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β-AMINO ALCOHOLS FROM AMINO ACIDS: CHELATION CONTROL VIA SCHIFF BASES.

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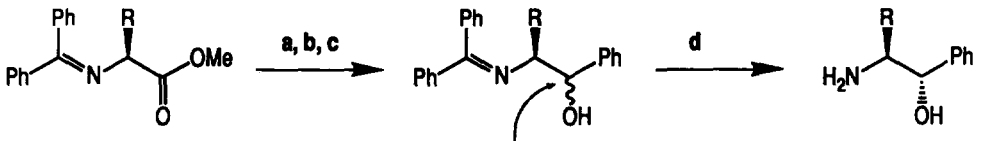
Summary: Sequential addition of iBu_2AlH and RLi or RMgX to Schiff base esters derived from amino acids provides a simple route to β-amino alcohols. The reaction procedes without racemization, and with high threo selectivity. Several representative sphingosines are synthesized.

As part of our program directed toward the synthesis of glycosphingolipids,[1] we became interested in protected amino aldehydes[2] for use as educts in Grignard-type reactions. It was clear from the literature that most examples of additions to amino aldehydes exhibited either no Cram selectivity, or poor to moderate selectivity for the *erythro* (unlike) product.[3] An additional complication is provided by the tendency of amino aldehydes to racemize. We would like to report a *threo* (like)-selective amino alcohol synthesis which does not involve the generation or isolation of the amino aldehyde, and thus can not racemize the original chiral center.[4]

The amino ester Schiff bases 1a - 1d were crystalline, and easily synthesized from the corresponding amino ester hydrochlorides using the published procedure of O'Donnell and Polt.[5] Treatment of Schiff bases 1a - 1d with iBu_2AlH in CH_2Cl_2 or $PhCH_3$ at -78°, followed by PhMgBr in Et_2O, and warming to 0° resulted in products 2 or 3, depending on the workup procedure. By quenching the reaction with $NaHCO_3$ the amino alcohols could be isolated (flash chromatography) in a protected form. Subsequent hydrolysis with 1N HCl gave the known[6] amino alcohols 3 in quantitative yield.

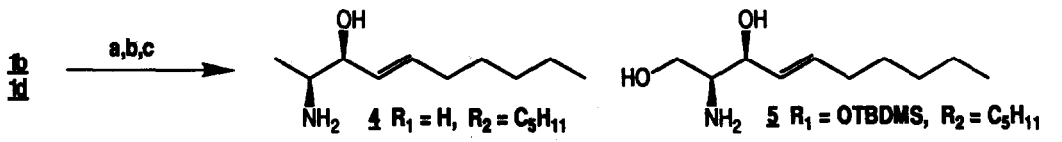


1a	R = H	2a	-	64%	3a[6a]
1b	R = CH_3	2b	18 : 1	54%	3b[6b]
1c	R = $PhCH_2$	2c	16 : 1	69%	3c[6c]
1d	R = TBDMS-OCH_2	2d	8 : 1	62%	3d[6d]

a) iBu_2Al-H / CH_2Cl_2 / -78° b) PhMgBr / Et_2O / -78° → 0° c) $NaHCO_3$ / H_2O d) H_3O^+

The use of higher temperatures resulted in poorer stereoselectivity. The use of donor solvents (e.g. THF, Et_2O) for the reduction likewise reduced the *threo*-selectivity, and increased the amount of over-reduction to the primary alcohol. Presumably this is because solvent lone-pairs can compete with the imine lone-pair for the electrophilic Al metal, thus destroying the chelate, and the "cyclic Cram transition state."[7] We are presently exploring other electrophilic metals to form tighter complexes, and expand the scope of this reaction.

Sphingosines 4 and 5 were synthesized in moderate yield (~50%), and excellent stereoselectivity (>20:1 by nmr)[8] by adding a mixture of tBuLi and *trans*-1-iodo-1-heptene in hexane to the Schiff base-DIBAL adduct at -78° and warming to 0°. The major side reaction is over reduction of the ester to the primary alcohol, which is a greater problem with alkyllithiums than with Grignards. This is consistent with what is known of aluminum "ate" complexes: as the electronegativity of the counterion decreases, the rate of β-elimination increases to yield an Al-H species capable of further reduction.[9]



a) IBu_2Al-H / CH_2Cl_2 / -78° b) *trans*-R_2CH=CH-I / tBuLi / -78° → 0° c) H_3O^+

In principle, one would expect that the stereoselectivity of this reaction could be reversed by inverting the order of addition of H^- and R^- to obtain the corresponding *erythro*-sphingosines, or add differing R'^- and R''^- to obtain 3-alkyl-substituted sphingosines stereoselectively. We are presently pursuing this line of research.

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8. Compounds **4** and **5** exhibited the expected ^1H and ^{13}C nmr spectra, mass spectra and were analytically pure by hplc.

4 - ^1H (250 MHz, $CDCl_3$) : δ 572 (dt, 1H, J = 7.0, 15.4 Hz), 5.41 (ddt, 1H, J = 1.2, 7.0, 15.4 Hz), 3.20 (t, 1H, J = 7.0 Hz), 2.79-2.73 (m, 1H), 2.03-2.00 (m, 2H), 2.00-1.77 (br s, 3H), 1.44-1.20 (m, 6H), 1.08 (d, J = 6.3 Hz), 0.88 (t, 3H, J = 6.8Hz) ^{13}C (62.5 MHz, $CDCl_3$) δ 133.9, 130.3, 77.4, 51.3, 32.2, 31.3, 28.7, 22.5, 20.5, 13.9 MS (CI isoButane) : 172 (M+1), 154 (M+1 - H_2O)

5 - ^1H (250 MHz, CDCl3) : δ 5.76 (dt, 1H, J = 6.7, 15.4 Hz), 5.46 (dd, 1H, J = 6.7, 15.4 Hz), 3.98 (t, 1H, 6.0 Hz), 3.69 (dd, 1H j = 4.3, 10.7 Hz), 3.54 (dd, 1H, J = 6.2, 10.7 Hz), 2.82-2.76 (m, 1H), 2.15-2.00, (m, 2H), 2.1-1.75 (br s, 4H), 1.44-1.20 (m, 6H), 0.88 (t, J = 6.8 Hz) ^{13}C (62.5 MHz, $CDCl_3$) δ 133.8, 129.8, 73.4, 64.0, 56.4, 32.2, 31.4, 28.8, 22.4, 13.9 MS (CI isoButane): 188 (M+1), 170 (M+1- H_2O)

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