 510.3197; measured: 510.3214.

Finally, sequential deesterification of **14** (aqueous NaOH, 1.2 equiv.), followed by treatment with excess Dowex-50 (H^+), gave thromboxane B_2 **16**, as a chromatographically homogeneous syrup (90%), which crystallized from a mixture of ethyl acetate, ether, and petroleum ether (30–60 °C); mp and mixture mp 91–93 °C.[6] Recrystallization from the same solvent mixture gave beautiful elongated plates, mp 95–96 °C; $[\alpha]_D^{25}$ +57.4° (*c* 0.26, EtOAc); ν_{max}(film) 1705 cm^{-1} (C=O), 3380 cm^{-1} (OH); *m/e* 335 (*M* − H_2O − OH) *m/e* 317 (*M* − $2H_2O$ − OH). The epimeric derivative **17**, was similarly prepared, and isolated as a syrup.

The synthesis of thromboxane B_2 by the sequence described in this paper encompasses the elements of practicality, efficacy, and versatility, and it also provides access to intermediates that could be useful in the preparation of analogs.[7] In addition, it further illustrates the utility of carbohydrates as chiral precursors in the total synthesis of natural products (11).

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[6]We thank Drs. N. A. Nelson, R. C. Kelly, and W. P. Schneider of the UpJohn Company for a sample of their synthetic material, which they reported to be identical to natural thromboxane B_2. Our preparation had chromatographic and ir spectral properties that were identical to those of the UpJohn sample.

[7]Since an optically active Wittig reagent corresponding to the C-15 side chain can be prepared from a readily available intermediate (see ref. 10), the synthesis of thromboxane B_2 can be considered as being entirely stereospecific.

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