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Ligand Assisted Asymmetric Synthesis. II. Diastereoselective Diels-Alder Additions with Lewis Acid attracting Auxiliaries derived from Pentitols

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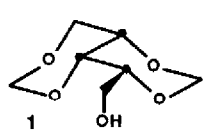
Key Words : Asymmetric Diels-Alder reaction; alditol; pentitol; methylene acetal

Abstract: *The dimethylene acetals of the three pentitols and methylene acetal of 1,2,4-butanetriol behave as effective templates for the diastereoselective Diels-Alder reaction. The chirality transfer occurs through a chelate-complex involving one of the dioxane rings.*

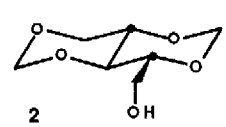
Simple sugar moieties are -so far- of relatively little use in the much studied asymmetric Diels-Alder reaction,[1] albeit they fulfill the requirement for natural and renewable sources. A few reports describe the cycloaddition of acrylates linked to a modified carbohydrate structure,[2a, b, c, d] of imines,[3] nitroso ether,[4] and of various dienes attached to glucoside derivatives.[5a, b, c] Literature references about the use of alditols as templates for the Diels-Alder reaction are even scarcer, although efficient Lewis acids have been built on the C_4O_4 framework of threitol.[6]

Recently, we described the diastereoselective Diels-Alder reaction of acrylates branched on chiral auxiliaries having a 1,3-dioxane ring, derived from threitol.[7] The methylene acetal function showed ligand properties providing with an heteroatom appropriately located to participate intramolecularly in the formation of a bidendate chelate-complex. The system proved effective at reducing the conformational mobility of the reacting species, insuring very high levels of stereoselection. In that respect, the 1,3:2,4-di-O-methylene acetal of pentitols (xylitol, ribitol, arabitol) could provide naturally more rigid chelates, able to increase even better the free energy difference of the diastereomeric transition states.

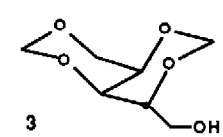
The three dimethylene acetals **1**, **2**, **3** are known compounds[8] and we significantly improved their synthesis by direct methylenation from dimethoxymethane.[9] They differ by the relative configurations of their 3 contiguous chiral centers (scheme 1), a fact that might help in the stereochemical knowledge of the transition state of stereocontrolled processes.



DMXylitol: T-T, (-)-(S,S,R)



DMRibitol: E-E, (S*,R*,R*)



DMArabitol: T-E, (+)-(R,R,R)

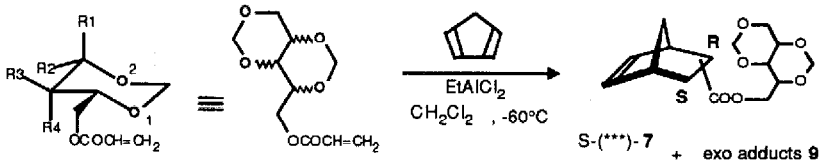
Scheme 1 : Configuration of dimethylene pentitol (DM: dimethylene; T: threo; E: erythro)

Chiral arabitol is available as either absolute configuration. Xylitol and ribitol are meso-compounds, but we prepared chiral dimethylene xylitol **1** from D-sorbitol.[10] For the sake of simplicity, dimethylene ribitol will be referred to as the (2S, 3R, 4R)-enantiomer.

The primary alcohols are esterified to the corresponding acrylates ($ClCOCH=CH_2$, NEt_3, CH_2Cl_2, -30°C, 1h, 66 to 77% yield). Those add to cyclopentadiene (20°C, 24h, 89-100% yield) to afford a chromatographically separable and identifiable mixture of endo adducts **7** - **8** (≈ 1:2), and exo adducts **9** (up to 38%).

The promoted reaction, with an essential excess of Lewis acid under the standard conditions we earlier defined (-60°C, CH_2Cl_2, 1.5 eq. $EtAlCl_2$),[7] affords excellent levels of endo/exo ratio and diastereoselectivity (Table I).

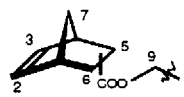
TABLE I - Diels-Alder addition of dimethylene pentitols and cyclopentadiene.

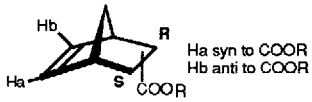


ACRYLATE	R1	R3	R2	R4	REACTION TIME	YIELD	ENDO : EXO	S-7 : R-8
Xylo (S,R,R)- **4**	H	H	CH_2	O	27h	65%	96 : 4	4 : 96
Ribo (S,S,R)- **5**	H	O	CH_2	H	6h	89%	98 : 2	<2 : >98
Arabino (R,S,R)- **6**	CH_2	O	H	H	3h	99%	97 : 3	0 : 100

The addition of norbornenyl acid chloride to dimethylene pentitols affords three sets of mixture, that allow to distinguish diastereomers **7** and **8** by 200 MHz ^1H and ^{13}C NMR spectroscopy. Therefore the reaction mixtures afforded by the Diels-Alder additions can be directly analyzed from their NMR spectra. Finally the $LiAlH_4$ reduction of the adducts to (+)-R-norbornenyl alcohol ascertains the absolute configuration of the major diastereomer in the xylo- and arabino- series. Moreover, the chiral auxiliary is recovered during the process. Correlation with the chiral series established the relative configuration of adducts **7**-**8** in the ribitol series. Table II displays the typical NMR signals of diastereomers.

TABLE II - 200 MHz, ^{13}C and ^1H NMR signals of **7** and **8**, δ ppm, $CDCl_3$

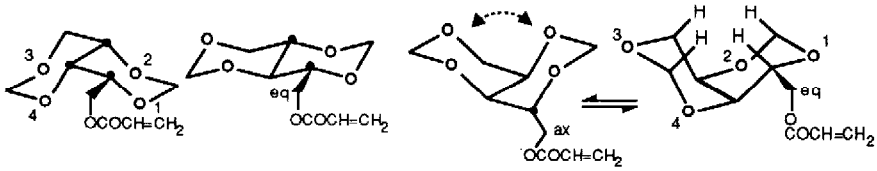




		C2	C3	C5	C6	C7	C9	Ha	Hb
Xylo	R-**8**	132.4	137.9	29.3	43.2	49.7		6.27, dd	6.06, dd, J=2.8, 5.6
	S-**7**	132.3	137.8	29.2	43.1	49.6		J = 3 , 5.6	5.93 - 6.0, m
Ribo	R-**8**	132.4					62.33	6.26, dd	6.04 - 6.08, m
	S-**7**	132.2					62.32	J = 3.02, 5.6	5.95 - 6.03, m
Arabino	R-**8**	132.3	137.9		43.1		60.95	6.28, dd	6.06, dd, J = 2.8, 5.6
	S-**7**	132.1	137.8		42.9		60.90	J = 3.1, 5.6	5.97, dd, J = 2.8, 5.6

The effective diastereoselection at dienophiles **4**, **5** and **6** can't be a consequence of the simple steric effect of the tetraoxadecalin unit upon the flexible acrylic methyl appendage. Rather, as we have already pointed out, one of the dioxane rings plays a crucial role through the intramolecular coordination of the Lewis acid already bound to the carbonyl oxygen, to form a chelate complex.[7] The most stable conformation of acrylate **4** should be O-inside[12] with equatorial appendage, and trans-decalin with equatorial appendage for acrylate **5**. Acrylate **6** may exist under 2 conformations: O-inside with axial appendage **6a**, or H-inside with equatorial appendage

6b.The differences between the melting points may justify this trend (scheme 2).

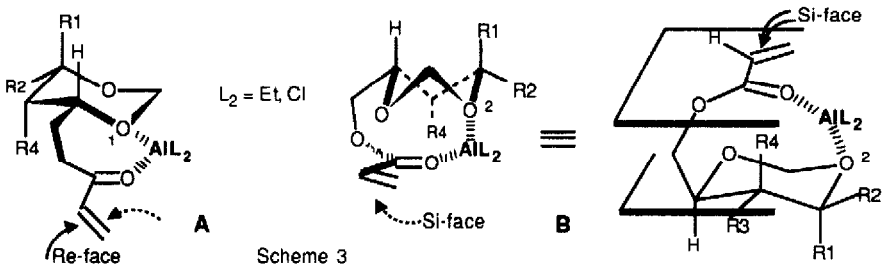


4 O-inside / eq F = 174-175°C $[\alpha]_{546}^{20}$ = - 16.7 (c 6,$CHCl_3$) **5** trans / eq F = 100-101°C **6 a** O-inside / ax **6 b** H-inside / eq F = 61-62°C $[\alpha]_{546}^{20}$ = +11.9 (c 10,$CHCl_3$)

Scheme 2

Out of the 4 oxygen atoms of the tetraoxadecalin, O^1, O^2 and O^4 are candidates to form the chelate-complex. The methyl acryloyl appendage rather shields O^1 and O^4 that are less accessible to electrophiles; a fact illustrated by our previous results[7] and several studies on the stereoselective opening of dioxane acetals.[11] On the other hand, coordination of the Lewis acid to O^1 or O^4 would lead to a chelate-complex **A**, from which little π-face stereodifferentiation due to the template or one of the Lewis acid ligands is expected (scheme 3). Even, assuming the *s*-cis conformation of the enoate (as it is established for chelate-complexes between Lewis acids and dienophiles),[7] **A** would lead to the partial shielding of the wrong face, affording preferentially **S-7**.

Considering conformation **6b** for the arabitol acrylate, the three pentitol acrylates present the same pattern regarding the substituted dioxane ring (scheme 4). From this pattern, O^2 behaves as the anchor to which an aluminum atom can coordinate to form chelate-complex **B** (scheme 3).



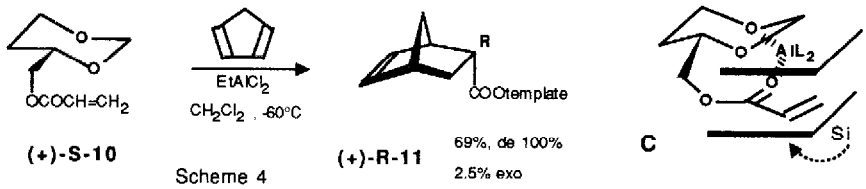
Scheme 3

The chair dioxane ring and the acrylic moiety lay over each other in two near parallel planes, and the diene reagent can approach the cisoid acrylate only from the Si-face. This transition state leads to diastereomer **8** in excellent yields.

Traces of diastereomer **7** noticed in the reaction of acrylates **4** and **5** certainly arise from some equilibrium between the anti- and syn-rotamer of the acrylate. The equilibrium may be a consequence of the reaction time needed to complete the additions. Reaction times can also be correlated to substituants R2 and R4, located on the concave face of the resulting cyclic complex **B**, and syn to the Lewis acid. For R2 = R4 = H (acrylate **6**) the shortest reaction time, and both the highest chemical and *de* yields are observed. The opposite is true for acrylate **4** in which R2 = CH_2 and R4 = O (table I).

Finally, selecting the naked involved dioxane pattern spectacularly demonstrates the proposed transition state **B**. Acrylate of S-butanetriol methylene acetal[13] **10**, made active with $EtAlCl_2$, adds to cyclopentadiene under the standard conditions previously defined, to afford pure adduct (+)-R-**11** (along with 2.5% of the exo

isomer). The synthesis of a mixture R, S-**11** and correlation to (+)-R-norbornenyl methanol confirm the diastereomeric purity of **11** (scheme 4).



(+)-S-10 Scheme 4 (+)-R-11 69%, de 100% 2.5% exo C

Methylenebutanetriol certainly constitutes one of the most unhindered and flexible structure involved in the transmission of a chiral message. Again, the layered transition state C best accounts for the Si-face approach and the total diastereoselection. To conclude with, methylene acetals of uneven polyols (1,2,4-butanetriol and the 3 pentitols) afford a new family of stable metal attracting templates. They efficiently transfer chirality during chelation controlled processes like the Lewis acid promoted Diels-Alder reaction.

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