Total synthesis of (+)-thromboxane B_2 from D-glucose. A detailed account[1]

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This paper is dedicated to Prof. Raymond U. Lemieux on the occasion of his 60th birthday

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The total synthesis of thromboxane B_2 from D-glucose is described, based on the recognition of hidden carbohydrate-type symmetry in the molecule. Methyl 2-deoxy-α-D-*ribo*-hexopyranoside was prepared from D-glucose and manipulated in such a way as to introduce C-branching at C-4 in a stereocontrolled manner. This crucial intermediate was then transformed into the target compound by adaptations of established methodology in the field.

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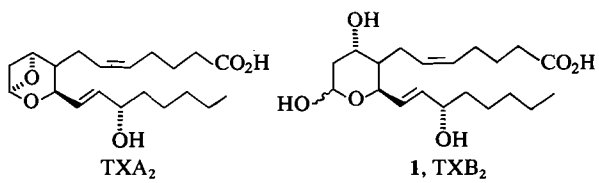
La synthèse totale du thromboxane B_2 à partir du D-glucose est décrite. La stratégie est basée sur la reconnaissance d'une symétrie type carbohydrate dans le squelette carboné de la molécule. Le méthyl 2-deoxy-α-D-*ribo*-hexopyrannoside préparé à partir du D-glucose a été manipulé afin d'introduire les substituants requis de façon régio- et stéréocontrôllée. Un intermédiaire crucial a été ainsi obtenu, qui, après modifications systématiques a donné accès au produit désiré.

The field of prostaglandin biosynthesis has been recently crowned by two landmark events, namely, the discovery of the thromboxanes (TXA_2 and TXB_2), and prostacyclin (PGI_2) (1). Pioneering studies have shown that PGI_2, the predominant product formed from endoperoxides in blood vessel linings, is capable of preventing the blood clotting process, while the same endoperoxides in platelets can be converted into TXA_2 which causes platelets to clump and aggregate. Thus, a common biosynthetic intermediate appears to be leading to two unique substances. A critical balance in the production of PGI_2 and TXA_2 appears to be a vital biological condition, and further knowledge gained from research on these naturally-occurring and structurally related bioregulatory agents will undoubtedly expand our understanding of the factors responsible for atherosclerosis and related disease states. Samuelsson and co-workers (2) have shown that TXA_2 is transformed rather rapidly into TXB_2, which unlike its precursor, is biologically inert as a platelet aggregating agent. Nevertheless, it is a valuable substrate for the study of a variety of biochemical processes.

The first syntheses of TXB_2 were reported by the Upjohn group (3) where $PGF_{2\alpha}$ and two of its synthetic intermediates were individually utilized as starting materials. Shortly thereafter, we announced our synthesis of TXB_2 from D-glucose (4), which was followed by a direct total synthesis of the racemic material (5) and other syntheses (6) leading to optically active intermediates of TXB_2. In this paper, we disclose the details of our original stereocontrolled synthesis of (+)-TXB_2 which is also adaptable to the preparation of analogs. Examination of the structure of TXB_2 shows the presence of a 6-membered lactol which can be related to a 2,4,6-trideoxy-D-*ribo*-hexopyranose (Scheme 1). Viewed in this perspective (7) it becomes apparent that the major synthetic challenge in attaining the intended objective is the regio- and stereocontrolled introduction of chain-branching at C-4 utilizing an appropriate carbohydrate precursor. The judicious choice of protecting groups compatible with otherwise well known operations in prostaglandin chemistry (8) becomes an important parameter in finalizing the general synthetic blueprint for such a structure.

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranose **2**, which is readily available in high yield from α-D-glucose (9), was an ideal starting material since it already contains a deoxy function as required in the tetrahydropyran portion of the target (Scheme 2). The corresponding crystalline benzoate **3** was subjected to hydrogenolysis and the resulting crystalline diol **4** was transformed into the highly crystalline *tert*-butyldiphenylsilyl ether **5** by treatment with *tert*-butyldiphenylsilyl chloride (10). The choice of protecting group for the primary



SCHEME 1

[1]For a preliminary account, see ref. 4.
[2]NRCC predoctoral fellow 1972–1976.

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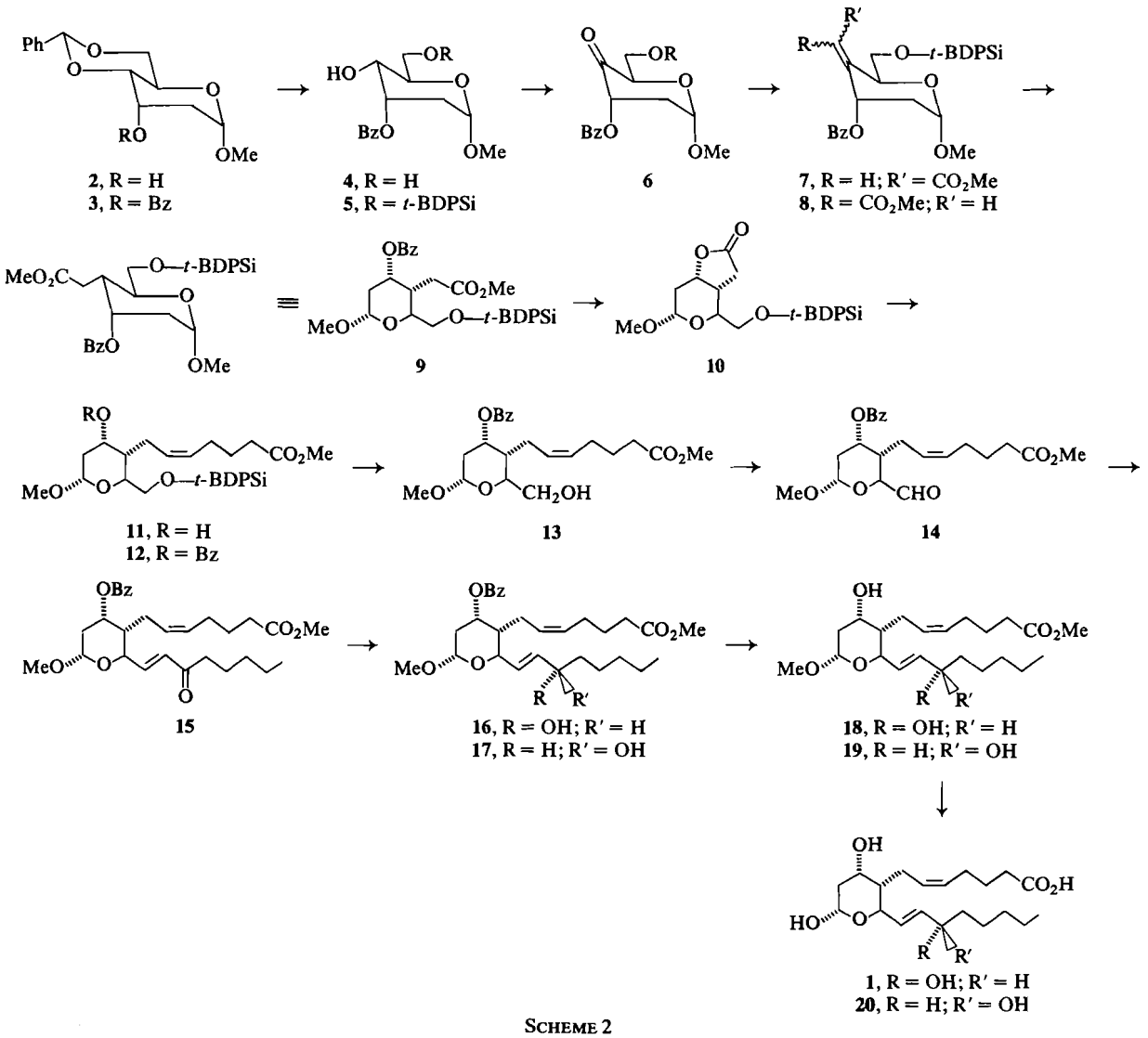
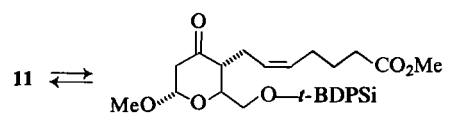


SCHEME 2

hydroxyl function was critical, since alternative options such as the commonly used trityl and *tert*-butyldimethylsilyl group (11) would not have been compatible with subsequent transformations envisaged in our synthetic scheme. Oxidation of the C-4 hydroxyl group in **5** could be effected with a variety of oxidants including DMSO – acetic anhydride. This led to the expected ketone **6** in 80% yield but contamination of the mother liquors with the methylthiomethyl ether derivative of **5** rendered the recovery of additional product somewhat lengthy. Oxidation of **5** in DMSO in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (12) and pyridinium trifluoroacetate led to the crystalline ketone derivative **6** in 94% yield without resorting to chromatography. That no epimerization at C-3 had taken place was evident from ^{1}Hmr data and from the chemistry that was to follow. Although this carbodiimide is better known as a reagent for peptide coupling (12), we have found it to be an excellent substitute for dicyclohexylcarbodiimide in Pfitzner–Moffatt oxidations (13), particularly in that the hydrochloride salt of the corresponding urea derivative is water soluble. Our initial attempts at chain-branching by treatment of **6** with (ethoxycarbonyl)methylenetriphenylphosphorane were unsuccessful and the ketone was recovered unchanged, even when the reaction was attempted in refluxing THF. With the more reactive tributylphosphine analog, a complex

mixture of products was obtained which was difficult to resolve by chromatography. Application of the phosphonate modification of the Wittig reaction proved much more practical, although the choice of base and solvent was critical. Thus, treatment of **6** with dimethyl(methoxycarbonyl)-methylphosphonate in the presence of sodium hydride in 1,2-dimethoxyethane, THF, or toluene, and at different temperatures, gave in all cases the expected exocyclic olefinic product (as a mixture of *E* and *Z* isomers), contaminated with another unknown olefinic product. However, adopting a published procedure (14) in which the carbanion was generated with potassium *tert*-butoxide in anhydrous toluene proved highly efficient in our case and led to the formation of a 1:1 mixture of the olefins **7** and **8** as the sole products in a combined yield of 90% after chromatographic purification. Based on spectroscopic data and literature precedents (9), the two products thus obtained were assigned as *E* and *Z* isomers respectively. In the *E* isomer, H-3 is found at δ 6.16 ppm ($J_{3,2a}$ = 10 Hz), downfield from the same signal in the parent ketone **6** by only 0.29 ppm, while in the *Z* isomer **8** H-3 is strongly deshielded, Δδ 0.98, due to the effect of the carbomethoxy group. By the same reasoning the deshielding patterns of H-5 in the respective isomers are reversed. The olefins **7** and **8** were individually oxidized with ozone and each was converted into the starting ketone **6** in high yield, thus providing chemical proof for their structures. The presence of an axial group at C-3 and the original choice of an α-glycoside were considered to be dominant factors in controlling the outcome of the catalytic hydrogenation of the exocyclic olefinic linkage. Not too surprisingly, however, there were substantial differences in the hydrogenation rates, although the product was the expected branched-chain derivative **9** in either case. Thus, whereas the *Z* isomer **8** was converted into **9** in the presence of 10% palladium-on-charcoal within 8 h, the *E* isomer **7** required 20% palladium hydroxide-on-charcoal and a 24 h exposure. The reasons for this are not immediately apparent, although inspection of molecular models reveals that in the *E* isomer, an interaction could exist between the methoxycarbonyl and the bulky *tert*-butydiphenylsilyl group, thus rendering the β-side somewhat less readily accessible to a weaker catalyst. Definitive proof for the orientation of the acetic acid side-chain was secured from spectroscopic data and chemical transformations. Having thus introduced the crucial branch-point at C-4, attention was next turned to the elaboration of the carboxyl-containing side chain of TXB_2. Treatment of the ester **9** with 1.4 equivalents of DIBAH in toluene at −78°C led to a mixture of the desired aldehyde and starting material. Using a large excess of reagent led to a mixture of several products. A practical recourse was to generate a lactone intermediate such as **10**. Thus, treatment of **9** with 0.3 equivalents of sodium methoxide in methanol led, after 4 days, to the crystalline lactone **10** in 76% yield. A more efficient procedure was to subject the ester **9** to methanolysis in the presence of anhydrous potassium carbonate, which led to the lactone **10** in higher yield (85%). Alkoxide mediated alcoholysis of diesters of the type **9** is expected to produce the corresponding hydroxy ester; however, using quasi-stoichiometric quantities of alkoxide the intramolecularly formed *cis*-lactone is apparently the thermodynamically more stable entity compared to the corresponding *cis*-hydroxy ester from which it is derived. Treatment of the lactone **10** with DIBAH following known methodology gave the corresponding lactol which was treated with the Wittig reagent generated from (4-carboxybutyl)-triphenylphosphonium bromide in the presence of lithium hexamethyldisilazane in HMPT (15). This led to the expected *cis*-olefin **11** in good yield after esterification. The prostaglandin literature (8) is replete with syntheses in which the *cis*-olefinic linkage of the carboxyl side chain has been introduced using the above mentioned phosphonium salt and dimsylsodium in DMSO as solvent. Until recently, however, few experimental details were available in the literature for this method (16). In our hands, we have found the Rosen procedure (15) to be convenient and highly reproducible from run to run and have used it in this as well as other instances, particularly when small quantities of materials were available for the Wittig reaction.

At this juncture, we deemed it necessary to secure chemical evidence concerning the correct orientation of substituents at C-3 and C-4, since epimerization at C-3 in **6** and a subsequent reduction of the products **7** and **8** from the α-side could have conceivably led to a *cis*-lactone with the opposite stereochemistry relative to **10**. Accordingly, **11** was oxidized with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in DMSO to the corresponding 3-keto derivative **21** (Scheme 3) in 86% yield. This was treated in methanol with



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SCHEME 3

TABLE 1. ^{13}C magnetic resonance data of compounds **4–9** (ppm from TMS)

Carbon atom	4	5	6	7	8	9	10
1	97.2	97.0	97.5	97.4	97.7	97.5	96.7
2	33.3	33.2	34.1	38.2	35.6	33.3	32.8
3	68.0	68.3[a]	71.7	69.3	65.1	68.4[a]	75.1
4	66.9	68.1[a]	204.7	[b]	[b]	36.8	34.9
5	69.9	69.7	77.2	72.5	66.4	68.8[a]	68.2
6	62.5	64.8	63.5	66.1	63.5	65.3	65.4
C(1)—O*Me*	55.2	55.0	55.1	55.4	55.1	54.9	55.2
CO_2Me				51.2	51.7	51.5	
Me_3—*C*		19.3	19.2	19.2	19.2	19.3	19.2
Ph=O	167.0	166.7	165.1	164.7	165.4	166.0	
				165.8	165.9		
CO_2R				157.9[c]	148.5[c]	172.2[c]	175.8
C(4)=*C*—*H*				111.3	117.6		
C(4)—CH_2						32.4	31.0

[a] These numbers can be reversed within the same column.
[b] Unresolved signal.
[c] R = Me.

potassium carbonate during 5 h after which chromatographic examination revealed the presence of the original ketone and a small quantity of a product arising from elimination. The ketone **21** was subsequently isolated from such a mixture (72.5%) and was found to be identical to the original material. Had the olefinic side-chain been in the axial orientation, it would have undergone base-catalyzed epimerization to the equatorial isomer. Reduction of **21** with sodium borohydride in methanol at 0°C led to **11** in 74% yield. From the experiments, it was clear that the stereochemical integrity at C-3 had been maintained during the oxidation and subsequent phosphonate condensation reaction, and that the reduction of the olefins **7** and **8** led, as expected, to the acetate side-chain with an α-orientation (D-*ribo* configuration as in **9**). The ^{13}Cmr spectral parameters for compounds **4–10** are listed in Table 1 and the assignments are based on correlations with known compounds and from literature data (17). Pursuing our synthetic scheme towards TXB_2, the hydroxyl group in **11** was protected by benzoylation to give **12** as a syrup, which was desilylated with fluoride ion (11) to the alcohol **13** and the latter was oxidized to the aldehyde **14** with the Collins reagent according to its adaptation to carbohydrates (18). The yields of these individual steps were high and the products were characterized by spectroscopic data. Chain extension of the aldehyde **14** was effected with *n*-tributylphosphoranylidene-2-heptanone (19) in the usual manner to give the α,β-unsaturated ketone derivative **15** in 79% yield after chromatography. In view of their modes of formation and genesis, all the intermediates to this point in the synthesis are optically pure. Reduction of **10** was effected with zinc borohydride in a mixture of 1,2-dimethoxyethane and ether, whereby two epimeric alcohols were formed in high yield and separated by thick layer chromatography. A slight preponderance (40%) of the "15-*S*" epimer **16** (later to be related to the natural product) was observed over the 15-*R* epimer **17** (33%). These compounds were individually transformed into TXB_2 and its "15-*R*" isomer by carefully executed deprotection techniques. Debenzoylation of **16** in the presence of potassium carbonate in methanol under a nitrogen atmosphere afforded the corresponding alcohol **18** as a syrup in 80% yield. The corresponding *O*-trimethylsilyl derivative showed a mass spectrum that was in complete accord with the expected structure and with the results published by Samuelsson and co-workers (2). The ester **18** was hydrolyzed with dilute alkali and the resulting sodium salt was treated with excess Dowex-50 (H^+) giving first the methyl glycoside derivative of TXB_2, which on longer contact with the acidic resin was hydrolyzed to TXB_2. The material crystallized from a mixture of ethyl acetate, ether, and petroleum ether to give beautiful plates, identical with an authentic sample. Similar treatment of the epimeric **17** gave the ester **19** and finally "15-epi" TXB_2, **20**, a syrup. The ^{13}Cmr data for compounds **11–18** in the natural series are listed in Table 2 and the assignments have been made based on literature precedents in the PG area. Since the Wittig reagent that provides the C-15 side-chain is available in optically pure form from malic acid (20), the sequence **14** → **16** can provide material with the natural "15-*S*" configuration directly, or indirectly by inversion of configuration of **17** as in the PG series (21). Thus, the entire synthesis of (+)-TXB_2 can be considered to be stereospecific. An X-ray crystallographic study of TXB_2 has shown that the unit

TABLE 2. ^{13}C magnetic resonance data of compounds **11, 12, 13, 18, 19**

Carbon atom	11	12	13	18	19
1	174.0	173.7	173.9	174.2	[b]
2	33.5	33.5	33.3	33.5	33.3
3	24.2	24.7	24.6	24.8	24.8
4	26.6	26.7[a]	26.7	26.6	26.5
5	[b]	[b]	[b]	129.2	128.9[a]
6	[b]	[b]	[b]	127.9	128.1[a]
7	25.3	26.3[a]	24.6	25.2	25.2
"8"	41.1	39.5	39.1	45.1	45.2
"9"	65.3	68.0	67.7	64.4	64.5
"10"	36.1	33.3	33.3	35.8	35.9
"11"	99.0	97.5	97.6	99.1	99.1
"12"	69.3	69.2	68.8	69.4	69.4
"13"	65.3	65.0	63.1	130.6	130.4
"14"				138.0	138.1
"15"				72.3	72.1
"16"				37.1	37.2
"17"				25.2	25.2
"18"				31.8	31.8
"19"				22.6	22.6
"20"				14.0	14.0
CO_2Me	51.3	51.2	51.3	51.5	51.5
C("11")—O*Me*	54.8	54.7	54.9	55.2	55.1
Ph*C*=O		165.9	166.0		
Me_3—*C*	19.4	19.4			
Me$_3$—C	26.9	26.9[a]			

[a] These numbers can be interchanged within the same column.
[b] Unresolved signal.

cell consists of α,β-anomers in the ratio of 35:65 (22).

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer automatic spectropolarimeter, model 141. The ^{1}Hmr spectra were recorded on a Jeol instrument at 60 MHz unless otherwise stated, with tetramethylsilane as internal standard, in deuterochloroform as solvent. The ^{13}C nmr spectra were recorded on a Bruker WH-90 instrument at 22.6 MHz. Mass spectra were recorded on an AEI-902 mass spectrometer at low resolution. Column chromatography was done using silica gel G254, with application of moderate suction. Solvents for tlc are as follows; solvent A: benzene–EtOAc, 10:1; solvent B: benzene–EtOAc, 10:3; solvent C: benzene–EtOAc, 10:6; solvent D: benzene–EtOAc, 1:1; solvent E: ethyl acetate – acetic acid, 99:1; solvent F: $CHCl_3$–MeOH, 10:1.

*Methyl 3-*O*-Benzoyl-4,6-*O*-benzylidene-2-deoxy-*α*-*D*-ribo-hexopyranoside (3)*

A solution containing 8 g (30 mmol) of **2** (9) in 60 mL of dry pyridine was treated with 4.2 mL (36 mmol) of benzoyl chloride at 0°C. The solution was stirred overnight at room temperature, then it was poured in a mixture of water, ice, and ether. Processing the organic layer in the usual way gave a syrup that crystallized from ether – petroleum ether to give the title compound in three crops (10.34 g, 93%). Recrystallization gave a pure sample, mp 100–101°C; $[\alpha]_D^{25}$ +182.9° (*c* 1.18, $CHCl_3$); λ_{max}(KBr): 1715 cm^{-1}; nmr data, δ (ppm): 2.08 (H_{2a}, $J_{2a,2e}$ = 15.7 Hz, $J_{2a,1}$ = 4 Hz, $J_{2a,3}$ = 3.5 Hz), 2.39 (H_{2e}, $J_{2e,2a}$ = 15.7 Hz; $J_{2e,3}$ = 3 Hz; $J_{2e,1}$ = 0.75 Hz), 3.37 (s, OCH_3), 4.75 (H_1, dd, $J_{1,2a}$ = 4 Hz, $J_{1,2e}$ = 0.75 Hz), etc. *Anal.* calcd. for $C_{21}H_{22}O_6$: C 68.10, H 5.99; found: C 68.58, H 6.15.

*Methyl 3-*O*-Benzoyl-2-deoxy-α-*D*-ribo-hexopyranoside (4)*

A solution of **3** (11 g, 30.5 mmol) in a mixture of ethyl acetate (150 mL) and methanol (75 mL) was hydrogenated in the presence of 20% palladium hydroxide on charcoal (1.5 g) (23). After 18 h, the catalyst was filtered and the filtrate was evaporated to dryness. The residue was crystallized from a mixture of dichloromethane, ether, and petroleum ether to give the title compound (7.93 g, 94%). An analytical sample was obtained, after two recrystallizations, from a mixture of hexanes and pentane, mp 112–114°C; $[\alpha]_D$ +158° (*c* 1.06, $CHCl_3$); R_f 0.57 (solvent F); λ_{max}(KBr): 3340 (OH), 1720 (C=O) cm^{-1}. *Anal.* calcd. for $C_{14}H_{18}O_6$: C 59.56, H 6.43; found: C 59.60, H 6.78.

*Methyl 3-*O*-Benzoyl-6-*O*-(tert-butyldiphenylsilyl)-2-deoxy-α-*D*-ribo-hexopyranoside (5)*

A solution containing **4** (7.48 g, 26.5 mmol) and imidazole (4.1 g, 59 mmol) in 53 mL of dry DMF was treated at 0°C with a 0.5 *M* solution of *tert*-butyldiphenylsilyl chloride (10) (58 mL, 29 mmol) in the same solvent. After stirring at room temperature for 20 h, the solution was diluted with water and ether. Processing the organic layer gave a crystalline residue that was recrystallized from ether – petroleum ether to give the title compound, mp 114–116°C (11.7 g, 85%). An analytical sample showed mp 116–118°C (hexanes); $[\alpha]_D$ +90.2° (*c* 1.1, $CHCl_3$); R_f 0.41 (solvent A); ms *m/e*: 489 (M^+ – Me_3C), etc. *Anal.* calcd. for $C_{30}H_{36}O_6Si$: C 69.20, H 6.97; found: C 69.05, H 6.76.

*Methyl 3-*O*-Benzoyl-6-*O*-(tert-butyldiphenylsilyl)-2-deoxy-α-*D*-erythro-hexopyranosid-4-ulose (6)*

To a cooled solution containing **5** (20.8 g, 40 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC·HCl) (4, 12) (23.04 g, 120 mmol) in 300 mL of dry DMSO was added successively 4.9 mL (60 mmol) of pyridine and 3.6 mL (50 mmol) of trifluoracetic acid and the solution was diluted with ether and ice-water; the organic layer was pro-

cessed as usual to give a viscous syrup which crystallized from a mixture of ether – petroleum ether to give compound **6** (19.94 g, 94%). Two recrystallizations gave an analytical sample, mp 86–88°C; $[\alpha]_D$ +148° (*c* 1.22, $CHCl_3$); R_f 0.68 (solvent A); λ_{max}(KBr): 1760 (C=O) cm^{-1}; ms *m/e*: 461 ($M^+ - Me_3C$), 429 ($M^+ - Me_4C - MeOH$), etc; *Anal.* calcd. for $C_{30}H_{34}O_6$ Si: C 69.47, H 6.61; found: C 69.97, H 7.07.

*Synthesis of Methyl 3-O-Benzoyl-6-O-(*tert*-butyldiphenylsilyl)-2,4-dideoxy-4-C-[E-(methoxycarbonyl)methylene]-*α*-D-erythro-hexopyranoside 7, and the Z Isomer, 8*

To a cooled suspension of potassium *tert*-butoxide (0.8 g, 7.2 mmol) in 100 mL of toluene was added dimethyl (methoxycarbonyl)methylphosphonate dropwise and with stirring. After 1 h, ketone **6** (3.1 g, 6.0 mmol) was added in one portion and the solution was stirred at room temperature for 8 h. The solution was diluted with ether, then treated with 10% dihydrogen sodium phosphate. Processing the organic layer gave a mixture of the *E* and *Z* isomers (3.26 g, 94%). Chromatographic separation (solvent A) gave the *Z* isomer **8** (1.68 g, 48.6%) and the *E* isomer **7** (1.46 g, 42.8%) in that order of elution. For **7**, $[\alpha]_D$ +199.3° (*c* 1.16, $CHCl_3$); nmr data, at 100 MHz, δ (ppm): 1.70 (m, H_{2a}, $J_{2a,2e}$ = 14 Hz, $J_{2a,3}$ = 10 Hz, $J_{2a,1}$ = 3.75 Hz), 2.90 (dd, H_{2e}, $J_{2e,2a}$ = 14 Hz, $J_{2e,1}$ = 7.0 Hz), 3.40 (s, OMe), 3.63 (s, CO_2Me), 5.0 (dd, H_1, $J_{1,2e}$ = 7.0 Hz, $J_{1,2a}$ = 3.75 Hz), 6.0 (s, C=CH), 6.15 (d, H_3, $J_{3,2a}$ = 10 Hz), etc; M^+ 574, ms *m/e*: 543 ($M^+ - MeO$), etc; for **8**, $[\alpha]_D$ +162.5° (*c* 1.0, $CHCl_3$); nmr data at 100 MHz, δ(ppm): 2.25 (m, H_{2a}, H_{2e}), 3.3 (s, OMe), 3.75 (s, CO_2Me), 6.0 (s, C=CH), 6.85 (m, H_3), etc; M^+ 543; ms *m/e*: 517 ($M^+ - Me_3C$), etc.

Ozonolysis of 7 and 8

A solution containing **7** (50 mg, 0.87 mmol) in 10 mL of methanol was treated with a stream of ozone (0.12 mmol/min) at −78°C. After 5 min of stirring (0.88 mmol ozone uptake; ~1 equivalent), nitrogen gas was passed through the solution, then 4 drops of dimethylsulfide were added. After standing at room temperature overnight, the solution was evaporated to dryness and the residue was purified by preparative tlc (solvent A, R_f 0.68) to give 36 mg (80%) of **6** as a homogeneous syrup. Crystallization was effected from petroleum ether to give 17 mg of **6**, mp and mixture mp 86–88°C; $[\alpha]_D$ +147.3°. Ozone treatment of the other isomer **8** gave essentially the same results.

*Methyl 3-O-Benzoyl-6-O-(*tert*-butyldiphenylsilyl)-2,4-dideoxy-4-C-[(methoxycarbonyl)methyl]-*α*-D-ribo-hexopyranoside, (9)*

From **7**: A solution containing 1.46 g (2.54 mmol) of **7** in a mixture of ethyl acetate and methanol (120:50 mL) was hydrogenated in the presence of 20% palladium hydroxide on charcoal (23) (0.5 g). After 24 h, the catalyst was filtered and the filtrate was processed as usual to give a syrup. Chromatography (solvent A, R_f 0.48) gave 1.11 g (70%) of the title compound as a viscous syrup, $[\alpha]_D$ +100.4° (*c* 1.17, $CHCl_3$); λ_{max}(film): 1737 (CO_2Me) cm^{-1}; nmr data, δ(ppm): 3.3 (s, OMe), 3.55 (s, CO_2Me), 4.85 (m, H_1), 5.4 (m, H_3), etc; ms *m/e*: 545 ($M^+ - MeO$), 519 ($M^+ - Me_3C$), etc. From **8**: hydrogenation of this isomer for 8 h gave the title compound (92%) having the physical constants described above.

*Methyl 6-O-(*tert*-Butyldiphenylsilyl)-4-C-(carboxymethyl)-2,4-dideoxy-*α*-D-ribo-hexopyranoside,γ-Lactone, (10)*

A solution containing **9** (0.836 g, 1.45 mmol) in 35 mL of dry methanol was treated with 0.2 g (1.45 mmol) of dry potassium carbonate and the suspension was stirred under nitrogen for 60 h. Neutralization with Rexyn 102 (H^+), and processing of the filtered suspension gave a colorless syrup which was purified by preparative tlc (solvent B, R_f 0.52) to give 0.518 g (85%) of the lactone **10**. Crystallization from petroleum ether gave 0.43 g of material with mp 80.5–81.5°C; $[\alpha]_D$ +41.8° (*c* 1.05, $CHCl_3$). An additional 70 mg was obtained from the mother liquors but remained as a syrup; λ_{max}(KBr): 1780 (C=O) cm^{-1}; ms *m/e*: 409 ($M^+ - MeO$), 383 ($M^+ - Me_3C$), 351 ($M^+ - Me_3C - MeOH$), etc. *Anal.* calcd. for $C_{25}H_{32}O_6$ Si: C 68.15, H 7.32; found: C 68.46, H 8.00.

Synthesis of 11

A solution of DIBAH (3.65 mL, 5.1 mmol) in hexanes was added to a solution containing the lactone **10** (1.5 g, 3.4 mmol) in anhydrous toluene at −78°C under nitrogen. After stirring for 30 min at −78°C, the solution was diluted with ether (25 mL) and saturated aqueous ammonium chloride (20 mL) while gradually allowing it to warm to room temperature after the additions. The solution was filtered over Celite and the latter was washed successively with water (30 mL) and ethyl acetate (100 mL). The organic phase was processed as usual to give the lactol derivative corresponding to **10**.

A solution of 1.58 *M* *n*-butyl lithium (17.2 mL, 27 mmol) in pentane was added to bis(trimethylsilyl)amine (3.16 g, 27.2 mmol) in 30 mL of dry ether at 0°C, under nitrogen. The solvents were evaporated under a current of dry nitrogen during 1 h and the resulting crystalline lithium bis(trimethylsilyl)amide was dissolved in 30 mL of dry HMPT. The solution was transferred into a solution of (4-carboxybutyl)triphenylphosphonium bromide (6.03 g, 13.6 mmol dried at 110°C, 0.02 Torr, 6 h) in 15 mL of HMPT. The *dark red* solution of the corresponding ylid was stirred under nitrogen for 1 h, then slowly transferred (25 min) into a cooled (0°C) solution containing the lactol (1.5 g, 3.4 mmol) in 15 mL of HMPT using a double tip needle under nitrogen pressure. After stirring at room temperature for 20 min, the solution was diluted with ether (250 mL) and ice-water and was acidified to pH ~ 2 with a 0.2 *M* solution of sodium bisulfate (250 mL). The organic phase was processed as usual to give an oil (3.57 g) which was dissolved in 10 mL of dichloromethane and 5 mL of methanol and treated with an excess of diazomethane in ether. Unreacted reagent was destroyed by addition of small portions of silica gel and the solution was filtered and the filtrate was evaporated to a syrup. Purification by preparative tlc (solvent A, R_f 0.34) gave 1.27 g (67%) of the title compound as a syrup; $[\alpha]_D$ +62.5° (*c* 1.09, $CHCl_3$); λ_{max}(film): 1738 (C=O) cm^{-1}; ms *m/e*: 509 ($M^+ - MeO$), 508 ($M^+ - MeOH$), etc.

Synthesis of 12

To a cooled solution of **11** (0.92 g, 1.7 mmol) in 15 mL of dry pyridine was added benzoyl chloride (0.42 g, 3 mmol) dropwise and with stirring. After stirring at room temperature overnight, the solution was poured into ice-water and ether, and the organic layer was processed as usual to give, after preparative tlc (solvent A, R_f 0.5) the title compound (0.91 g, 89%) as a colorless syrup; $[\alpha]_D$ +92.6° (*c* 1.04, $CHCl_3$); λ_{max}(film): 1736 (CO_2Me), 1715 (OBz) cm^{-1}; ms *m/e*: 612 ($M^+ - MeOH$), 587 ($M^+ - Me_3C$), 555 ($M^+ - Me_3C - MeOH$), 491 ($M^+ - MeOH - PhCO_2$) etc.

Synthesis of 13

A solution containing **12** (0.885 g, 1.37 mmol) in 5 mL of dry tetrahydrofuran was treated with a 1 *M* solution of tetra-*n*-butylammonium fluoride (3 mL). After stirring at room temperature for 3 h, the solution was evaporated to dryness and the residue was purified by preparative tlc (solvent B, R_f 0.20) to give the title compound **12** as a syrup (0.5 g, 89.5%); $[\alpha]_D$ +130° (*c* 1.02, $CHCl_3$); λ_{max}(film): 1735 (CO_2Me), 1715 (OBz) cm^{-1}; M^+ 406; ms *m/e*: 375 ($M^+ - MeO$), 343 ($M^+ - MeO - MeOH$), etc.

Synthesis of 14

A solution containing **13** (0.5 g, 1.22 mmol) in 15 mL of dry

dichloromethane was added rapidly to a solution of the Collins reagent prepared from chromium trioxide (1.46 g, 14.6 mmol) in pyridine (2.36 mL, 29.3 mmol) and dichloromethane (100 mL), under nitrogen. After stirring vigorously for 30 min the mixture was poured into ice-water and dichloromethane; the organic layer was processed as usual to give a syrup. The latter was dissolved in toluene (50 mL), the solution evaporated to dryness, the residue was taken up in ether, filtered, and the filtrate was evaporated to a syrup (0.446 g, 91%) which was used as such in the next step. The chromatographically homogeneous material showed λ_{max}(film): 1738 (CO_2Me, CHO), 1718 (OBz) cm^{-1}; R_f 0.4 (solvent B).

Synthesis of 15

A solution containing 1-tributylphosphoranylidene 2-heptanone (19) (0.42 g, 1.32 mmol) in dry ether (5 mL) was added to the aldehyde **14** (0.446 g, 1.1 mmol) in 20 mL of ether. The solution was stirred at room temperature for 3 h, it was then evaporated to dryness and the residue was purified by preparative tlc (solvent B, R_f 0.68) to give the title compound as a syrup (0.438 g, 79%); $[\alpha]_D$ +153.0° (*c* 1.14, $CHCl_3$); λ_{max}(film): 1736 (CO_2Me), 1718 (OBz), 1637 (C=C—*C*=*O*), 1636 (*C*=*C*—C=O) cm^{-1}; nmr data at 100 MHz, δ ppm: 2.26 ($H_{"16"}$, t, J = 7.5 Hz), 3.32 (s, OMe), 3.58 (s, CO_2Me), 4.68 ($H_{"12"}$, dd, $J_{"12,8"}$ = 10 Hz, $J_{"12,13"}$ = 6.25 Hz), 4.83 ($H_{"11"}$, d, $J_{"11"}$ = 3.73 Hz), 6.45 ($H_{"14"}$, d, $J_{"14,13"}$ = 15.6 Hz), 6.89 ($H_{"13"}$, dd, $J_{"13,14"}$ = 15.6 Hz, $J_{"13,12"}$ = 6.25 Hz), etc; M^+ 500; ms *m/e*: 468 (M^+ − MeOH), 437 (M^+ − MeOH − MeO), 399 (M^+ − $(CH_2)_3$ CO_2Me), 378 M^+ − $PhCO_2H$), 347 (M^+ − MeOH − $PhCO_2$), 315 (M^+ − 2MeOH − $PhCO_2$), 279 (M^+ − $PhCO_2H$ − $C_5H_{11}C$), etc.

Zinc Borohydride Reduction of 15. Isolation of the "C-15" Epimeric Alcohols 16 and 17

A 0.5 *M* solution of zinc borohydride (3 mL) in 1,2-dimethoxyethane was added to the enone **15** (0.37 g, 0.74 mmol) in 15 mL of anhydrous ether under nitrogen. The mixture was stirred for 3 h at room temperature, then it was diluted with ether (20 mL) and saturated ammonium chloride (20 mL). Processing the organic phase gave a 1:1 mixture of the epimeric alcohols **16** and **17** (0.354 g). Separation by preparative tlc (solvent C) gave the two products as syrups.

For the "15*S*" alcohol **16**: 0.15 g (40%), R_f 0.43; $[\alpha]_D$ +137.8° (*c* 1.19, $CHCl_3$); nmr data at 100 MHz, δ ppm: 3.34 (OMe), 3.60 (CO_2Me), 4.18 ($H_{"15"}$, m), 4.44 ($H_{"12"}$, dd, $J_{"12,8"}$ = 9.5 Hz, $J_{"12,13"}$ = 7.0 Hz), 4.79 ($H_{"11"}$, d, J = 3.75), 5.70 ($H_{"13"}$, dd, $J_{"13,14"}$ = 15.6 Hz, $J_{"13,12"}$ = 7.0 Hz), 6.08 ($H_{"14"}$, dd, $J_{"14,13"}$ = 15.6 Hz, $J_{"14,15"}$ = 5.6 Hz), etc; M^+ 502; ms *m/e*: 484 (M^+ − H_2O), 470 (M^+ − MeOH), 399 (M^+ − MeOH − C_5H_{11}), 348 (M^+ − MeOH − $PhCO_2H$), 330 (M^+ − $(CH_2)_3CO_2Me$ − C_5H_{11}), 304 (M^+ − C_5H_{11} − CH=CH$(CH_2)_3CO_2Me$), 227 (M^+ − MeOH − $PhCO_2H$ − C_5H_{11}), etc.

For the "15 *R*" isomer **17**: 0.125 g (33.7%); R_f 0.50; $[\alpha]_D$ +132.0° (*c* 0.91, $CHCl_3$); nmr data at 100 MHz, δ ppm: 3.36 (s, OMe), 3.60 (s, CO_2Me), 4.10 ($H_{"15"}$, m), 4.46 ($H_{"12"}$, dd, $J_{"12,8"}$ = 9.5 Hz, $J_{"12,13"}$ = 7 Hz), 4.70 ($H_{"11"}$, d, J = 3.75 Hz), 5.72 ($H_{"13"}$, dd, $J_{"13,14"}$ = 15.6 Hz, $J_{"13,12"}$ = 7 Hz), 5.92 ($H_{"14"}$, dd, $J_{"14,13"}$ = 15.6 Hz, $J_{"14,15"}$ = 5.6 Hz), etc; M^+ 502; ms *m/e*: 484 (M^+ − H_2O), 470 (M^+ − MeOH), 399 (M^+ − MeOH − C_5H_{11}), 348 (M^+ − MeOH − $PhCO_2H$). For the M^+ − MeOH fragment ($C_{27}H_{50}O_5Si_2$): calcd. 510.3197; observed, 510.3214.

Synthesis of 18

A solution of the ester **16** (0.15 g, 0.3 mmol) in anhydrous methanol (15 mL) containing potassium carbonate (0.14 g, 1 mmol) was stirred at room temperature in a nitrogen atmosphere for 96 h. The solution was then neutralized with Rexyn-102 (H^+) and processed in the usual way to give a residue which was chromatographed on silica gel (solvent D, R_f 0.38) to give **18** (0.094 g, 80%) as a colorless syrup; $[\alpha]_D$ +95.8° (*c* 1.09, $CHCl_3$); for the M^+ − MeOH − H_2O fragment ($C_{21}H_{32}O_4$): calcd. 348.2249; found 348.2246; ms *m/e*: 366 (M^+ − MeOH), etc; R_f 0.68 (solvent E). The corresponding bis-trimethylsilyl derivative (R_f 0.8, solvent C) had a mass spectral fragmentation pattern identical to the published report (2). For the M^+ − MeOH fragment ($C_{27}H_{50}O_9Si_2$): calcd. 510.3197; found 510.3214.

Synthesis of 19

A solution of the ester **17** (0.125 g, 9.25 mmol) was treated as described for the preceding compound to give **19** as a syrup (0.071 g, 71.5%); $[\alpha]_D$ +93.8° (*c* 1.1, $CHCl_3$); ms *m/e*: 380 (M^+ − H_2O), 366 (M^+ − MeOH), 348 (M^+ − MeOH − H_2O), etc; R_f 0.73 (solvent E).

(+)-Thromboxane B_2, (1): {2R-[2α(1E, 3S), 3β(Z), 4β, 6(α, β)]}-7-[tetrahydro-4,6-dihydroxy-2-(3-hydroxy-1-octenyl)-2H-pyran-3-yl]-5-heptenoic Acid

A solution of **18** (0.032 g, 0.08 mmol) in 1 mL of 0.1 *M* NaOH and 1 mL of methanol was stirred at room temperature for 8 h. The solution was evaporated to dryness below 35°C, the residue was dissolved in 4 mL of water and treated with Dowex-50 (H^+) (5 mL). After a few minutes the solution became somewhat opalescent, then gradually cleared during the course of 1 h. The formation of the "methyl glycoside" derivative of thromboxane B_2 could be easily monitored by tlc (solvent D or E). The resin was removed by filtration, the filtrate was extracted with a 2:1 mixture of ethyl acetate and ether (150 mL, total), and the extracts were processed as usual to give a syrup (0.025 g, 85%). Crystallization was effected by dissolving the syrup (0.025 g) in 4 drops of ethyl acetate, adding 2 mL of ether followed by 4 mL of petroleum ether or hexanes to give a turbid solution. After standing overnight, crystals of thromboxane B_2 were obtained (0.016 g), mp 91–93°C (lit. (3), mp 92–94°C). Recrystallization from the same solvent mixture gave material with mp 95–96°C, undepressed upon admixture with an authentic sample;[3] R_f 0.40 (solvent E); $[\alpha]_D$ +57.4° (*c* 0.26, EtOAc); λ_{max}(film): 1705 (C=O); ms *m/e*: 335 (M^+ − H_2O − HO), 317 (M^+ − $2H_2O$ − HO), 272 (M^+ − $3H_2O$ − CO_2), 246 (M^+ − $2H_2O$ − HO − C_5H_{11}), etc.

"15"-Epi Thromboxane B_2, 20

A solution of the "15 *R*" derivative **19** (0.03 g, 0.075 mmol) was treated as described for the preparation of **1** to give the title epi-derivative as a syrup (0.024 g, 86%); R_f 0.44 (solvent E); $[\alpha]_D$ +50.2° (*c* 1.0, EtOAc).

Oxidation and Reduction of Intermediate 11

To a solution containing **11** (0.061 g, 0.113 mmol) in 1 mL of DMSO were added successively 0.013 g of pyridine, 0.017 g of trifluoroacetic anhydride, and 0.067 g (0.37 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC·HCl). After 3 h of stirring under nitrogen, the solution was diluted with ether (50 mL) and water. Processing the organic phase as usual gave a syrup which was purified by preparative tlc to give the ketone **21** as a syrup (0.052 g, 86%); R_f 0.43 (solvent A); $[\alpha]_D$ +51.4° (*c* 1.0, $CHCl_3$); λ_{max}(film): 1738 (CO_2Me), 1720 (C=O) cm^{-1}; M^+ 538; ms *m/e*: 507 (M^+ − MeO), 481 (M^+ − Me_3C), 450 (M^+ − Me_3C − MeO), 449 (M^+ − Me_3C − MeOH), 379 (M^+ − MeOH − CH=CH$(CH_2)_3CO_2Me$), etc.

Attempted epimerization of **21** (K_2CO_3, MeOH, pH 10, 5 h, N_2) showed some elimination (5–10%). Neutralization with Rexyn-102 (H^+) and processing gave a syrup which was identical to the starting ketone **21**; $[\alpha]_D$ +50.8°; ir, nmr, R_f.

[3]We thank Drs. N. A. Nelson, R. C. Kelly, and W. P. Schneider of the Upjohn Co. for a sample of thromboxane B_2.

Reduction of the above obtained material (0.036 g) with sodium borohydride (0.02 g) in methanol at 0°C gave, after work-up and preparative tlc, the alcohol **11** (0.027 g, 74%), identical with material obtained previously according to the synthetic scheme ($[\alpha]_D$, nmr, ir, R_f).

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