Stereoselective Mono- and Bis-homologation of L-Serinal *via* 2-Trimethylsilylthiazole Addition. The Thiazole Route to Amino L-Sugars and D-*erythro*-Sphingosines

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anti-Addition [92% diastereoselectivity (d.s.)] of 2-trimethylsilylthiazole (**2**) to *O,N*-protected L-serinal (**1**) and deblocking the formyl group in the resulting adduct, leads to the (2*S*,3*S*)-2,4-dihydroxy-3-aminobutanal derivative (**7**), which serves as a precursor both to masked 4-amino-4-deoxy-L-ribose/L-arabinose and D-*erythro*-C_{20}-sphingosine.

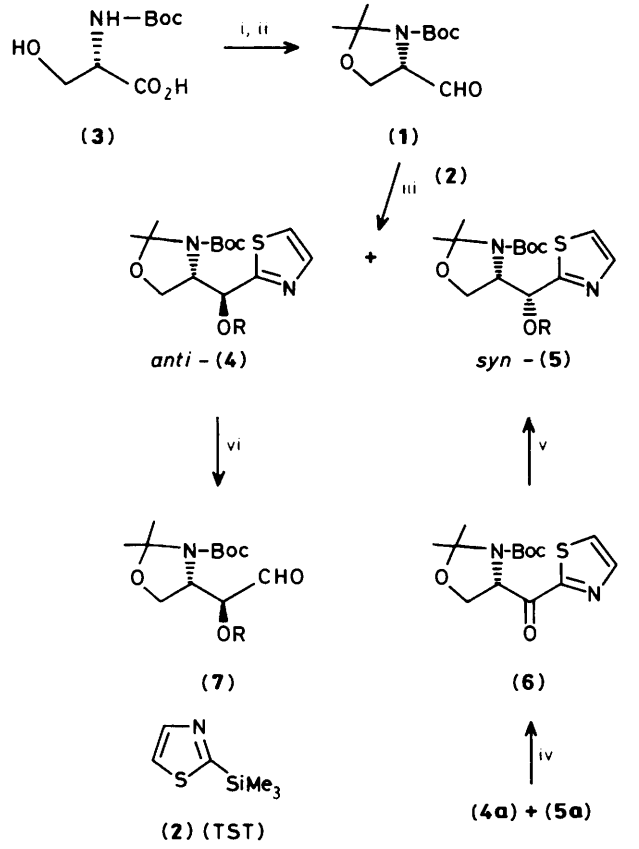
Optically pure α-amino aldehydes, readily available from natural amino acids.[1] (pool of chiral building blocks),[2] have been sporadically used with success as chiral auxiliaries in organic synthesis. Although various *N*-protecting groups have been employed,[3] most of the intermediates are unstable and configurationally labile. Thus, additions of organometallic reagents to amino aldehydes have been plagued by poor yields and/or lack of diastereoselectivity.[4] Good stereoselectivity has recently been reported[5] for the Lewis acid-catalysed cycloaddition of electron-rich dienes to the L-serine derivative aldehyde (**1**).

We recently reported[6] a new sequence for the stereoselective homologation of aldoses, *i.e.* chiral α-hydroxy aldehydes, wherein the *anti*-addition of 2-trimethylsilylthiazole (**2**) (TST) to the carbonyl group constitutes the key carbon–carbon bond forming step; the resulting adduct is then converted to the homologous aldose by deblocking the formyl group from the thiazolyl moiety. Herein, we report the successful extension of this concept to the chiral α-amino aldehyde (**1**), thus providing the first example of highly stereoselective addition of an organometallic reagent to an amino aldehyde in good yield (Scheme 1). Treatment of *N*-(t-butoxycarbonyl)-L-serinal acetonide (**1**), readily available from *N*-Boc-L-serine (**3**) and configurationally stable,[4,7] with the silylthiazole (**2**) in CH_2Cl_2 at room temperature followed by *in situ* desilylation with Bu^n_4NF produced a 92:8 ratio† of the diastereoisomeric amino alcohols (**4a**) and (**5a**) which were isolated in 85% overall yield after chromatography.‡ Attempts to separate

† Ratio determined by ^1H n.m.r. (80 or 200 MHz) spectral analysis.

‡ Chromatography was carried out on silica with light petroleum–ethyl acetate (80:20) as eluant. All new compounds gave satisfactory analytical and spectral data.

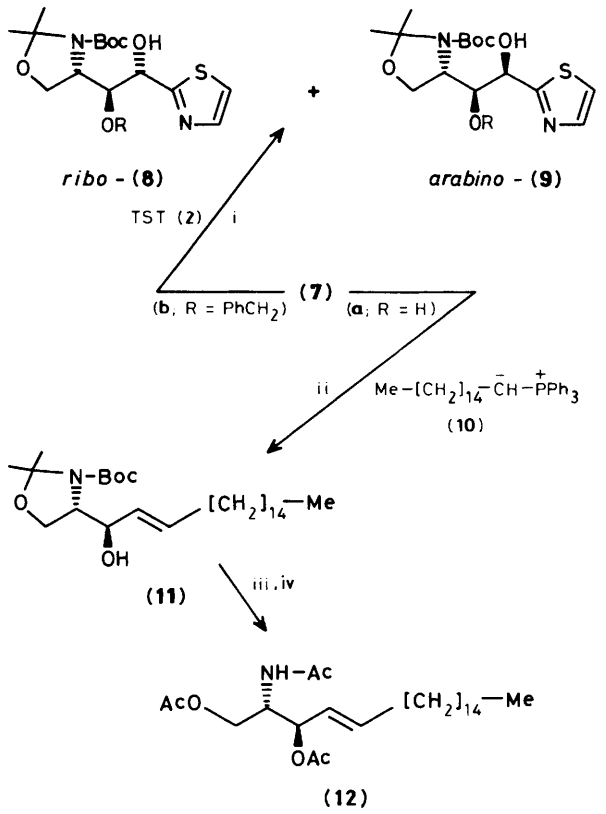
Selected ^1H n.m.r. and i.r. data: (**4a**), δ ($CDCl_3$–D_2O): 5.22 (d, 1H, *J* 2.8 Hz). 7.30 (d, 1H, *J* 3.2 Hz), 7.76 (d, 1H, *J* 3.2 Hz); (**5a**) δ ($CDCl_3$–D_2O): 5.10 (d, 1H, *J* 8.7 Hz), 7.34 (d, 1H, *J* 3.2 Hz), 7.77 (d, 1H, *J* 3.2 Hz); (**7b**) δ ($CDCl_3$): 9.63 (d, 1H, 3.2 Hz); $\nu_{max.}$ (film), 1740, 1700 cm^{-1}; (**8**), δ ($CDCl_3$–D_2O): 5.16 (d, 1H, *J* 3.6 Hz), 7.71 (d, 1H, *J* 3.2 Hz); (**9**), δ ($CDCl_3$–D_2O): 5.02 (br.s, 1H), 7.81 (d, 1H, *J* 3.2 Hz); (**12**), δ (200 MHz, $CDCl_3$): 0.88 (t, 3H, *J* 6.6 Hz), 1.26 (s, 26H), 1.97—2.15 (m, 11H), 4.04 (dd, 1H, *J* 11.6, 3.7 Hz), 4.31 (dd, 1H, *J* 11.5, 5.6), 4.37—4.51 (m, 1H), 5.22—5.47 (m, 2H), 5.60—5.90 (m, 2H); $\nu_{max.}$ ($CHCl_3$) 1740, 1680 cm^{-1}.



a; R = H
b; R = $PhCH_2$
c; R = Ac

Boc = t-Butoxycarbonyl

Scheme 1. *Reagents and conditions*: i, $Me_2C(OMe)_2$ (3 equiv.), (*p*-$MeC_6H_4SO_3H$, trace); dimethylformamide (DMF), 100 °C; ii, CH_2N_2, Et_2O, then di-isobutylaluminium hydride (DIBAL-H), toluene, −70 °C; iii, (**1**) → (**4a**) + (**5a**): (**2**) (TST) (1.2 equiv.), CH_2Cl_2, room temp., 12 h, then Bu^4NF–THF; (**4a**) → (**4b**): NaH (1.1 equiv.) then $PhCH_2$ (1.1 equiv.), Bu_4NI (0.1 equiv.), THF, room temp.; (**4a**) → (**4c**): AcCl–Et_3N (1.5 equiv.), CH_2Cl_2, room temp.; iv, $KMnO_4$ (1.5 equiv.), TDA-1 (0.5 equiv.), CH_2Cl_2, 12 h, room temp.; v, $NaBH_4$ (1 equiv.), MeOH, room temp.; vi, MeI (10 equiv.), MeCN, reflux, 8 h; $NaBH_4$ (2 equiv.), MeOH, −10 °C; $HgCl_2$ (1.2 equiv.), MeCN–H_2O (4 : 1), room temp.



Scheme 2. *Reagents and conditions:* i, (**2**) (TST) (1.5 equiv.), CH_2Cl_2 or THF, room temp., 12 h, then Bu_4NF–THF; ii, phosphorane (**10**) (1.2 equiv.), Et_2O–toluene (1 : 15), −30 °C; iii, CF_3CO_2H–H_2O (98 : 2), room temp.; iv, Ac_2O (4 equiv.), pyridine, room temp.

individual diastereoisomers by flash chromatography failed. Hence, the pure major isomer (**4a**), m.p. 168—171 °C, $[\alpha]_D^{23}$ −48.3° (*c* 0.87, $CHCl_3$), was obtained directly from the mixture by crystallization (CH_2Cl_2–n-hexane), whereas the minor isomer (**5a**), m.p. 86—88 °C, $[\alpha]_D^{23}$ −0.8° (*c* 0.825, $CHCl_3$), was obtained by processing the mixture as follows: oxidation with $KMnO_4$ in the presence of tris(3,6-dioxaheptyl)amine (TDA-1) to give the aminoketone (**6**), followed by *syn*-diastereoselective (d.s. 94%) carbonyl reduction ($NaBH_4$). Compound (**5a**) obtained therefrom was demonstrated to be optically pure by ^1H n.m.r. spectroscopy using the chiral shift reagent Eu(hfc)$_3$ {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)}. The stereochemistry of the major product *anti*-(**4a**), and minor product *syn*-(**5a**), was assigned on the basis of the methyne protons coupling constants at the newly formed stereogenic centres, since their relative values [(**4a**) J_{HH} 2.8 Hz; (**5a**) J_{HH} 8.7 Hz] were in the same order as those of the *anti*- and *syn*-adducts obtained from the reaction of (**2**) with D-glyceraldehyde acetonide.[6] Similar to that suggested for the latter reaction, the high diastereoselectivity in favour of the *anti*-product (**4a**) is consistent with a Cram–Felkin (non-chelate) open-chain mode[8] of addition of (**2**) to (**1**). Unmasking the formyl group from the thiazolyl moiety of (**4a**), as well as those of the *O*-benzyl and *O*-acetyl derivatives (**4b**) and (**4c**) by our standard procedure[6] (*N*-methylation, reduction, and hydrolysis), gave, respectively, the corresponding (2*S*,3*S*)-2,4-dihydroxy-3-amino-butanal (3-amino-3-deoxy-L-erythrose) derivatives (**7a**), (**7b**), and (**7c**) in excellent overall yields (65, 73 and 60%, respectively).

The readily available chiral aldehyde (**7**) was seen as an optically active building block for synthetic targets of substantial interest such as amino sugars[9] and sphingosines[10] (Scheme 2). Thus, a further one-carbon chain extension was carried out by addition of (**2**) to the *O*-benzyl derivative (**7b**) [tetrahydrofuran (THF), 0 °C). After chromatography this reaction provided an 85 : 15 ratio† of diastereoisomeric amino alcohols (**8**) and (**9**) in 75% combined yield. The configuration arising from *anti*-diastereoselective addition was assigned to the major isomer (**8**) since this corresponds to the exclusive or dominant stereochemical outcome usually observed in reactions of (**2**) with chiral α-hydroxyaldehydes.[6,10] In view of the well established thiazolyl–formyl group equivalence,[6] compounds (**8**) and (**9**) represent masked amino pentoses, *i.e.* 4-amino-4-deoxy-L-ribose and 4-amino-4-deoxy-L-arabinose, respectively. Hence, a new entry to amino sugars from an amino acid[11] with retention of the configuration at the

amino-bearing centre, centred on thiazole as an auxiliary (Thiazole Route), is at hand.

The aldehyde (**7a**) was also subjected to Wittig reaction with hexadecanylidenetriphenylphosphorane (**10**), in the presence of an excess of lithium bromide to ensure a high *trans*-selectivity.[12c,13] This reaction produced exclusively (shown by n.m.r.) *O*,*N*-protected D-*erythro*-C_{20}-sphingosine (**11**) which was isolated in 31% yield after chromatography. For confirmation of structural assignment, (**11**) was converted by conventional procedures into the known triacetyl-sphingosine (**12**) (95% yield), m.p. 103—105 °C (CH_2Cl_2–light petroleum), $[\alpha]_D^{23}$ −22.5° (*c* 1.07, AcOH) {lit. data[13c]: m.p. 104 °C, $[\alpha]_D^{21}$ −22.3 (*c* 2, AcOH)}. In addition to providing a new direct route to a sphingosine from an amino acid (L-serine), the structural identification of (**11**) confirms the configuration of (**4**) as described. This confirms the *anti*-selective addition of (**2**) to (**1**) and the retention of the chiral integrity of L-serine (**3**) throughout the various synthetic manipulations.

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References

1 J.-A. Fehrentz and B. Castro, *Synthesis*, 1983, 676; C. F. Stenfield, J. E. Parker, and P. Kanellis, *J. Org. Chem.*, 1981, **46**, 4797.
2 D. Seebach and H.-O. Kalinowski, *Nachr. Chem. Tech.*, 1976, **24**, 415.
3 W. D. Lubell and H. Rapoport, *J. Am. Chem. Soc.*, 1987, **109**, 236, and references therein.
4 H. Newman, *J. Am. Chem. Soc.*, 1973, **95**, 4098; P. Tkaczuk and E. R. Thornton, *J. Org. Chem.*, 1981, **46**, 4393; K. Mori and Y. Funaki, *Tetrahedron*, 1985, **41**, 2379; Y. Saitoh, Y. Moriyama, T. Takahashi, and Q. Khuong-huu, *Tetrahedron Lett.*, 1980, **21**, 75; G. J. Hanson and T. Lindberg, *J. Org. Chem.*, 1985, **50**, 5399.
5 P. Garner and S. Ramakanth, *J. Org. Chem.*, 1986, **51**, 2609.
6 A. Dondoni, M. Fogagnolo, A. Medici, and P. Pedrini, *Tetrahedron Lett.*, 1985, **26**, 5477; A. Dondoni, G. Fantin, M. Fogagnolo, and A. Medici, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 835; A. Dondoni, G. Fantin, M. Fogagnolo, and A. Medici, *Tetrahedron*, 1987, **43**, 3533.
7 P. Garner, *Tetrahedron Lett.*, 1984, **25**, 5855; P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361.
8 E. E. Eliel, 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2, ch. 5.
9 G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, *J. Carbohydrate Chem.*, 1984, **3**, 125; V. Jäger, I. Müller, R. Schohe, M. Frey, R. Ehrler, B. Häfele, and D. Schröter, *Lect. Heterocycl. Chem.*, 1985, **8**, 79; F. M. Hauser and S. R. Ellenberger, *Chem. Rev.*, 1986, **86**, 35; S. J. Danishefsky and C. Maring, *J. Am. Chem. Soc.*, 1985, **107**, 7762, and previous papers; S. Hanessian and J. Kloss, *Tetrahedron Lett.*, 1985, **26**, 1261.
10 S. Hakamori, 'Handbook of Lipid Research,' vol. 3, 'Sphingolipid Biochemistry,' eds. J. M. Kaufer and S. Hakamori, Plenum Press, New York, 1983, p. 1—150.
11 P. J. Maurer, C. G. Knudsen, A. D. Palkowitz, and H. Rapoport, *J. Org. Chem.*, 1985, **50**, 325.
12 Synthesis of sphingosines: see ref. 4 and (a) G. Cardillo, M. Orena, S. Sandri, and C. Tomasini, *Tetrahedron*, 1986, **42**, 917; (b) M. Obayashi and M. Schlosser, *Chem. Lett.*, 1985, 1715; (c) R. R. Schmidt and P. Zimmermann, *Tetrahedron Lett.*, 1986, **27**, 481, and references therein.
13 M. Schlosser, H. B. Tuong, and B. Schaub, *Tetrahedron Lett.*, 1985, **26**, 311.