New Approaches in the Synthesis of Ulosonic Acids and Analogues

Claudia H. Sugisaki, Yvan Ruland, Ingrid Le Clezio, Michel Baltas*

Synthèse et Physicochimie de Molécules d'Intérêt Biologique, UMR 5068 CNRS - Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse cedex 04, France
Fax +33(561)556011; E-mail: baltas@chimie.ups-tlse.fr
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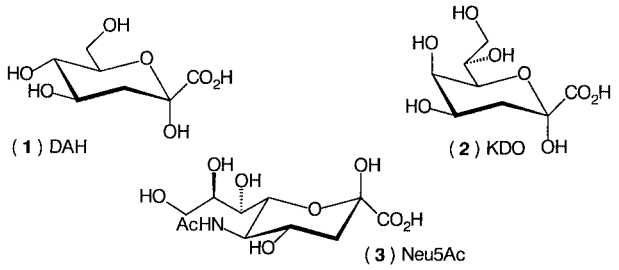
Abstract: A direct synthesis of bicyclic precursors of ulosonic acids is achieved by reaction of *cis*-α,β-epoxyaldehydes with ethyl 2-(trimethylsilyloxy)-2-propenoate in the presence of boron trifluoride diethyl etherate.

Key words: aldol reaction, epoxides, higher carbohydrates, ring opening, bicyclic products

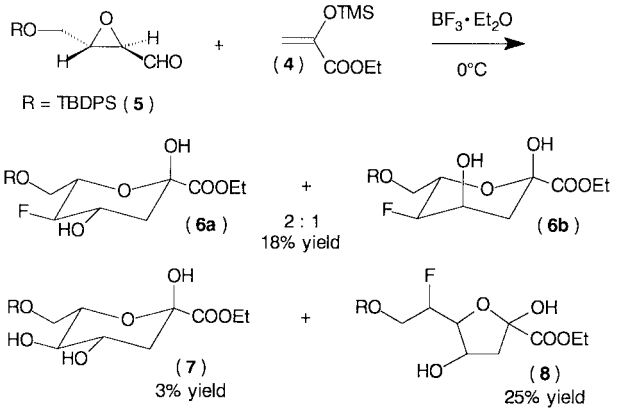
Higher 3-deoxy-2-ulosonic acids are natural carbohydrates possessing between 7 and 9 carbon atoms along with a ketone functionality at the α-position of a carboxylic acid. Ulosonic acids act in many important biological processes. An example is 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH; **1**) which, in its 7-phosphate form, is an important intermediate in the shikimic acid pathway.[1] 3-Deoxy-D-*manno*-octulosonic acid (KDO; **2**), which, in its 8-phosphate form, is a component of the outer membrane lipopolysaccharide of Gram-negative bacteria[2] and it is an important target for the design of inhibitors for enzymatic cell wall assembly. 5-*N*-Acetyl neuraminic acid (Neu5Ac; **3**) has emerged as a key biomolecule in cellular recognition, adhesion phenomena and in cell infection by certain viruses (Figure).[3]



Figure

Work towards the elaboration of ulosonic acids and analogues has accelerated and several such endeavors, including enzymatic and chemoenzymatic syntheses, starting from carbohydrates and *de novo* ones have already appeared in the literature.[4–9]

Some years ago, we reported[10] a versatile synthesis of a protected DAH, starting from a non-carbohydrate precursor. The methodology was based on [4+2+1] carbon atom incorporation, starting from an α,β-epoxyaldehyde. The target compound was obtained in 7 steps and 19% yield. Recently, exploring a more direct access to heptulosonic analogues, we have developed a new methodology based on [4+3] carbon atom incorporation.[11] The Mukaiyama reaction of *trans*-α,β-epoxyaldehydes with ethyl 2-(trimethylsilyloxy)-2-propenoate **4**, in the presence of the Lewis acid BF_3-etherate, led to the direct synthesis of a separable mixture of 5- and 6-fluoroheptulosonic analogues in their pyranosidic or furanosidic form (Scheme 1).



Scheme 1

These promising results led us to investigate this reaction further. We would like to report in this work a completely distinct reaction pathway observed when *cis*-, instead of *trans*-α,β-epoxyaldehydes, are employed.

Three *cis*-α,β-epoxyaldehydes were synthesized, possessing n = 4 carbon atoms **17** and n = 5 with identical or distinct hydroxyl protecting groups **15**, **16**. These two last epoxyaldehydes **15** and **16** were prepared as potential precursors to octulosonic analogues via [5+3] carbon atom incorporation. Racemic *cis*-α,β-epoxyaldehyde **17** was synthesized in 3 steps, starting from commercially available *cis*-1,4-butene-2-diol, in 48% total yield.[12] *Cis*-α,β-epoxyaldehydes **15** and **16** were synthesized from commercially available compound **9**. Reduction of the ester group, acetate protection of the primary hydroxyl group and deprotection of the acetonide were easily realized in good yield. The desired differentiation of hydroxyls can be achieved in the next step: firstly, the primary hydroxyl group was protected by using 1.2 equivalents of TBDMSCl, in the presence of DMAP (1.8 equivalents) in CH_2Cl_2. The monoprotected compound was exclusively

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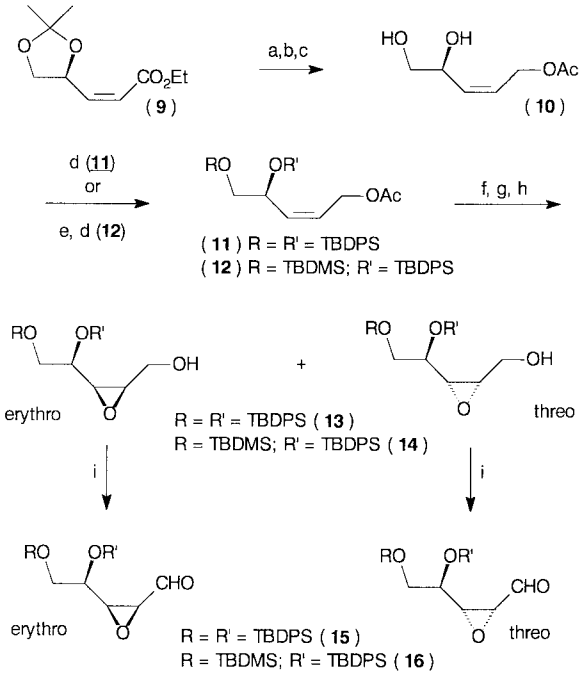
obtained in 86% yield. The secondary hydroxyl group was then protected as a *tert*-butyl diphenyl silylether group (TBDPS) resulting in the compound **12** (Scheme 2).[13]

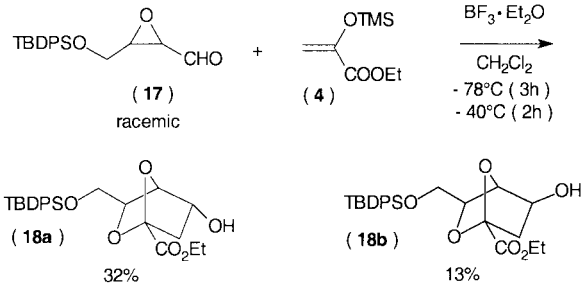


Scheme 2 Reagents and conditions: a) DIBAL-H/CH_2Cl_2/0 °C, 95%; b) Et_3N/DMAP/Ac_2O/CH_2Cl_2/r.t., 98%; c) 2 M HCl (aq)/CH_3CN/0 °C → r.t., 85%; d) TBDPSCl/imidazole/CH_2Cl_2/r.t., 70%; e) TBDMSCl (1.2 equiv)/DMAP/CH_2Cl_2/r.t., 86%; f) KOH/MeOH/r.t., 92%; g) *m*-CPBA/$NaHCO_3$/CH_2Cl_2/0 °C r.t., 75% for **13**, 85% for **14**; h) diastereoisomers separation by HPLC; i) $Cl_2(CO)_2/Et_3N$/DMSO/–78 °C, 95%

The epoxidation step was realized employing *meta*-chloroperbenzoic acid (*m*-CPBA) at 0 °C in CH_2Cl_2 in the presence of sodium bicarbonate. After 16 hours the mixture was purified yielding the two diastereoisomers in good total yield (75% for **13** and 85% for **14**). The *erythro*:*threo* diastereoselectivity was (66:34) and (86:14), respectively.[14] Finally, Swern oxidation led to the desired *cis*- α,β-epoxyaldehydes **15** and **16**.

In some initial experiments α,β-epoxyaldehyde **17** was treated with ethyl 2-(trimethylsilyloxy)-2-propenoate **4**[15] in the presence of different promoters for a Mukaiyama aldol reaction ($BiCl_3/ZnI_2$ or NaI, Eu(fod)$_3$, $LiClO_4$, $Sn(OTf)_2$, TMSOTf, BF_3-etherate). Only the use of BF_3-etherate gave satisfactory results. Consequently all aldol reactions of *cis*- epoxyaldehydes were realized in the presence of Lewis acid BF_3-etherate.[16] In all cases, bicyclic products were obtained. Starting from *cis*-α,β-epoxyaldehyde **17**, *anti* and *syn* aldolisation products were formed leading to epimers **18a** and **18b**, in 45% yield (Scheme 3).

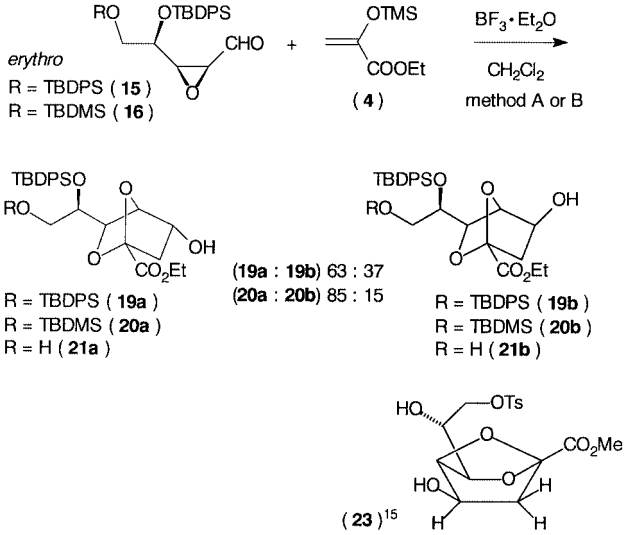
Initial aldol reactions employing *erythro cis*-α,β-epoxyaldehyde **15** afforded compounds **19a** and **19b** in 41% yield together with 47% of recovered aldehyde (method A, Scheme 4). Gratifyingly, modifications of the reaction conditions (method B, Scheme 4) led to an improved result, and bicyclic products **19a** and **19b** were obtained in 78% yield.



Scheme 3

This good result was also obtained starting from *erythro cis*-α,β-epoxyaldehyde **16** and employing this optimized condition. Thus compounds **20a** and **20b** were obtained in 78% yield. Compounds **21a** and **21b**, resulting from deprotection of the TBDMS group, were also obtained, in 10% yield (total yield of 88%). A Mukaiyama reaction was also realized with the *threo cis*-α,β-epoxyaldehyde diastereoisomers **15** and **16**, the corresponding bicyclic diastereoisomers of **19** and **20** being obtained in moderate yields (50% and 55%, respectively).

The structural assignment of the bicyclic compounds was established on the basis on NMR spectroscopy[17] and literature data. In fact there is only one example in the literature where bicyclic compounds of this type have been synthesized as masked octulosonic acids. The group of Baasov[18] has reported a multistep synthesis (13 steps) starting from a differentially protected arabinose derivative, where an enolpyruvate moiety is introduced undergoing Lewis acid intramolecular condensation. An X-ray

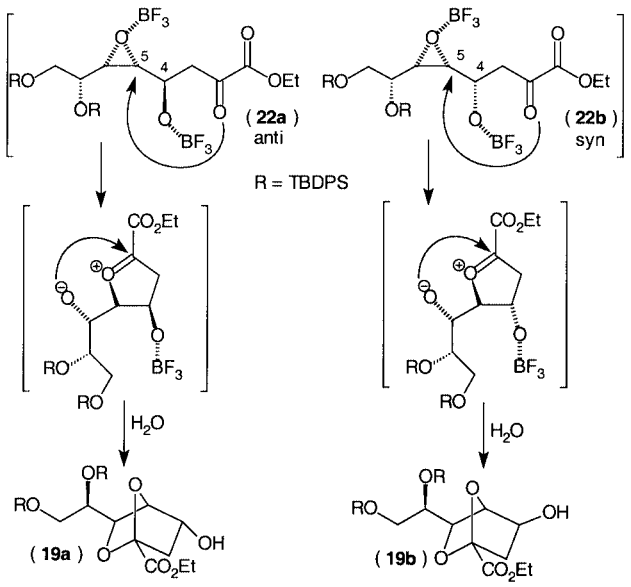


Scheme 4 Reagents and conditions: Method A: **4** (1.5 equiv)/CH_2Cl_2/BF_3-Et_2O (1 equiv)/–78 °C (3 h) → –40 °C (1 h), 41% for **19a** and **19b**; Method B: **4** (4.6 equiv)/CH_2Cl_2/BF_3-Et_2O (6.9 equiv)/–40 °C (6 h), 78% for **19a** and **19b**, 78% for **20a** and **20b**, 10% for **21a** and **21b**

structure of one of the synthesized bicycles, along, with NMR data are available. According to these data, similarities of the bicyclic frame **23** are observed with compound **19b**: a) $^1H_{3b}$ displays only one coupling constant ($J_{H3a-H3b}$ = 13.5 Hz); b) $^1H_{3a}$ resonates as dd with J_{H3a-H4} = 6.5 Hz; c) $^1H_5$ (δ = 4.64 ppm) does not couple with any vicinal proton (singlet); d) $^1H_6$ resonates at higher field (δ = 3.69 ppm) compared to $^1H_6$ of the isomer **19a** (δ = 4.77 ppm) as in the case of Baasov's compound.

Bicycle formation could be explained by the following mechanism: first a Mukaiyama aldolisation reaction occurs leading to intermediates β-hydroxy γ,δ-epoxy ketoesters **22a** and **22b**, which are diastereoisomers at C-4, in a 63:37 *anti*:*syn* ratio in the case of epoxyaldehyde **15** (Scheme 5). The cyclisation process at the C-5 carbon atom of these epoxyketoesters can be triggered by Lewis acid mediated intramolecular attack of the carbonyl oxygen atom of the ketone on the epoxide function. Such a cyclisation process would lead to the formation of an oxocarbenium ion which may react in situ with the just formed alkoxide, forming the cyclic ketal and thus the bicyclic compounds. The C-4 epimeric bicycles obtained, reflect the diastereoisomeric ratio of the aldolisation reaction. Considering the cyclisation reaction, these results are in agreement with all previously reported by our group[19–21] concerning the Lewis acid mediated intramolecular cyclisation of γ,δ-epoxy β-hydroxyesters. In fact, in the case of compounds almost symmetrically substituted around the *cis* epoxy function, the regioselectivity of the reaction always leads to the smaller ring on the basis of steric requirements and better antiparallel alignment of the incipient and rupturing bonds.

In conclusion we have found a very direct and efficient method for a one step synthesis of heptulosonic and octulosonic bicyclic precursors through [4+3] and [5+3] carbon atom incorporation by using *cis*-α,β-epoxyaldehydes and ethyl 2-(trimethylsilyloxy)-2-propenoate. Many analogues of ulosonic acids, starting from differently protected hydroxy groups of the bicyclic compounds, can thus be easily accessed. It is noteworthy that the aldolisation reaction leads to completely different compounds when using *trans*-α,β-epoxyaldehydes as we have reported earlier.[11]



Scheme 5

Acknowledgement

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(16) **Typical Procedure**: To a solution of epoxyaldehyde and ethyl 2-(trimethylsilyloxy)-2-propenoate in anhyd dichloromethane, at temperature indicated in the schemes, was slowly added $BF_3{\cdot}Et_2O$. After the time of reaction, the mixture was quenched with a sat. $NaHCO_3$ solution and extracted with dichloromethane and ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was chromatographed on silica gel (petroleum ether–ethyl acetate, 90:10→70:30→0:100).

(17) Spectral data of compound **19a**: **^{1}H NMR (250 MHz, $CDCl_3$)**: δ (ppm)= 7.73–7.29 (m, 20 H, CH-TBDPS); 4.77 (d, 1 H, J = 6.1 Hz, H-6); 4.71 (d, 1 H, $J_{5/4}$ = 4.6 Hz, H-5); 4.49–4.43 (m, 1 H, H-4); 4.23 (m, 2 H, CH_2 ethyl); 3.94 (td, 1 H, $J_{7/8a} = J_{7/8b}$ = 3.7 Hz, $J_{7/6}$ = 6.1 Hz, H-7); 3.64 (dd, 1 H, $J_{8a/7}$ = 3.7 Hz, and $J_{8a/8b}$ = 10.9 Hz, H-8a); 3.56 (dd, 1 H, $J_{8b/7}$ = 3.7 Hz and $J_{8a/8b}$ = 10.9 Hz, H-8b); 2.38 (dd, 1 H, $J_{3a/4}$ = 9.9 Hz and $J_{3a/3b}$ = 12.6 Hz, H-3a); 1.81 (d, 1 H, $J_{3b/3a}$ = 12.7 Hz and $J_{3b/4}$ = 3.6 Hz, H-3b); 1.23 (t, 3 H, J = 7.2 Hz, CH_3 ethyl); 1.07 (s, 9 H, *t*-Bu); 1.02 (s, 9 H, *t*-Bu). **^{13}C NMR (50 MHz, $CDCl_3$)**: δ (ppm)= 165.7 (C-1); 136.1, 135.9, 135.7, 129.7, 127.5 (CH phenyl); 134.1, 133.6 (Cq phenyl); 105.7 (C-2); 79.8 (C-5); 74.4, 73.8 (C-6 and C-7); 68.5 (C-4); 64.9 (C-8); 61.9 (CH_2CO_2Et); 43.1 (C-3); 27.0, 26.9 (CH_3-*t*-Bu); 19.5, 19.3 (Cq-*t*-Bu); 14.0 (CH_3-ethyl). **Elemental Analysis**: Anal. Calcd for $C_{42}H_{52}O_7Si_2$: C, 69.58; H, 7.23. Found: C, 69.48; H, 7.38. Spectral data of compound **19b**: **^{1}H NMR (250 MHz, $CDCl_3$)**: δ (ppm)= 7.69–7.25 (m, 20 H, CH-TBDPS); 4.64 (s, 1 H, H-5); 4.27 (q, 2 H, J = 7.6 Hz, CH_2 ethyl); 4.06 (d, 1 H, $J_{4/3a}$ = 6.4 Hz, H-4); 3.81 (ddd, 1 H, $J_{7/8a}$ = 3.3 Hz, $J_{7/8b}$ = 2.8 Hz, $J_{7/6}$ = 5.9 Hz, H-7); 3.76 (d, 1 H, $J_{6/7}$ = 5.9 Hz, H-6); 3.59 (dd, 2 H, $J_{8a/7}$ = 3.3 Hz and $J_{8a/8b}$ = 10.7 Hz, H-8a); 3.50 (dd, 1 H, $J_{8b/7}$ = 2.8 Hz and $J_{8b/8a}$ = 10.7 Hz, H-8b); 2.50 (dd, 1 H, $J_{3a/4}$ = 6.5 Hz and $J_{3a/3b}$ = 13.5 Hz, H-3a); 1.65 (d, 1 H, $J_{3b/3a}$ = 13.5 Hz, H-3b); 1.29 (t, 3 H, J = 7.6 Hz, CH_3 ethyl); 1.08 (s, 9 H, *t*-Bu); 1.03 (s, 9 H, *t*-Bu). **^{13}C NMR (50 MHz, $CDCl_3$)**: δ (ppm)= 165.5 (C-1); 136.0, 135.8, 135.6, 129.6, 127.6 (CH phenyl); 133.9, 133.2 (Cq phenyl); 103.9 (C-2); 83.6 (C-5); 76.1, 73.4 (C-6 and C-7); 72.0 (C-4); 64.6 (C-8); 62.0 (CH_2CO_2Et); 47.0 (C-3); 27.0, 26.9 (CH_3-*t*-Bu); 19.5, 19.3 (Cq-*t*-Bu); 14.0 (CH_3-ethyl). **Elementary Analysis**: Anal. Calcd for for $C_{42}H_{52}O_7Si_2$: C, 69.58; H, 7.23. Found: C, 69.13; H, 6.86.

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