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Novel Approach to the Synthesis of Chiral Oxacycles via Ring Closure of Sugar-Derived Vinyl Sulfones

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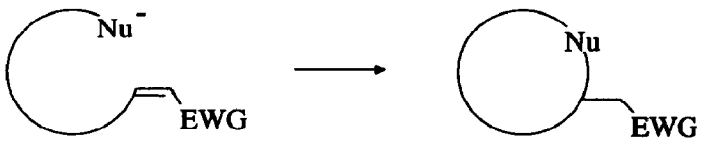
Key Words : thiosugars; vinyl sulfones; heterocyclization; 5-exo-trig; chiral oxolans.

Abstract : Sugar-derived vinyl sulfones were found to undergo a Michael-initiated ring closure process to build up a chiral polysubstituted oxolan system with high stereoselectivity.

A large number of biologically-significant natural products such as C-glycosides, acetogenins or polyether ionophores contain medium-size cyclic ether structural units.[1] For this reason, synthetic routes to stereochemically-defined tetrahydropyran and tetrahydrofuran systems have received considerable attention, which is highlighted in recent reviews.[2,3]

A particularly challenging aspect consists in the stereocontrolled construction of 2,5-disubstituted tetrahydrofuran units, specially those displaying a *cis* relationship between substituents at the 2- and 5-positions. For this purpose, miscellaneous cyclization methodologies have been developed[4] but relatively few involving a Michael-initiated ring closure reaction (simply referred to as the *MIRC* reaction[5]) of the following type :



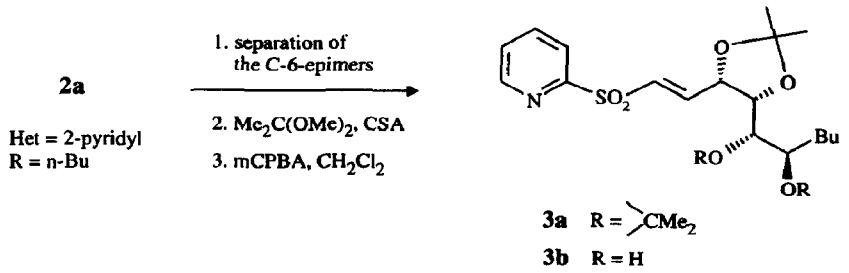
To our knowledge, the Michael-acceptor property of vinylic sulfones has been applied only twice[6,7] in a 5-*endo*-trig cyclization procedure.[8]

In our laboratory, a new Grob-type heterolytic fragmentation process[9] based on cooperative aza/thia-assistance[10] has been applied to aza-heterocycle / thiosugar hybrids **1**,[11] to yield (E)-configurated vinyl sulfides of type **2** with a high diastereoisomeric excess :

1 **2**

Vinyl sulfides **2** can readily undergo oxidation on the sulfur centre - with or without prior reprotection of

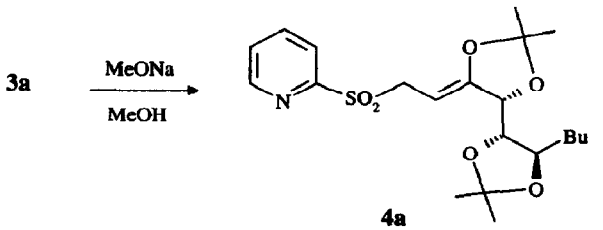
the 5,6-diol segment - to yield compounds **3**, in which a vinyl sulfone moiety is engrafted upon a stereochemically-defined polyoxygenated appendage. In the specific case of **2a** (Het = 2-pyridyl, R = n-butyl) a major 6*R* epimer[12] is presented in this paper :



3a R = $\diagup\!\diagdown$CMe$_2$

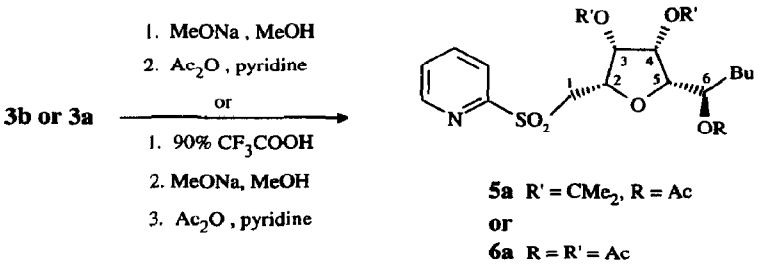
3b R = H

In a parallel study, the electrophilic behaviour of the 5,6-O-isopropylidene protected sulfone **3a** towards miscellaneous representative reagents has been summarily evaluated.[13] Reaction of **3a** with catalytic sodium methoxide in methanol does not produce the expected β-methoxy adduct,[14] but a double bond migration occurs instead to give the isomeric allylic sulfone **4a** in 81% yield[15] :



4a

When applied to a vinyl sulfone bearing free hydroxyl groups, the same reaction should lead to different results.[6,7] Indeed, compound **3b** smoothly reacted in similar conditions to give a cyclized compound which was isolated (60% yield) and characterized[16] in its acetylated form **5a** :



5a R' = CMe$_2$, R = Ac

or

6a R = R' = Ac

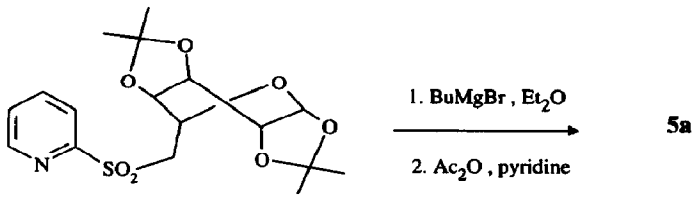
In a different attempt, **3a** was fully deprotected (90% TFA hydrolysis) prior to being submitted to the base-induced cyclization procedure : after peracetylation of the crude reaction mixture, the chiral tetrahydrofuran **6a** was isolated in 72% yield[17].

In both cases, the observed *MIRC* regioselectivity demonstrates that the 5-*exo*-trig process is strongly favoured over the 6-*exo*-trig option : this is in full agreement with Baldwin's general conclusions[8,18] based on the compared stereochemical requirements of the respective transition states.

On the other hand, the *MIRC* process proves highly stereoselective in producing almost exclusively the all-*syn* stereoisomer, as shown by thorough NMR data examination.[19] The (2*S*)-*syn* configuration of C-2 results from the O-3 sterically-directed *anti*-attack of O-5 onto the Michael-acceptor moiety : thermodynamical constraints in such cyclic structures were previously shown to favour the same *endo* relative stereochemistry,[20] whereas empirical force-field calculations effected on 1-C-methyl-1,4-anhydropentitols have pointed out the *endo-lyxo* form as the most stable stereoisomer.[21]

In order to try and improve the applicability potential of this ring-closure procedure in multi-step synthesis, we have shortened the reaction sequence in skipping isolation of the intermediate vinyl sulfones **3a** or **3b**.

The sugar-derived pyridyl sulfone **7a** was prepared by MCPBA oxidation of hybrid **1a** (Het = 2-pyridyl).[22] When submitted to the Grignard reagent, **7a** readily underwent fragmentation to yield a mixture of compounds from which **5a** could be eventually isolated (after acetylation) in 55% yield.



In summary, we report a novel approach to the synthesis of chiral polysubstituted oxolans from sugars. Particularly noteworthy in this D-*galacto* series preliminary results is: i) the easy synthetic access to the sulfone precursors ii) the Baldwin rules-governed regioselectivity iii) the high stereoselectivity, in agreement with what could be anticipated. Further elaboration of this methodology is now under way in this laboratory and will be reported in due course.

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12. All new compounds gave satisfactory spectroscopic and microanalytical data. Selected data for **3a**: syrup; $[\alpha]_D$ + 27 (c 1.0, $CHCl_3$); ^{1}H-RMN ($CDCl_3$, 300MHz), δ ppm (J Hz): 0.91 (t, 3H, nBu), 1.23, 1.33,

1.37, 1.52 (4s, 12H, 4 Me), 1.30 to 1.60 (m, 6H, nBu), 3.48 (dd, 1H, $J_{2,1}$ 8.0, $J_{2,3}$ 1.9, H-2), 3.90 (m, 1H, H-1), 4.25 (dd, 1H, $J_{3,4}$ 7.1, H-3), 4.90 (ft, 1H, $J_{4,5}$ 5.6, H-4), 6.91 (d, 1H, $J_{6,5}$ 15.2, H-6), 7.19 (dd, 1H, H-5), 7.52 (dd, 1H, $J_{5\pi,4\pi}$ 7.7, $J_{5\pi,6\pi}$ 4.4, H-5π), 7.94 (ft, 1H, $J_{4\pi,3\pi}$ 7.7, H-4π), 8.08 (d, 1H, H-3π), 8.73 (d, 1H, H-6π). Hπ refers throughout to the pyridyl moiety.

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15. Selected data for **4a** : syrup; $[\alpha]_D$ + 42 (c 0.5, $CHCl_3$); ^{1}H-RMN ($CDCl_3$) : 0.91 (t, 3H, nBu), 1.18, 1.31, 1.34, 1.35 (4s, 12H, 4 Me), 1.30 to 1.60 (m, 6H, nBu), 3.66 (dd, 1H, $J_{2,1}$ 8.3, $J_{2,3}$ 2.2 , H-2), 3.81 (m, 1H, H-1), 4.16 (dd, 1H, $J_{6a,5}$ 7.7, $J_{6a,6b}$ 14.1, H-6a), 4.22 (dd, 1H, $J_{6b,5}$ 7.6, H-6b), 4.39 (ft, 1H, H-5), 4.53 (s, 1H, H-3), 7.49 (dd, 1H, $J_{5\pi,4\pi}$ 7.7, $J_{5\pi,6\pi}$ 4.4, H-5π), 7.89 (ft, 1H, $J_{4\pi,3\pi}$ 7.7, H-4π), 8.04 (d, 1H, H-3π), 8.72 (d, 1H, H-6π).
16. Selected data for **5a** : mp 104°C; $[\alpha]_D$ - 52 (c 1.0, $CHCl_3$); ^{1}H-RMN ($CDCl_3$): 0.85 (t, 3H, nBu), 1.27, 1.42 (2s, 6H, 2 Me), 1.30 to 1.60 (m, 6H, nBu), 1.96 (s, 3H, AcO), 3.42 (dd, 1H, $J_{5,4}$ 8.7, $J_{5,6}$ 3.9, H-5), 3.75 (dd, 1H, $J_{1a,1b}$ 14.6, $J_{1a,2}$ 5.5, H-1a), 3.95 (dd, 1H, $J_{1b,2}$ 6.3, H-1b), 4,04 (m, 1H, $J_{2,3}$ 6.2 , H-2), 4.63 (dd, 1H, H-6), 4.74 (dd, 1H, $J_{3,4}$ 3.7, H-3), 5.11 (dd, 1H, H-4), 7.52 (dd, 1H, $J_{5\pi,4\pi}$ 7.7, $J_{5\pi,6\pi}$ 4.4 , H-5π), 7.89 (ft, 1H, $J_{4\pi,3\pi}$ 7.7, H-4π), 8.03 (d, 1H, H-3π), 8.71 (d, 1H, H-6π).
17. Selected data for **6a** : syrup; $[\alpha]_D$ - 12 (c 0.8, $CHCl_3$); ^{1}H-RMN ($CDCl_3$): 0.85 (t, 3H, nBu), 1.07 to 1.40 (m, 6H, nBu), 1.97, 2.03, 2.08 (3s, 9H, 3AcO), 3.67 (dd, 1H, $J_{1a,1b}$ 14.5, $J_{1a,2}$ 3.6, H-1a), 3.81 (dd, 1H, $J_{1b,2}$ 7.3, H-1b), 4.06 (ft, 1H, $J_{5,4}$=$J_{5,6}$ 5.5, H-5), 4.56 (ddd, 1H, $J_{2,3}$ 11.8, H-2), 5,00 (m, 1H, H-6), 5,22 (ft, 1H, $J_{3,4}$ 5,6, H-3), 5.46 (ft, 1H, H-4), 7.52 (dd, 1H, $J_{5\pi,4\pi}$ 7.7, $J_{5\pi,6\pi}$ 4.4, H-5π), 7.89 (ft, 1H, $J_{4\pi,3\pi}$ 7.7, H-4π), 8.04 (d, 1H, H-3π), 8.72 (d, 1H, H-6π).
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22. Selected data for **7a** : mp 146°C; $[\alpha]_D$ - 63 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : 1.28, 1.31, 1.38 and 1.52 (4s, 12H, 4 Me), 3.53 (dd, 1H, $J_{6b,5}$ 3.5, $J_{6b,6a}$ 15.3, H-6b), 3.85 (dd, 1H, $J_{6a,5}$ 7.8, H-6a), 4.22 (dd, 1H, $J_{4,3}$ 7.8, $J_{4,5}$ 1.8, H-4), 4.25 (dd, 1H, $J_{2,1}$ 4.9, $J_{2,3}$ 2.6, H-2), 4.42 (m, 1H, H-5), 4.60 (dd, 1H, H-), 5.21 (d, 1H, H-1), 7.58 (dd, 1H, $J_{5\pi,4\pi}$ 7.9, $J_{5\pi,6\pi}$ 4.7, H-5π), 7.94 (ft, 1H, $J_{4\pi,3\pi}$ 7.9, H-4π), 8.10 (d, 1H, H-3π), 8.73 (d, 1H, H-6π).

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