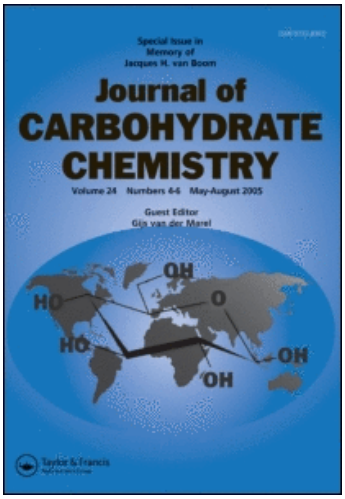

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REVIEW

ACCESS TO THROMBOXANE COMPOUNDS: SYNTHESES FROM CARBOHYDRATES, AS NATURAL CHIRAL POOLS

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1. INTRODUCTION

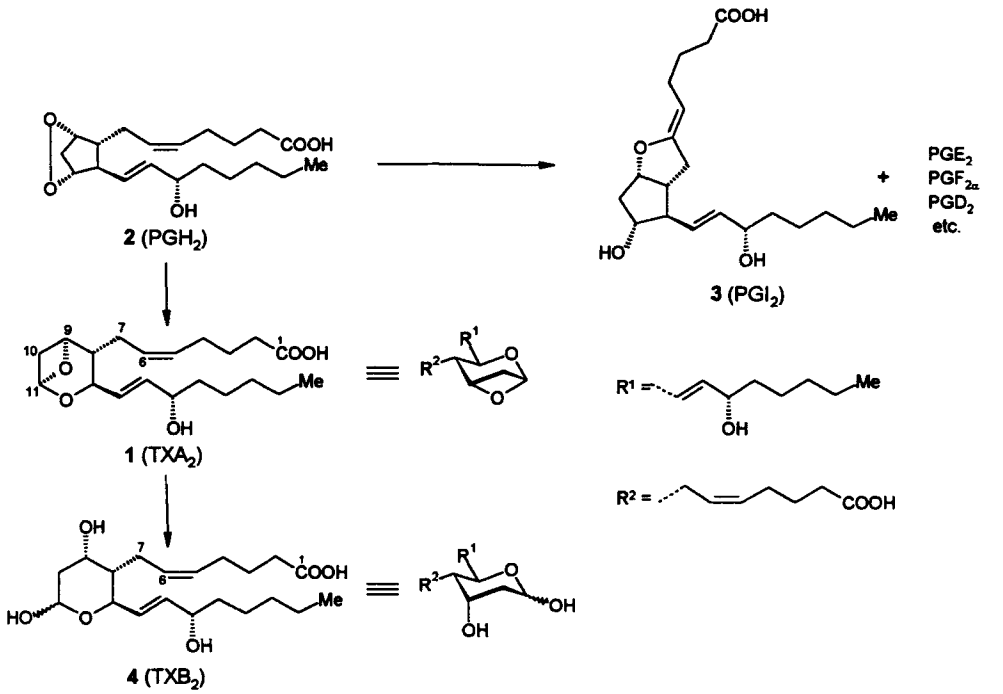
The cascade of biosynthetic products[1,2] derived from arachidonic acid involves several oxygenated heterocycles, including thromboxanes A_2 and B_2 (in the following TXA_2 and TXB_2, respectively, Scheme 1). In the biological pathway TXA_2 (**1**) is produced directly from prostaglandin H_2 (PGH_2, **2**), and this same compound is the common precursor of the previously known prostaglandins (i.e. PGE_2, $PGF_{2\alpha}$ and PGD_2, etc.), as well as of the more recently discovered "beneficial" prostaglandin I_2 (PGI_2, **3**). Upon hydrolysis under biological conditions TXA_2 (**1**) is converted into the more stable thromboxane B_2 (TXB_2, **4**).

Recognition of the opposite biological effects of PGI_2 and TXA_2 is clearly one of the most important developments in prostanoid compounds research. Namely, these two molecules of the same origin are biosynthesized in the body in order to exert a delicate modulation of opposing biological functions. In blood vessels PGH_2 transforms into PGI_2, which prevents platelets from aggregating and adhering to blood vessel walls. In addition, PGI_2 causes smooth muscles (particularly blood vessels) to relax. On the other hand, platelets convert PGH_2 into TXA_2, which induces platelets to aggregate and to adhere to blood vessels, which causes the vessels to contract.

Both PGI_2 and TXA_2 are extremely unstable, possessing half-lives of less than a minute under physiological conditions. At the same time both substances are exceptionally active, requiring only tiny quantities to exert biological effects.

The "beneficial" prostaglandin PGI_2 and its several analogues and congeners have already found application, or have been suggested as useful in coronary by-pass operations, haemodialysis, certain vascular diseases and in angina and myocardial infarct.

Since PGI_2 and TXA_2 exert opposing effects on platelet aggregation, and PGH_2 is converted by platelets into TXA_2, it is anticipated that inhibitors of the TXA_2 synthase enzyme (TSIs), or thromboxane receptor antagonists (TRAs) would exhibit many of the desired properties of a PGI_2 agonist. Accordingly, during the past decade numerous



Scheme 1

attempts have been made[2–9] to synthesize substances with the hope of obtaining biologically active TSIs and TRAs—thus to reduce fatalities in patients at risk from thrombosis and heart attack. In clinical trials most of the hitherto prepared TSIs, with different structures, performed rather poorly. This is attributed to PGH_2 (**2**) which accumulates from inhibition of thromboxane synthase, and whose agonist activity nullifies the benefits of reducing TXA_2 levels.[3] Simultaneous administration of a TSI and a TRA (with the benefit of dual action) appears to be more promising;[3] the TRA would weaken the effects of the produced TXA_2 (and of accumulated PGH_2), while TSI would redirect PGH_2 metabolism towards the vasodilator/antiplatelet aggregatory (i.e. "beneficial") prostaglandins: PGI_2 and PGH_2, etc.. Therefore, in an extensive search for TRAs many compounds modeled after TXA_2 and TXB_2 have been prepared[2–9] by various synthetic strategies. However, in most cases racemic compounds were obtained, due to the

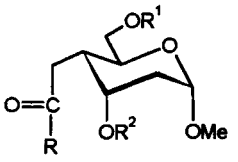
application of achiral starting materials or to the lack of sufficient stereocontrol in the employed synthetic transformations.

An appropriate approach to overcome such difficulties is carbohydrate-based synthesis of TXA_2 and TXB_2 models, as the heterocyclic framework of the parent natural compounds is related to the 2,4,6-trideoxy-D-*ribo*-hexopyranose structure[10] (cf. Scheme 1).

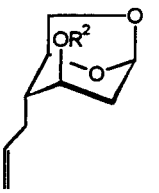
The present review, covering the literature of the topic through April 1997, is aimed at discussing the already developed and published, but still not entirely exploited possibilities of obtaining thromboxane compounds and related models from carbohydrates, as readily accessible and inexpensive chiral pools.

2. SYNTHESIS OF THE OPTICALLY ACTIVE KEY INTERMEDIATES FROM SUGARS

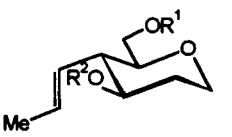
Pioneering research on this topic was accomplished by the groups of Corey, Hanessian, Hernandez, Ohrui and Kelly et al. The basic strategy of these and subsequent approaches consists of the construction of a 2,4-dideoxysugar derivative, such as **A**, **B** or **C**, carrying a two- or three-carbon branch at *C*-4, suitable for functionalization with the two prostanoid side chains R^1 and R^2 (Scheme 1, and Section 3.) to obtain the TXB_2 (**4**) framework.



A



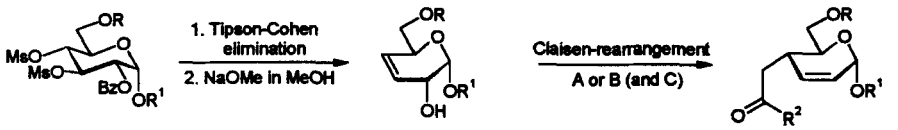
B



C

R = OAlkyl, OH or NMe_2
$R^1 = R^2$ = protecting groups

Further development of the 9,11-anhydro ring, present in TXA_2 (**1**) along this line would provide a synthesis of the quite unique 1,3-anhydro-α-hexopyranose system. So far preparation of only the corresponding *C*-2 substituted β-analogues has been reported (Section 4.1.).



	R	R^1
5	Bz	Me
6	Tr	Me
7	Si(*t*Bu)Me_2	Me
8	Si(*t*Bu)Ph_2	Me
9	Bz	All
10	Si(*t*Bu)Me_2	All

	R	R^1
11	H	Me
12	Tr	Me
13	Si(*t*Bu)Me_2	Me
14	Si(*t*Bu)Ph_2	Me
15	H	All
16	Si(*t*Bu)Me_2	All

	R	R^1	R^2	Method	Ref.
17	H	Me	NMe_2	A	11, 13-15
18	Tr	Me	NMe_2	A	13-15
19	Si(*t*Bu)Me_2	Me	NMe_2	A	16
20	H	All	NMe_2	A	16
21	Si(*t*Bu)Me_2	All	NMe_2	A	16
22	Si(*t*Bu)Ph_2	Me	NMe_2	A	18
23	Tr	Me	OMe	B	12
24	Si(*t*Bu)Me_2	Me	OMe	B	16
25	Si(*t*Bu)Me_2	Me	OH	B + C	16
26	Si(*t*Bu)Me_2	All	OMe	B	16
27	Si(*t*Bu)Me_2	All	OEt	B	16
28	Si(*t*Bu)Me_2	All	OH	B + C	16

Methods

A: $MeC(OMe)_2NMe_2$, heat; neat[13-16, 18] or in diglyme[11]

B: $MeC(OMe)_3$ or $MeC(OEt)_3$ /cat. propionic acid, heat; neat[16], or in xylene[12]

C: alkaline hydrolysis

Scheme 2

2.1. The "Corey procedure" and related recent methods

In the original Corey procedure[11] and in subsequent modifications[12–18] thereof the key step is the introduction of the required two-carbon *C*-4 branch by means of the Claisen-Meerwein-Eschenmosher amide-acetal[11,13–16,18] or the Claisen ortho ester[12,16] rearrangements of alkyl hex-3-enopyranoside derivatives (Methods A and B, respectively, Scheme 2). For preparation[16] of 3,4-unsaturated sugars the Tipson-Cohen reductive elimination procedure[19] has been employed most frequently.

Thus, vicinal 3,4-bis-*O*-methanesulfonyl esters **5-10**—available from alkyl α-D-glucopyranosides upon direct dibenzoylation[20] (such as **5**), or more efficiently, either by sequential regioselective benzoylation[16,21] at *O*-2 and then *O*-6 etherification (or in the reverse way[12–15]) and subsequent mesylation—were treated[19,20] with zinc/copper in hot *N,N*-dimethylformamide in the presence of sodium iodide (Scheme 2).

The resulting alkyl 3,4-dideoxy-α-D-*erythro*-hex-3-enopyranosides **11-16** were isolated in 50–80% yield after Zemplén transesterification. It is to be noted that partial hydrolysis of the benzoyl ester function at *O*-2 always accompanied[20] the Tipson-Cohen reductive elimination, and that the 6-*O*-*tert*-butyldiphenylsilyl ether moiety has been found[16] less

suitable for such a transformation. Compound **8** suffered a considerable (~20%) desilylation, to furnish only 37% of **14**. At the same time, both the glycosidic allyl group (in **9** and **10**) and the 6-*O*-*tert*-butyldimethylsilyl ether function (in **7** and **10**) were shown[16] to be quite compatible with the reaction conditions of the Tipson-Cohen reductive elimination procedure.[19]

The construction of the two-carbon branch unit at *C*-4 of **11-16** (representing carbons *C*-6 and *C*-7 in TXA_2 and TXB_2) was then accomplished by means of the amide-acetal (A) or ortho ester (B) Claisen rearrangements to afford the alkyl 4-*C*-[(dimethylcarboxamido)methyl]- (**17-22**)[11,13–16,18] and alkyl 4-*C*-[(methoxy- and ethoxycarbonyl)-methyl]-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides (**23**,[12] **24**,[16] **26**[16] and **27**[16]). As expected, a complete chirality transfer from *C*-2 to *C*-4 was observed in each case, and when the α-D-*threo*-isomer of **12** was subjected[14] to similar amide-acetal rearrangement, the *threo* analogue of the 4-*C*-dimethylacetamide **18** was obtained exclusively. Slight modifications of the original reaction conditions outlined (without experimental details) by Corey et al.[11] and Hernandez[12] (i.e., continuous distillative removal[13–16] of the alcohol produced from the reagents; cf. Methods A and B , Scheme 2) have improved the conversion in both rearrangements up to 60–70% on a 3–5 mmole scale. However, with larger quantities of the hex-3-enopyranosides neither of the two transformations could be executed with yields exceeding 55%. Even after repeated addition of excess of reagents, and by prolonged reaction time the starting material was recovered.

In order to obtain the optically pure lactone **29** (Scheme 3), previously applied[22] for the synthesis of TXB_2 and its derivatives, the halolactonization of the *C*-4 branched hex-2-enopyranosides **17**, **18** and **23** was studied.[11–14] Moreover, further examinations have been accomplished recently with the aim of deriving the *C*-2 bromo analogue (**30**)[17] of **29**, as well as compound **41**[18] the bromine substituent of which might exert an inhibitory effect on the biological and chemical hydrolysis of the subsequently developed[23,24] 1,3-oxetane ring in a TXA_2 model with potential TRA properties.

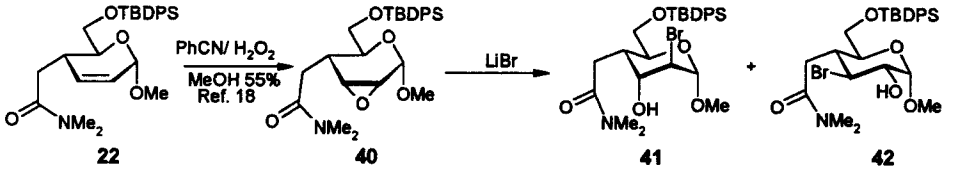
Iodolactonization of the 4-*C*-(dimethylaminocarbonylmethyl) derivatives **17**,[11] **18**,[13–15] **21**[17] and of the 4-*C*-(carboxymethyl) compound **23**[12] with an excess of iodine in

17-28

Methods

A: 3 eq. of I_2 or Br_2 in THF-H_2O
B: i. Bu_3SnH / $NaBH_4$; ii. HCl
C: i. $NaBD_4$; ii. HCl
D: Br_2 / Tl_2CO_3 in CH_2Cl_2 [25]
E: Br(sym-Coll)$_2ClO_4$ in $CHCl_3$ [26]

	X	Y	R	R^1	Method	Ref.
29	H	H	H	Me	A + B	11-15
30	Br	H	H	Me		
31	I	H	H	Me	A	11
32	I	H	Tr	Me	A	12-15
33	I	H	H	All	A	17
34	D	H	H	Me	A + C	13, 14
35	Br	H	H	$C_3H_5Br_2$	A	17
36	Br	H	Si(*t*Bu)Me_2	Me	D or E	17
37	Br	H	Si(*t*Bu)Me_2	$C_3H_5Br_2$	D or E	17
38	Br	Br	H	Me	D or E	17
39	Br	Br	Si(*t*Bu)Me_2	$C_3H_5Br_2$	D or E	17



22 **40** **41** **42**

Scheme 3

aqueous tetrahydrofuran (Scheme 3, Method A) resulted in the (2*S*)-iodolactones **31**, **32** and **33** in 80–90% yield. Reductive removal (B) of the iodo function from **31** and **32** with tributylstannane–sodium borohydride[11-15] and hydrolytic cleavage of the trityl ether function afforded the hydroxylactone **29**. The *C*-2 deuterium analogue **34** of **29** was also prepared[13,14] in an essentially similar way (A+C).

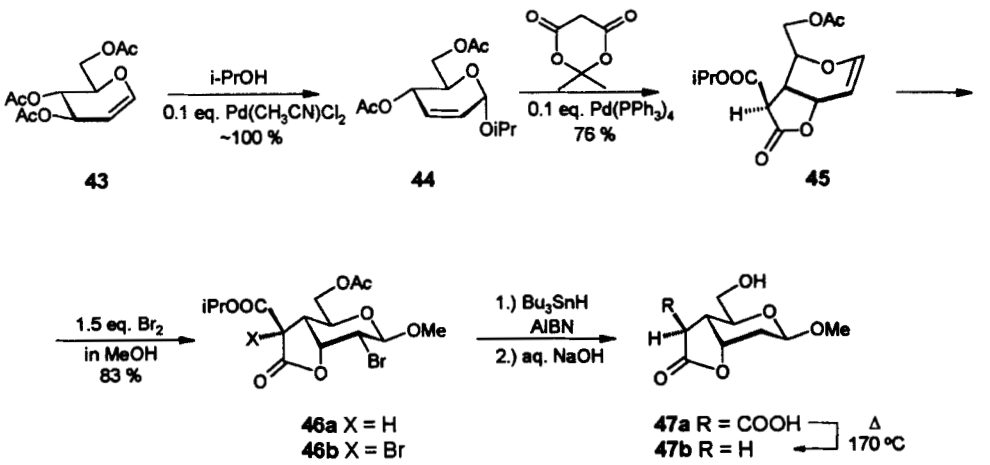
Bromolactonization[17] of the 4-*C*-dimethylamide **21** in aqueous medium (A) gave 85% of the (2*S*)-bromolactone **35** which, as expected, was also brominated in the glycosidic allyl moiety.

Bromolactonization[17] of the carboxylic acids **25** and **28**, and the ester **26**, under anhydrous conditions, with thallium(I) carbonate/bromine[25] (D), or with bromonium di-*sym*-collidine perchlorate[26] (E) readily afforded the (2*S*)-bromolactones **36** (78%) and **37** (76%), respectively. However, when the corresponding 4-*C*-(dimethylamino-carbonyl-methyl)-hex-2-enopyranosides **17** and **21** were subjected[17] to bromolactonization by

employing analogous, strictly anhydrous conditions (D or E), an unexpected α-bromination in the lactone ring at *C*-7 also occurred, to give the (2*S*,7*R*)-dibromolactone **38** (90%) and the 1,2-dibromopropyl glycoside of the (2*S*,7*R*)-dibromolactone **39** (95%). The steric position of the *C*-7 bromo substituent could be unequivocally proved by means of homonuclear NOE difference NMR spectroscopic investigations. The difference between the mechanisms of the bromination of the carboxylate and dimethylamide derivatives has been explained.[17]

In order to synthesize the *C*-4 branched 2-bromosugar **41**, epoxidation of **22** was studied[18] in detail (Scheme 3). Application of 3-chloroperoxybenzoic acid led to a 1:1 mixture of the *allo* epoxide **40** and the corresponding 2-hydroxylactone (produced by intramolecular opening of the anhydro ring of the *manno*-isomer of **40**). In contrast, stereoselective epoxidation of **22** occurred[18] by treatment with benzonitrile–hydrogen peroxide in methanol (Payne conditions) to give the epoxide **40** in 55% yield. It is to be noted that related epoxidations of the *C*-4 epimer of **22** remained practically unsuccessful. Anhydro-ring opening of **40** with lithium bromide gave[18] the halohydrins **41** and **42** in a 3:2 molar ratio, the former being a suitable candidate to undergo Mitsunobu-cyclization (Scheme 12).

A short, facile synthesis of the β-methyl glycoside analogue (**47b**) of the lactone **29** from 3,4,6-tri-*O*-acetyl-D-glucal (**43**) was elaborated by the Verdoorn group[27a] (Scheme 4). Palladium–assisted Ferrier rearrangement of **43** with 2-propanol gave the hex-2-enopyranoside **44**, whose reaction with Meldrums' acid in the presence of $Pd(PPh_3)_4$ furnished 76% of the bicyclic lactone **45** *via* the formation and transformation of an intermediary η^3-palladium complex. The mechanism of this cascade of reactions has been discussed[27a] in detail. Bromomethoxylation of **45** resulted in a mixture of the monobrominated and dibrominated compounds **46a** and **46b**, respectively. Reductive debromination of this mixture using tributylstannane and α,α'-azobisisobutyronitrile, and subsequent selective removal of the ester groups in the presence of the lactone function with aq sodium hydroxide led to 81% of the desired product **47a**. The final step of the procedure involved thermal decarboxylation of the *C*-4' carboxylic acid side chain of **47a** allowing the isolation of the target lactone **47b** in an overall yield of 48% from the glucal



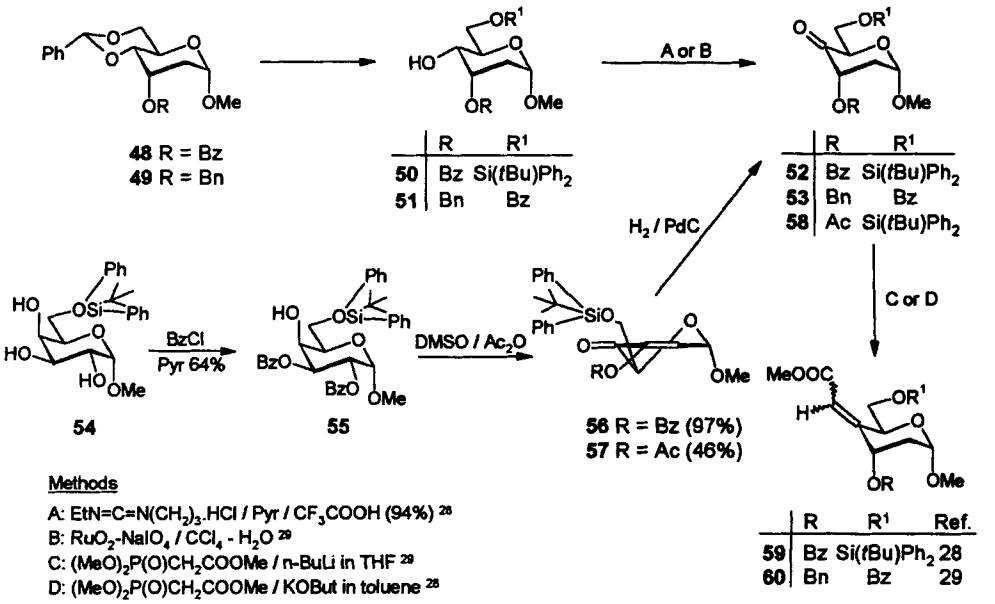
Scheme 4

43. In a novel palladium-catalyzed procedure[27b] the di-*O*-benzoyl analogue of **44** was treated with *N,N*-diethyl(phenylsulfonyl)acetamide to obtain, following desulfonylation, iodolactonization and reductive dehalogenation, the 6-*O*-benzoyl ester of the *i*-propyl glycoside analogue of **29**. It is to be noted that another palladium(0)–assisted method[27c] employed the reaction of 1,6-anhydro-2-chloro-2,3,4-trideoxy-β-D-*erythro*-hex-3-eno-pyranose with the sodium salt of active methylene compounds affording 1,6-anhydro-*C*-4-branched-hex-2-enopyranosides. Thus, this method offered an alternative to the Claisen rearrangement for the synthesis of **17**, a candidate to convert into the lactone **29**.

Application of the above lactone derivatives for the preparation of TXB_2 and TXA_2, and their models, is discussed in detail in Sections 3. and 4.

2.2. The "Hanessian-Ohrui approach"

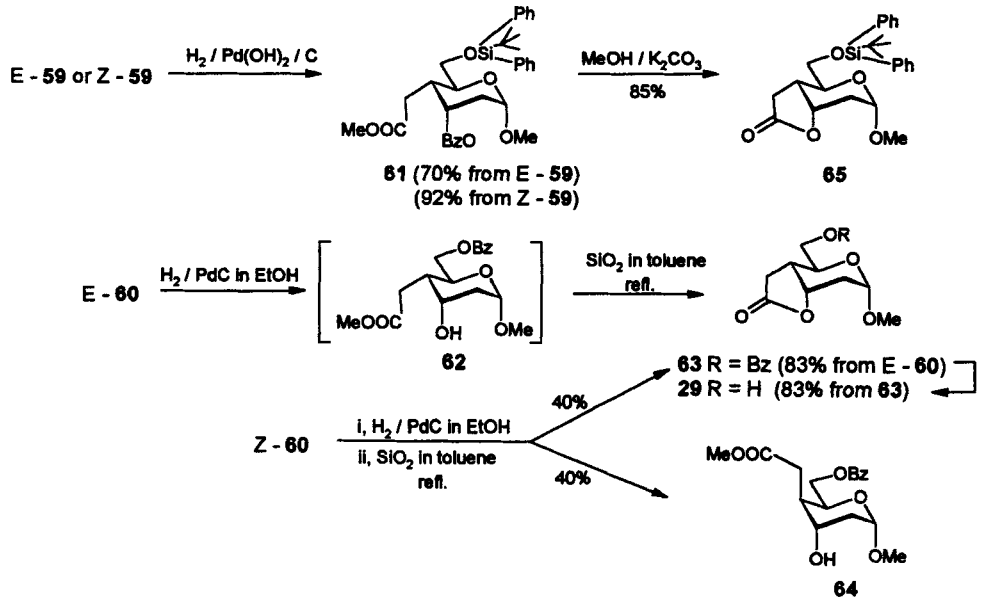
The synthetic target of the procedures elaborated independently by Hanessian and Lavallee[28] and Ohrui and Emoto[29] were essentially similar and, again, aimed at constructing the 6-hydroxylactone **29** (cf. Scheme 3). However, introduction of a *two-carbon branch unit* into a hexopyranose at *C*-4 was realized by means of Wittig-type reactions in these procedures (Scheme 5).



Scheme 5

Methyl 3-*O*-benzoyl (**48**)[28] and methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**49**),[29] readily available from D-glucose in a few straightforward steps, were converted into the 6-*O*-silyl (**50**)[28] and 6-*O*-benzoyl (**51**)[29] derivatives, following hydrogenolytic[28] or hydrolytic[29] removal of the benzylidene acetal moiety. In the presence of the *tert*-butyldiphenylsilyl ether moiety of **50**, oxidation of the free *C*-4 hydroxyl group was found to be best accomplished[28] by means of 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide and pyridinium trifluoroacetate in dimethyl sulfoxide (A) to give 94% of the ketone **52**. In the case of **51** the oxidation was effected[29] with ruthenium tetraoxide (B), and the resulting *C*-4 uloside **53** was used for the Wittig reaction without isolation.

The Cirelli group has recently reported[30] an alternative four-step procedure for the preparation of the *C*-4 uloside **52** from methyl α-D-galactopyranoside, which compares favourably in yield and simplicity with the above routes. Thus, methyl 6-*O*-(*tert*-butyl-diphenylsilyl)-α-D-galactopyranoside (**54**) was regioselectively benzoylated (Scheme 5)

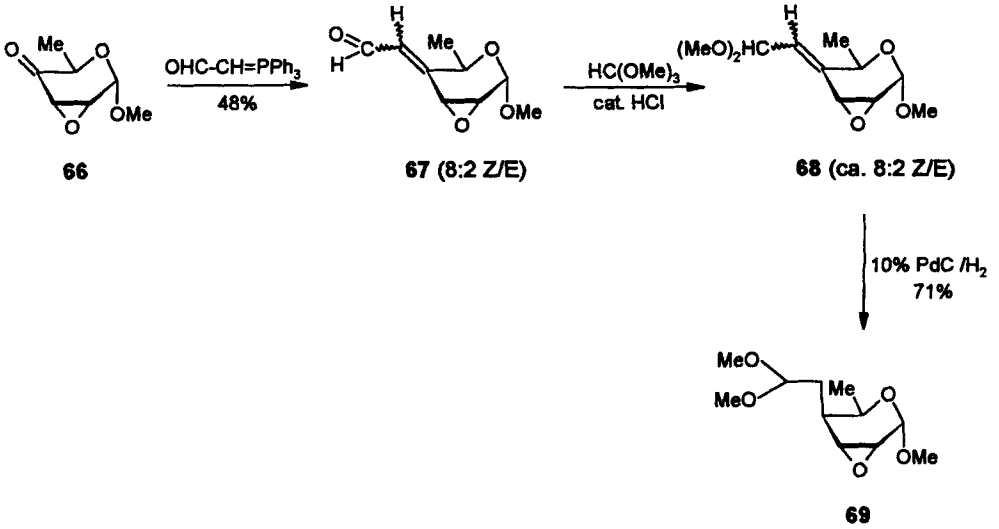


Scheme 6

and the resulting 2,3-di-*O*-benzoate **55** was oxidized with DMSO/Ac_2O to furnish methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**56**) in almost quantitative yield. When the 2,3-di-*O*-acetyl analogue of **55** was used for the oxidation, the product (**57**) was isolated in only 46% yield. Stereoselective hydrogenation of **56** and **57** gave the target uloside **52** (69%) and the corresponding 4-*O*-acetyl derivative **58** (92%), respectively.

Treatment[29] of **53** with the ylide derived from trimethyl phosphonoacetate and *n*-butyllithium (C) afforded 60% of a separable 1:1 mixture of the stereoisomeric olefinic esters (**60**). Hanessian and Lavallee[28] also obtained the unsaturated ester **59** in form of a 1:1 *E/Z* mixture (91%) by using the reaction conditions indicated with D.

After separation of the isomers by means of chromatography, the individual compounds were subjected to catalytic hydrogenation (Scheme 6). Hanessian[28] disclosed that although saturation of the exocyclic double bond of *E*-**59** and *Z*-**59** proceeded with remarkably different rates (hydrogenation of *Z*-**59** could be completed under milder



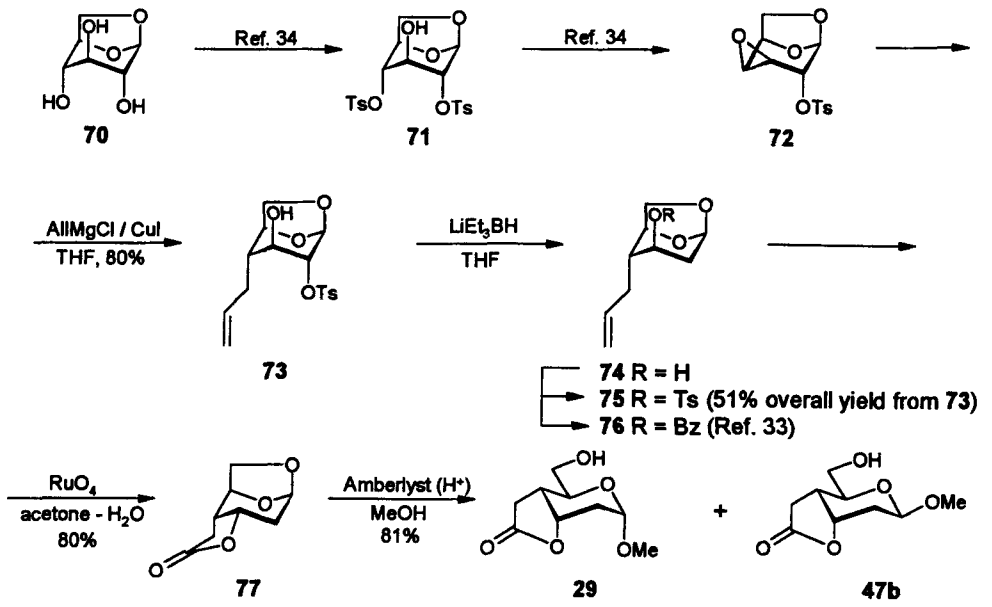
66 67 (8:2 Z/E) 68 (ca. 8:2 Z/E) 69

Scheme 7

conditions), both of the isomers were transformed exclusively into the desired 4-*C*-(methoxycarbonylmethyl) sugar **61** with the D-*ribo* configuration. In contrast, Ohrui and Emoto[29] reported that pure *E*-**60** was exclusively hydrogenated to the D-*ribo* *C*-4 acetic acid ester **62**, which forms spontaneously, or upon mild acidic conditions, the lactone **63**. However, the *Z* isomer of **60** furnished a ca. 1:1 mixture of the D-*ribo*-lactone **63** and the *C*-4 epimeric *xylo* *C*-4-branched acetic ester **64** (Scheme 6) after treatment with SiO_2 in hot toluene.

In a closely related approach (Scheme 7) to thromboxane A_2 model substances, Mohn[24] observed that the two-carbon Wittig chain-extension of the 2,3-anhydrohexo-pyranosid-4-ulose **66** with formylmethylenetriphenylphosphorane produces an 8:2 mixture of the *Z* and *E* α,β-unsaturated aldehydes **67**. Acid-catalyzed acetal formation with trimethyl orthoformate resulted in the dimethyl acetal **68** (ca. 8:2 *Z/E* ratio), which was hydrogenated to give the *C*-4-branched 2,3-anhydro-4,6-dideoxy-α-D-gulopyranoside **69** in a 71% yield.

Mild alkaline hydrolysis of **61** and **63** resulted in the 6-*O*-silyl- (**65**)[28] and 6-*O*-hydroxy (**29**)[29] lactones (Scheme 6), applicable for conversion into TXB_2 and its analogues, as discussed in Section 3.

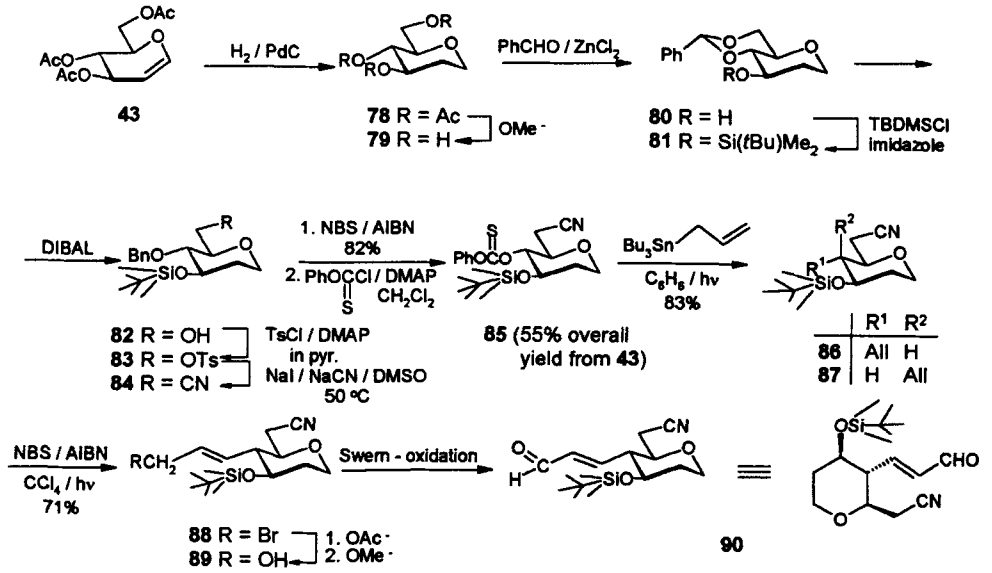


Scheme 8

2.3. The "Levoglucosane-approach"

Due to its rigid, bicyclic framework, levoglucosane (1,6-anhydro-β-D-glucopyranose **70**) has become a popular starting material for natural products syntheses,[31] which require highly regio- and stereoselective transformations. In 1980 A.G. Kelly et al.,[32] and then in 1984 Kálé et al.[33] employed **70** for the preparation of thromboxane derivatives. The key step in those syntheses was the stereoselective introduction of a three-carbon (allyl) branch at *C*-4 of a suitably "activated" analogue of levoglucosane.

By means of classical operations[34] levoglucosane (**70**) was converted into the 2,4-di-*O*-tosylate **71**, and then into the 3,4-anhydro derivative **72** (Scheme 8). Regio and stereoselective opening of the epoxide ring of **72**[32,33] by treatment with allylmagnesium chloride in the presence of cuprous iodide permitted isolation of the single product **73** carrying the *C*-4-branch function with the proper stereochemistry related to the target thromboxane compounds. Following deoxygenation with lithium triethyl borohydride, the resulting *C*-4-branched bicyclic alcohol **74** was tosylated (**74**→**75**) and then oxidized, with ruthenium tetraoxide in aqueous acetone, yielding directly the tricyclic lactone **77**.[32,33]



Scheme 9

The latter compound was readily transformed into a 1.6:1 mixture (81%) of **29** and its β-anomer (**47b**), for conversion into the target thromboxane compounds (Sections 3. and 4.). The synthesis of 10-fluorothromboxane A_2 from levoglucosane derivatives has also been reported.[34d]

2.4. Radical displacement of O-4-thionocarbonate esters

In connection with the synthesis of 9-deoxy-8,9-oxaprostaglandin analogues M.J. Kelly et al.[35a,b] employed, as the key step in the reaction sequence, the radical replacement of an *O*-4 thionocarbonate with an allyl unit to achieve the required chain extension of appropriate carbohydrate derivatives.

By means of standard transformations (Scheme 9), 3,4,6-tri-*O*-acetyl-D-glucal (**43**) was converted into the 3-*O*-silyl-protected 4,6-*O*-benzylidene acetal **81**. Reductive cleavage of the acetal function in **81** with DIBAL furnished the primary alcohol **82**, which was converted into the nitrile **84** *via* the 6-*O*-tosylate **83**. Whereas conventional *O*-debenzylation procedures at *O*-4 failed, this could be readily achieved (82%) under radical

bromination conditions[35c] with *N*-bromosuccinimide. The resulting alcohol was transformed into the 4-*O*-thionocarbonate ester **85** in an overall yield of 55% based on the glucal **43**.

The photochemically induced reaction of **85** with allyltributylstannane afforded 83% of a ca. 6:1 inseparable mixture of the D-*arabino*- (**86**) and D-*lyxo* (**87**) 4-*C*-allyl compounds. Radical allylic bromination of this mixture afforded the ω-bromo derivative **88** (71%), which was transformed into the α,β-unsaturated aldehyde **90** by means of acetate-displacement, followed by saponification and Swern-oxidation of the resulting alcohol **89**.

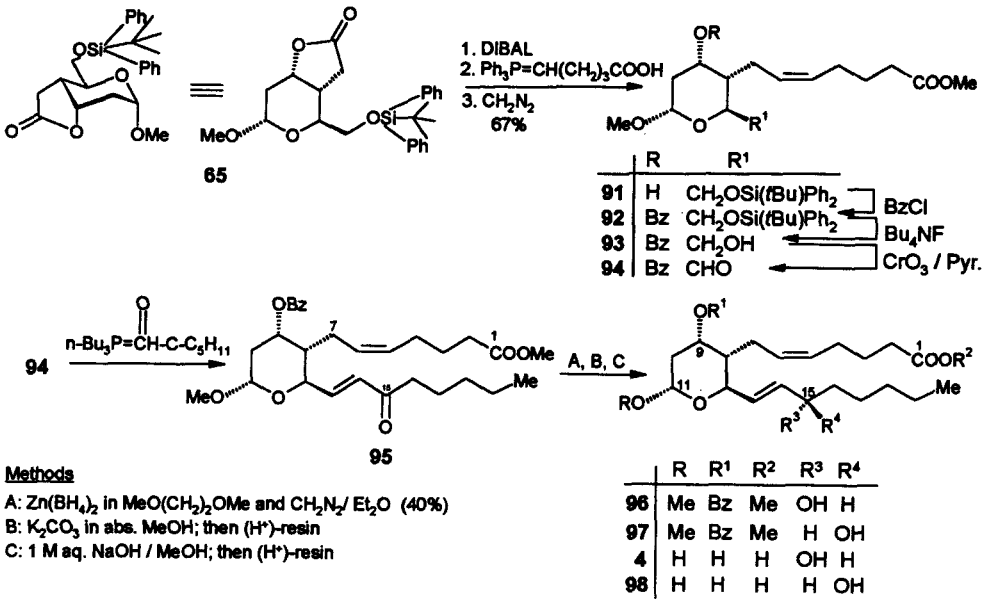
The aldehyde **90** served[35a,b] as the key intermediate for the conversion into novel prostanoid substances, including a recently discovered metabolite of PGI_2 (**3**), designated as *Stable Metabolite X* (*SMX*). At the same time, **90** might also be useful for the synthesis of 11-deoxy-9-*epi*-thromboxane B_2 derivatives and compounds modeled after this substance.

3. EXTENSION OF THE CARBOHYDRATE-BASED KEY INTERMEDIATES WITH THE PROSTANOID SIDE-CHAINS

3.1. Preparation of TXB_2 analogues

The transformation of the 6-hydroxylactone **29**, previously prepared from noncarbohydrate materials,[22] or its 6-*O*-silyl ether derivative **65** (cf. Schemes 3 and 6 in Section 2.) represents the first example of completing the carbohydrate-based builtup of TXB_2.

This methodology, designed by Hanessian and Lavallee[28] (Scheme 10), involved treatment of the lactone **65** with DIBAL, to derive the corresponding lactol, followed by Wittig reaction of the latter with (4-carboxybutyl)triphenylphosphorane and then esterification with diazomethane to give 67% of the *cis*-olefinic product **91**. After benzoylation of the free hydroxyl group (**91**→**92**) the silyl ether function was removed upon treatment with fluoride (**92**→**93**), and the resulting primary alcohol **93** was oxidized using the modified Collins method[36] to give the aldehyde **94**. Chain elongation of **94** was achieved by treatment with 1-[(tri-*n*-butyl)phosphoranylidene]-2-heptanone[37] to



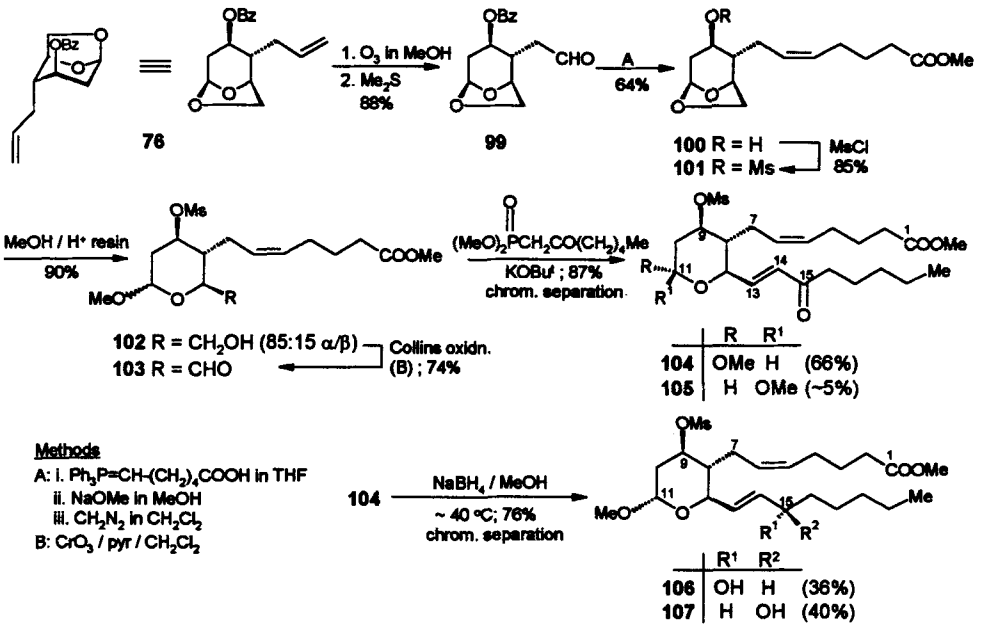
Scheme 10

furnish 79% of the α,β-unsaturated ketone **95**. Reduction of the *C*-15 keto function in **95** with zinc borohydride (A) gave 40% of the natural (15*S*)-diastereomer **96** and 33% of the corresponding (15*R*)-alcohol **97**, separable by preparative layer chromatography. These two isomers were separately transformed[28] into TXB_2 (**4**) and its "unnatural" (15*R*)-isomer (**98**) upon sequential removal of the protecting groups involving *O*-9 debenzoylation (B) and mild alkaline hydrolysis (C).

It should be noted that an essentially similar strategy was applied by Fürst[14] when preparing optically active TXB_2 derivatives, including certain deuterated analogues.

3.2. Preparation of key-intermediates to 9,11-thiathromboxane A_2 methyl ester

Utilization of the 4-*C*-allyl levoglucosane derivative **76** (Scheme 8 in Section 2) for the synthesis of the already known key intermediate **106**[38] to 9,11-thiathromboxane compounds was accomplished (Scheme 11) by employing[33] a very similar methodology to that used by Hanessian et al.[28] for the carbohydrate-based formation of TXB_2 (Scheme 10).



Scheme 11

Thus, ozonolysis of the allyl side-chain of **76** gave rise to the 4-*C*-branched aldehydosugar **99**, which was converted[31] into the chain-extended *Z* derivative **100** employing a Wittig reaction (Method A in Scheme 11). Following mesylation (**100**→**101**), methanolysis of the 1,6-β-anhydro ring of **101** afforded 90% of the methyl glycoside **102** (α/β ratio: 85/15), whose primary hydroxyl group was oxidized according to Collins' procedure (B) to the aldehydes **103**. Treatment of **103** with (2-oxoheptyl)phosphonate/potassium *tert*-butoxide gave a separable mixture of the *C*-11 epimeric 15-oxo-TXB_2 analogues **104** and **105**. The isolated "α-anomer" **104** was subjected to sodium borohydride reduction at low temperature, to furnish the (15*S*) TXB_2-diester **106** and its (15*R*)-analogue **107** in a ratio of nearly 1:1.

The 15-benzoyl ester of **106**, derived from non-carbohydrate starting materials, involving, as a crucial step, inversion of configuration at *C*-9, was used by Ohuchida et al.[38] for the synthesis of 9α,11α-thia-TXA_2 methyl ester (Section 4.3.) in which the oxygen atom of the oxetane ring of TXA_2 was replaced by sulfur. Since the configuration of carbon *C*-9 in **106** corresponds to the requirements of the Ohuchida method, this

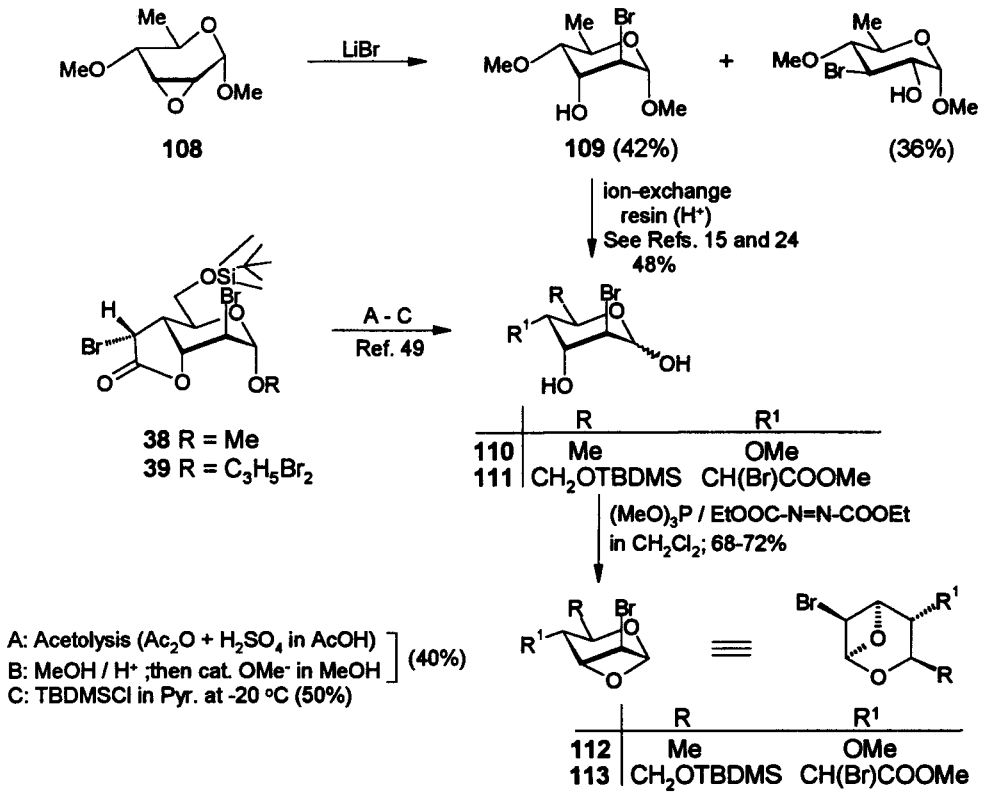
compound is considered a readily available key-intermediate to 9,11-thia-TXA_2 and TXB_2 derivatives from carbohydrate precursors.

4. ATTEMPTS TO THE DEVELOPMENT OF THE 9,11-OXETANE RING SYSTEM OF TXA_2 AND ITS MODELS

Regarding carbohydrate-nomenclature[10] the bicyclic 9,11-oxetane ring of TXA_2 (1) corresponds to a 1,3-anhydro-2,4,6-trideoxy-α-D-*ribo*-hexopyranose system. Due to its extreme lability both under physiological and chemical conditions, considerable efforts have been devoted[2–9] to develop structurally related substances, or certain analogues, in which the oxygen atom in the oxetane ring is replaced by a sulfur atom[38] or by a methylene group. Furthermore, to obtain more stable derivatives of TXA_2, and of the compounds modeled after TXA_2 (as possible TRAs), numerous attempts have been made either to stabilize[15,16,23,24] the 2,6-dioxabicyclo[3.1.1]heptane framework of TXA_2 with an electronegative halogen atom[39] (most preferably with fluorine) at position *C*-10 (prostaglandin nomenclature), or to replace the labile oxetane ring by an apparently more stable tetrahydrofuran moiety.[40] Regarding the topic of this review, in this Section only the carbohydrate-based procedures of the above-mentioned approaches are discussed in detail.

4.1. Synthetic efforts towards the generation of the 9,11-oxetane ring of TXA_2 and its models

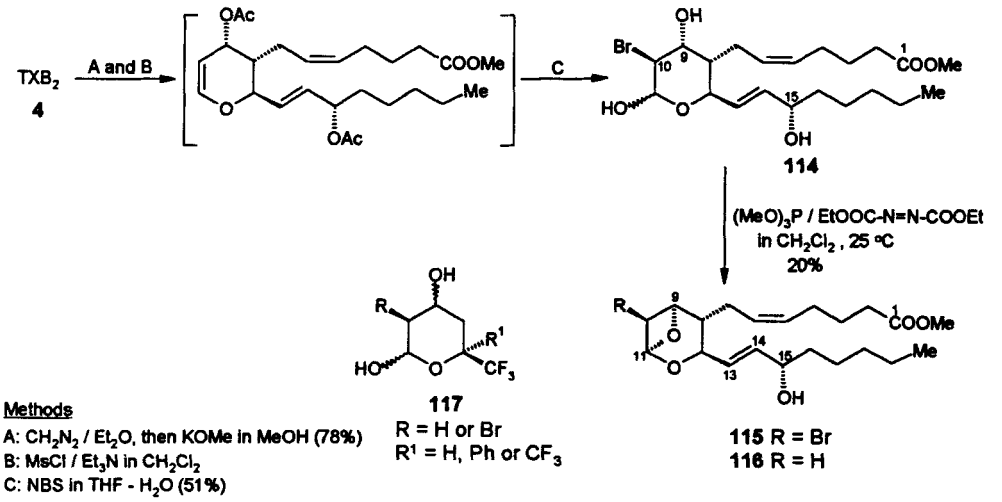
On the basis of a survey of the "carbohydrate field" literature it is quite surprising that so much has been reported on the development of the 1,3-anhydro-β-derivatives of various hexopyranoses[41] (β-D-gluco,[42,43] β-D-manno,[44–46] β-D-galacto,[47] β-L-talo[47] and β-L-rhamno[48] configuration). However, very little has been published on the construction of the corresponding 1,3-anhydro-α-hexopyranoses. Apparently, the only reported examples involve transformation of 2,6-dideoxy-2-bromo-4-*O*-methyl-α,β-D-altropyranose **110**[15,24] and the 4-*C*-branched compound **111** derived[49] from the dibromolactones **38** and **39** in a three-step conversion (A–C) into the 1,3-α-anhydro analogues **112** and **113** (Scheme 12) under modified Mitsunobu conditions.[23,50]



Scheme 12

Thus, in order to obtain the 2-bromosugar **110**, methyl 2,3-anhydro-6-deoxy-4-*O*-methyl-α-D-allopyranoside (**108**) was prepared from D-glucose in several, known steps.[15,24] As expected, due to the lack of a conformationally rigid system, epoxide ring opening could not be executed in a regio- and stereoselective manner, and a ca. 1:1 mixture of the 2,3-*diaxial*-2-bromo- (**109**; 42%) and the 2,3-*diequatorial*-3-bromo (36%) compounds was obtained (cf. the conversion[18] **40** → **41** + **42** on Scheme 3).

Due to the stabilizing effect of the electronegative *C*-2 bromo substituent in **109** of the acetal system, hydrolytic cleavage of the methyl glycosidic function could only be effected in moderate yield (48%) to give the *C*-2 bromosugar **110**. The glycosidic bond of related "stabilized" glycosides could also be cleaved[49] by means of acetolysis. In the case of **38** and **39** this is accompanied by simultaneous lactone ring-opening to produce the 4-*C*-branched sugar **111** after *O*-deacetylation and silylation of the primary hydroxyl group.

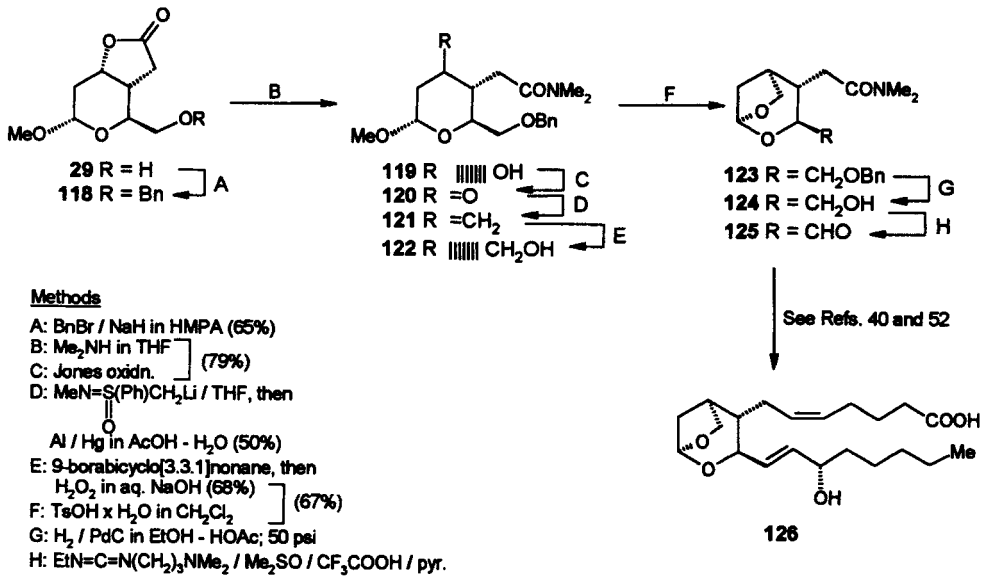


Scheme 13

"Phosphite" Mitsunobu dehydrocyclization of **110** and **111**, according to the method described by the group of Still,[23] gave the desired 1,3-anhydrosugars **112**[15,24] and **113**[49] with the unique α-configuration. Under hydrolytic conditions the dioxabicycloheptane system in **112** has been shown[24] to be rather stable, most particularly under physiological conditions, but acidic methanolysis cleaved the 1,3-α-anhydro ring with formation of an ca. 1:1 mixture of the starting α-methyl glycoside **109** and the corresponding β-anomer.

Free radical debromination, with tributylstannane, of **112** resulted in cleavage of the oxetane ring, as well as in partial dehalogenation to provide a 1:2 mixture of **110** and its 2-deoxy analogue.[15]

The above-mentioned Mitsunobu dehydrocyclization procedure was originally described by Still et al. in 1985, first to obtain TXA_2 model compounds,[50] and then to prepare the natural TXA_2 and its *C*-10 bromo derivative.[23] In the latter case TXB_2 (**4**) was transformed (Scheme 13) into the 10-bromo-TXB_2 methyl ester **114** by means of elimination of the anomeric hydroxyl group (B) and subsequent immediate bromohydrin formation (C). Upon Mitsunobu dehydrocyclization, **114** afforded 20% of the desired 10-bromo-9,11-anhydro (i.e. TXA_2) derivative **115**, together with 25% of the starting **114**



Scheme 14

and by-products. It should be noted, that with certain model compounds, carrying bulky (geminal) substituents at a position vicinal to the ring-oxygen atom, such as in **117**, Mitsunobu cyclodehydration has completely failed.[39] Since free-radical debromination of **115** failed to give the TXA_2 ester **116**, the Still group[23] finally applied the same reaction sequence (**114**→**115**) with the 1,15-macrolactone derivative of **114**. Although the yield of the Mitsunobu 9,11-dehydrocyclization was again rather poor (21%), polymer-bound tin hydride reduction[51] resulted in the demanded debromination. However, cleavage of the 1,15-lactone ring could not be achieved without splitting the 9,11-oxetane function, and thus finally 1,15-anhydro-TXB_2 was isolated.

4.2. Synthesis of 9,11-epoxymethanothromboxane A_2

For the synthesis of 9,11-epoxymethanothromboxane A_2, (**126**, Scheme 14), exhibiting TXA_2 agonist activity without showing antagonist effects and thromboxane synthase inhibitory properties, the Pfizer team[40] applied the lactone **29** (cf. Scheme 3).

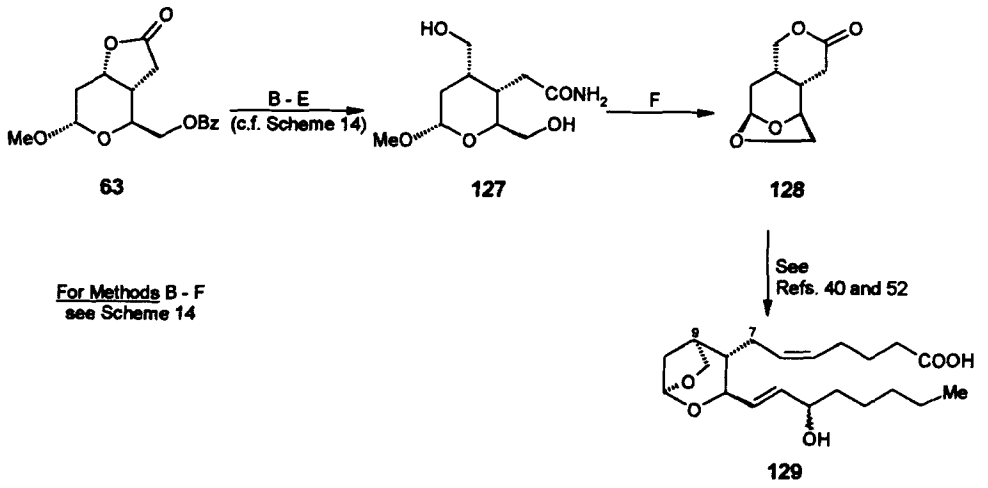
The key step in this procedure was the construction of a bridged tetrahydrofuran ring to replace the obviously less stable 9,11-oxetane system of TXA_2, *via* stereoselective insertion of a methylene unit into the lactone moiety of **29** at *C*-3 (carbohydrate nomenclature).

Thus, after conversion (A) of **29** into the 6-*O*-benzyl ether **118**, the lactone ring was opened (B) with dimethylamine, and the free hydroxyl group of **119** was oxidized using the Jones reagent (C). The oxo function of the resulting ketone **120** was replaced with a methylene unit by means of reductive elimination of the β-hydroxysulfoximine derivative, generated (D) by treatment of **120** with the lithium salt of *N,S*-dimethyl-*S*-phenylsulfoximine, to furnish **121**. Hydroboration (E) of the exocyclic double bond in **121** resulted in the *C*-3-branched hydroxymethyl sugar **122** with the proper D-*ribo* configuration for the development of the required bicyclic system. The reaction of **122** with *p*-toluenesulfonic acid monohydrate in dichloromethane (F) generated the tetrahydrofuran ring (**123**), and after removal (G) of the benzyl ether function, the resulting primary hydroxymethyl moiety of **124** was oxidized (H) into the aldehyde **125**. Sequential extension of **125**, at positions *C*-4 and *C*-6, with the two prostanoid side-chains, based essentially on previous methodology developed by Corey et al.,[50] then led to the target 9,11-epoxymethanothromboxane A_2 (**126**).

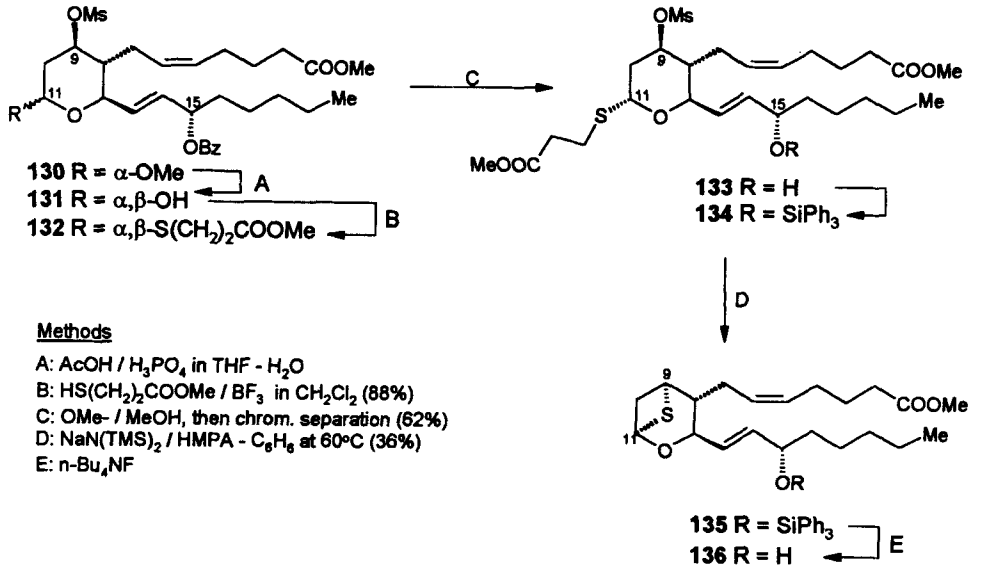
By applying an essentially similar methodology,[40] the 6-*O*-benzoyl ester derivative[29] (**63**) of the lactone **29** was subjected to the reaction conditions B–E to give the 3,6-di(hydroxymethyl) sugar **127** (Scheme 15). On treatment of this latter compound with *p*-toluenesulfonic acid (F), the δ-lactone derivative of an 1,6-β-anhydro sugar (**128**) was obtained presumably as a result of thermodynamic control, and this levoglucosane derivative was converted by DIBAL reduction into the corresponding lactol, and then into a structurally related analogue (**129**) of **126**, by employing an established reaction sequence.[52]

4.3. The preparation of 9α,11α-thiathromboxane A_2 methyl ester

Although the title compound has been synthesized[38] from "non-carbohydrate"-derived materials, a brief outline concerning the development of the 9,11-thietane ring



Scheme 15



Scheme 16

present in **136** might be of interest for the construction of such derivatives in the hexopyranose series. In addition, since the 15-benzoyl ester (**130**) of **102** (see Scheme 16) was essentially derived[33] from carbohydrate precursors (cf. Section 3.2.), discussion of the methodology applicable for its conversion into **136** is appropriate.

Careful acid hydrolysis[38] of α-**130**[33] (A, Scheme 16) gave rise to the hemiacetal **131**, suitable for introduction[38] of the internal thionucleophile by treatment with methyl 3-mercaptopropionate (B), to afford an inseparable *C*-11 epimeric mixture (**132**) of the 11-thio derivatives. Following 15-*O*-debenzoylation (C) the anomeric mixture could be separated, and the α-anomer **133** (62%) was isolated together with 20% of the corresponding β-anomer. Compound **133** was converted into the *O*-15 triphenylsilyl ether **134**. For construction of the required thietane ring by intramolecular attack of sulfide anion liberated with base, employment of sodium bis(trimethylsilyl)amide (D) proved to be[38] most effective, although the yield was rather moderate (36%). The target 9α,11α-thiathromboxane A_2 methyl ester (**136**) was then prepared from the resulting **135** by means of *O*-15 desilylation achieved with tetrabutylammonium fluoride in the usual way (E).

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