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Diastereoselectivity In The Addition of Organocerium Reagents To 4- and 5-Oxazolidonecarbaldehydes: Synthesis Of *Syn*- and *Anti*-Alcohols.

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Abstract: Chiral non-racemic 4- and 5-oxazolidonecarbaldehydes, typified by **2** and **7**, react highly diastereoselectively with organocerium reagents to give moderate to good yields of *syn*- and *anti*-alcohols, respectively. Rationalizations for the observed diastereoselectivities are presented. The synthetic potential of this method is exemplified by the synthesis of C-18-D-*ribo*-phytosphingosine which was obtained as its tetraacetate.
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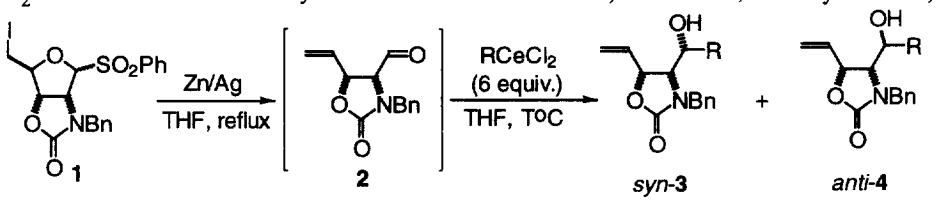
The *vic*-amino alcohol moiety is a common structural subunit that is found in many naturally occurring and medicinally important compounds such as sphingolipids,[1a] hydroxylated alkaloids,[1b] and amino acids.[1c] The most widely used method for the synthesis of *vic*-amino alcohols is the nucleophilic addition of C-centered nucleophiles to amino aldehydes.[2] However, some limitations of the method have been noted; for example, the amino aldehyde is prone to racemization under the reaction conditions[2b] and the diastereoselectivity of the reaction is usually not as high as expected.

In comparison, the use of oxazolidones for the synthesis of *vic*-amino alcohols has not been extensively investigated. Two aspects that make them attractive synthetic intermediates are (a) the 2-oxazolidone moiety can be considered as a protected amino alcohol synthon, which can be subsequently unmasked to reveal the amino alcohol unit, and (b) the reactions carried out on oxazolidone derivatives are usually highly stereoselective.[3]

Herein, we report that the nucleophilic addition reaction of chiral non-racemic 4- and 5-oxazolidonecarbaldehydes with organocerium reagents proceeded with good to excellent diastereoselectivity to give *syn* or *anti*-products in moderate to good chemical yields. A procedure was developed for the generation and *in situ* reaction of 4-oxazolidonecarbaldehydes, as exemplified by **2**, with organocerium reagents.

The aldehyde **2** was readily prepared via Zn/Ag[4] reductive elimination of the iodo phenylsulfone **1**[5] in dry THF (Scheme 1). The use of dry THF is necessary because it permits the direct reaction of **2** with organocerium reagents. The THF solution of **2** was then transferred, via cannula, to the preformed organocerium reagent[6] (6 equiv.) at -78°C. The results are collected in the Table. Grignard-derived and organolithium-derived organocerium reagents reacted well with **2**. The nucleophilic addition reaction produced crystalline, diastereomeric mixture of alcohols **3** and **4** in which alcohol **3** was present as the predominant or exclusive product. For reactions in which Grignard-derived $RCeCl_2$ reagents are used, it was advantageous to

warm the reaction mixture to 0°C and to maintain the reaction at 0°C for at least 1 h. Thus, quenching the $PhCeCl_2$ reaction after 5h at -78°C yielded 29% of a mixture of **3f,4f**. However, a 52% yield of **3f,4f** was



Scheme 1. **a**, R= Me; **b**, R= CH_2=CH; **c**, R= CH_2CO_2Bu-*t*; **d**, R= PhC≡C; **e**, R= 2-furanyl; **f**, R= Ph

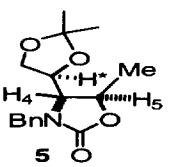
Table: Reaction of Oxazolidonecarbaldehydes **2** and **7** With $RCeCl_2$.

Entry	RCHO	$RM/CeCl_3$[a]	T°C/h	syn-**3**:anti-**4**[c,d]	Yield(%)[f]
1	**2**	MeLi	-78/5	95:5	85
2	**2**	MeLi[b]	-78/5	89:11	35
3	**2**	CH_2=CHMgBr	-78/5	>99:1	85
4	**2**	CH_2=CHMgBr[b]	-78/5	83:17	40
5	**2**	CH_2=C(OBu-t)O$^-$Li$^+$	-78/5	86:14[e]	92
6	**2**	PhC≡CLi	-78/5	>99:1	94
7	**2**	2-furanylLi	-78/5	>99:1	85
8	**2**	PhMgBr	-78/5; 0/1	88:12	52
				anti-**8**[c]	
9	**7**	MeLi	-78/5	>99:1	62
10	**7**	MeLi[b]	-78/5	decomp.	0
11	**7**	CH_2=CHMgBr	-78/5	>99:1	59
12	**7**	CH_2=CHMgBr[b]	-78/5	>99:1	21
13	**7**	$C_{14}H_{29}MgBr$	-78/5; 0/1	>99:1	69
14	**7**	$C_{14}H_{29}MgBr$	-78/5	>99:1	40
15	**7**	PhC≡CLi	-78/5	>99:1	85
16	**7**	2-furanylLi	-78/5	>99:1	64
17	**7**	CH_2=C(OBu-t)O$^-$Li$^+$	-78/5	>99:1	84

a; Reactions were quenched with satd. NH_4Cl solution at -78°C or at 0°C. b; Reaction was performed without $CeCl_3$. c; All new compounds gave satisfactory ^{1}H and ^{13}C NMR and HRMS and/or elemental analysis. d; Alcohols were inseparable. Ratio was based on the integration of Me resonance in the ^{1}H NMR of acetate derivatives. e; Ratio was based on the integration of the *t*-Bu singlet. f; Isolated yields of chromatograpically pure compounds.

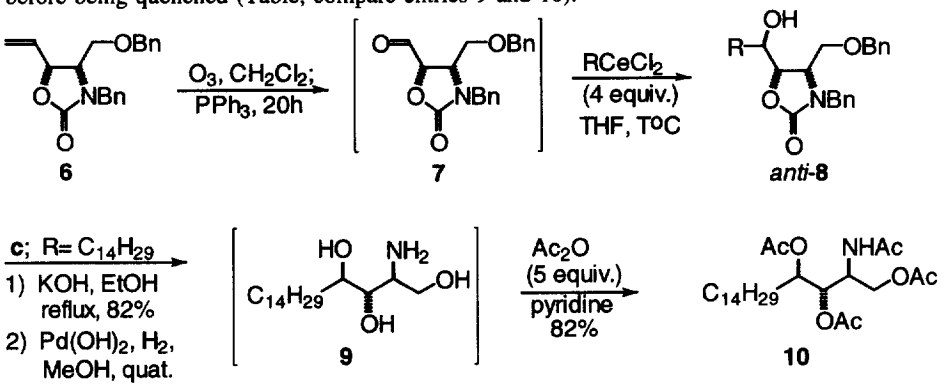
obtained when the mixture was warmed to and maintained at 0°C for 1 h (entry 8). For the CH_2=CHMgBr/$CeCl_3$ reaction, the reaction mixture must be conducted at -78°C because the organocerium reagent is unstable at 0°C.[6b] The use of Grignard and organolithium reagents alone resulted in lower diastereoselectivity and poorer chemical yields of products (compare entries 1,2 and 3,4).

The relative stereochemistry of the hydroxyl group and the benzylamino moiety of the oxazolidone unit in **3** was assigned as *syn* based on data obtained from decoupling experiments performed on oxazolidone **5**. Compound **5** was synthesized from **3a,4a** using standard functional group manipulations. Decoupling of the methyl doublet (δ 1.25) in **5** collapsed the H-5 quintet (broad, δ 4.42) to a doublet, $J_{5,4}$= 4.4 Hz. Similarly, irradiation of H* multiplet (δ 4.00–4.18) simplified the H-4 triplet (δ 3.11) to a doublet, $J_{4,5}$= 4.4 Hz. Based on this small vicinal coupling constant,[7] the relative



stereochemistry of the methyl and dioxalanyl groups was, therefore, assigned as *trans*.

The addition reaction in 5-oxazolidonecarbaldehyde **7** was next investigated. Aldehyde **7** was prepared by ozonolysis of the benzyl ether **6**[5b] (Scheme 2). A THF solution of crude **7**[8] was then added to $RCeCl_2$ (4 equiv.) at -78°C. Again, the reactions involving Grignard-derived organocerium reagents were allowed to warm to 0°C before being quenched (Table, compare entries 9 and 10).



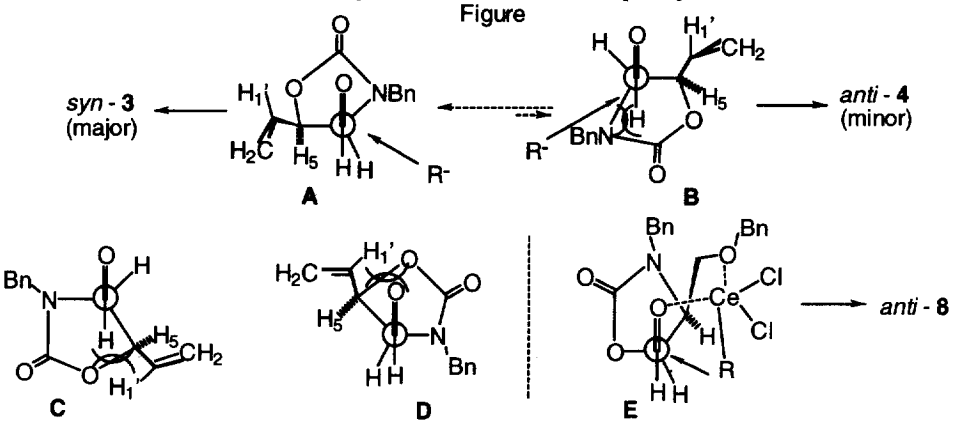
Scheme 2. **a**, R= Me; **b**, R= CH_2=CH; **c**, R= $C_{14}H_{29}$; **d**, R= PhC≡C; **e**, R= 2-furanyl; **f**, R= CH_2CO_2Bu-*t*

The reaction furnished the secondary alcohol **8** in moderate to good yields (Table). Only one diastereomer was obtained based on ^1H and ^{13}C NMR; the other epimer was not detected. The use of MeLi only resulted in the complete decomposition of **7** (compare entries 9,10) and the use of CH_2=CHMgBr gave a lower yield of *anti*-**8** (compare entries 11,12). The relative stereochemistry between the hydroxyl and the oxygen atom of the oxazolidone unit was assigned as *anti*. This assignment was confirmed by the conversion of compound **8c** ($[\alpha]_D^{22}$= +35.0; c= 1.50, $CHCl_3$) to the naturally occurring and biologically important C-18-D-*ribo*-phytosphingosine **9** which was more conveniently characterized as its tetraacetate derivative **10** ($[\alpha]_D^{21}$= +4.0, c= 1.25, DMF; $[\alpha]_D^{21}$= +28.9, c= 0.95, $CHCl_3$); Lit:[9a] $[\alpha]_D^{30}$= +4.4; c= 1.12, DMF; Lit:[9b] $[\alpha]_D^{24}$= +28.0; c= 1.30, $CHCl_3$). Compound **10** showed spectroscopic data identical to those reported in the literature.[9]

The diastereoselectivity observed in the reaction of aldehyde **2** can be understood if we considered the two reactive conformers **A** and **B** (Fig.). In each of the conformers, the preferred orientation of the C_5-vinyl substituent with respect to the rigid, planar oxazolidone unit is the one in which the vinyl H-1' hydrogen is aligned antiperiplanar to the oxazolidone H-5 hydrogen. This arrangement is adopted in order to relieve $A^{1,3}$ strain.[10] Conformer **A**[11a] is more stable than **B** because in the latter a destabilizing interaction is present. Preferential nucleophilic attack via the sterically less hindered side in **A** leads to the major *syn*-diastereomer **3** whereas attack via the sterically encumbered side in **B** results in the minor *anti*-diastereomer **4**. The conformers **C** and **D** correspond to the Felkin-Anh-type model[11] but are considered less stable than **A** and **B** because of the presence of destabilizing steric interactions. **C** is destabilized by the steric interaction between the aldehydic hydrogen and the *cis*-vinyl group and especially H-1'. Similarly, steric interaction between the *cis*-vinyl group/H-1' and the oxygen of the carbonyl function in **D** results in its destabilization. Nevertheless, the involvement of **C** and **D** cannot be entirely ruled out. The involvement of a five-membered chelate intermediate resulting from coordination of the carbonyl oxygen and the nitrogen atom of the NBn moiety to Lewis acidic Ce(III)[6] is not likely because of the reduced basicity of the nitrogen atom resulting from conjugation of the nitrogen lone pair of electrons with the π-bond of the carbonyl group of the oxazolidone

unit. In the case of **7**, a possible explanation for the unexpectedly high diastereoselectivity is the involvement of a seven-membered Ce(III) chelate **E** (Fig.).[12] Its formation is entropically favoured because of the *cis*

Figure



relationship of the aldehyde and $BnOCH_2$ moieties. Also, it is well documented that the oxygen atom in benzyl ethers show a propensity to coordinate to Lewis acids.[13] The chelate can also accommodate a Felkin-Anh[11] arrangement. Thus, both chelation control and stereoelectronic effects reinforce each other in controlling the diastereoselectivity of the reaction. Intramolecular or intermolecular delivery of R^- will occur from the less hindered side of the carbonyl function leading to *anti*-**8**.[14]

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