Homologation of L-Threonine to α-Epimer β-Amino-α,γ-dihydroxy Aldehydes and Acids *via* Stereoselective Reduction of 2-Thiazolyl Amino Ketones

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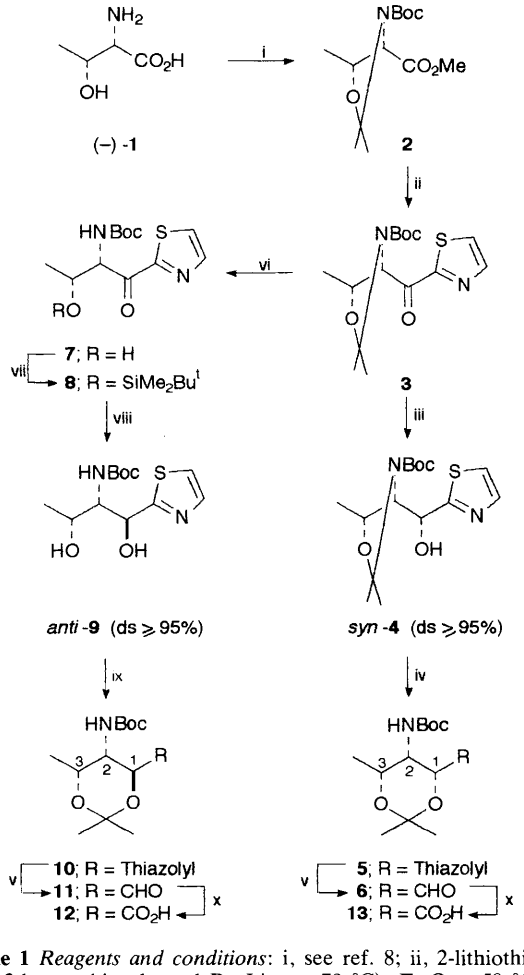
The differentially protected 2-thiazolyl amino ketones **3** and **7** obtained in high yield from the L-threonine derived methyl ester **2** and 2-lithiothiazole serve as key intermediates to aldehydes **6** and **11** by *syn*- and *anti*-stereoselective reduction (diastereoselectivity ≥ 95%) of the carbonyl and liberation of the formyl group from the thiazole ring; the latter compounds are smoothly oxidized to acids **12** and **13**.

Recent investigation from this laboratory has provided a stereoselective route to *syn* and *anti* α-hydroxy-β-amino aldehydes by one-carbon chain-elongation of differentially protected α-amino aldehydes employing 2-trimethylsilylthiazole as a masked formyl anion equivalent.[1] The synthetic utility of these functionalized aldehydes for the preparation of amino sugars and sphingosines has been demonstrated.[1] Further application of these compounds may be foreseen as advanced intermediates to α-hydroxy-β-amino acids,[2] a class of synthetic targets of considerable interest because of their presence in various peptidic enzyme inhibitors such as bestatin and pepstatin.[3] In this communication we describe the conversion of the L-threonine derived methyl ester **2** as a model system to epimer aldehydes **6** and **11** *via* the 2-thiazolyl amino ketone **3**. This key intermediate can be readily prepared on a multigram scale by high yield substitution on the ester **2** with 2-lithiothiazole without substantial side reactions.[4] The sequence shows a convenient route to chiral units of synthetic utility from an α-amino acid[5] employing a new thiazole-based strategy[6] which circumvents the use of the corresponding α-amino aldehyde as intermediate.[7]

Treatment of the *N-tert*-butoxycarbonyl-2,3-isopropylidene-L-threonine methyl ester[8] **2** in diethyl ether at low temperature with 2-lithiothiazole produced the 2-thiazolyl amino ketone **3**† in *ca.* 80% yield (Scheme 1).‡ The ketone **3** was identical by optical rotation and NMR spectroscopy to the compound obtained by addition of 2-trimethylsilylthiazole to *N*-Boc-L-threoninal acetonide[1b] and oxidation of the resulting alcohol under neutral conditions.[9] This indicates that the chiral integrity of ester **2** and ketone **3** is preserved under the conditions above. The carbonyl reduction of **3** in methanol with $NaBH_4$ occurred with a high level of diastereoselectivity (ds ≥ 95% by NMR) to afford the expected[9] non-chelation controlled product, *i.e.* the alcohol *syn*-**4** which was isolated in 95% yield. The sense and level of diastereofacial selectivity did not change by using various hydride releasing agents,[9,10] such as $LiAlH_4$–LiI, $LiBH(Bu^s)_3$ (L-Selectride), $NaAlH_2(OEtOMe)_2$ (Red-Al). The all *syn* arrangement of substituents in **4** was confirmed following its conversion into the 1,3-dioxane **5** (98%) by acid-catalysed migration of the acetonide protection. The ^1H NMR spectrum of **5** showed relatively small coupling constants (*J*) between H-1–H-2 (1.9 Hz) and H-2–H-3 (1.3 Hz) and the ^{13}C NMR spectrum exhibited two distant signals for the acetonide methyl groups[11] (δ 18.24 and 28.74) in agreement with a *cis* equatorial–axial disposition of the 1,3-dioxane ring protons and a chair-conformation. Compound **5** subjected to the standard one-pot thiazolyl-to-formyl deblocking protocol[1] gave the aldehyde **6**† (72%).

In order to reverse the sense of the diastereofacial selectivity of the carbonyl reduction we decided to change the



Scheme 1 *Reagents and conditions*: i, see ref. 8; ii, 2-lithiothiazole (from 2-bromothiazole and Bu^nLi at −78 °C), Et_2O, −50 °C; iii, $NaBH_4$, MeOH, −60 °C, 1 h; iv, 0.5 mol dm^{-3} CF_3CO_2H, CH_2Cl_2, room temp., 5 min; v, see ref. 1; vi, 0.5 mol dm^{-3} CF_3CO_2H, CH_2Cl_2, room temp., 15 min; vii, Bu^tMe_2SiCl, imidazole, dimethylformamide, 60 °C, 45 min; viii, L-Selectride [$LiBH(Bu^s)_3$], THF, −78 °C, 1 h then Bu_4^nNF, room temp., 1 h; ix, $Me_2C(OMe)_2$, (1*S*)-10-camphorsulphonic acid (CSA), acetone, room temp., 2 h; x, $KMnO_4$, Bu^tOH, KH_2PO_4 (buffer, pH = 7), room temp., 3 min

† *Selected spectroscopic data* for **3**: oil, $[\alpha]_D^{20} = -42.7°$ (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1700; ^1H NMR (80 MHz, $CDCl_3$, 340 K) δ 1.31 (s, 9H), 1.45 (d, 3H, *J* 6.4 Hz), 1.67 (bs, 6H), 4.20 (m, 1H), 5.35 (d, 1H, *J* 6.3 Hz), 7.68 (d, 1H, *J* 3.2 Hz), 8.01 (d, 1H, *J* 3.2 Hz). For **6**: oil, $[\alpha]_D^{20} = -4.0°$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 3H, *J* 6.1 Hz), 1.42 (s, 9H), 1.50 (s, 3H), 1.53 (s, 3H), 4.05 (ddd, 1H, *J* 10.3, 2.2 and 1.7 Hz), 4.19 (dq, 1H, *J* 6.1 and 1.7 Hz), 4.51 (d, 1H, *J* 2.2 Hz), 5.09 (d, 1H, *J* 10.3 Hz), 9.51 (bs, 1H). For **11**: oil, $[\alpha]_D^{20} = -24.3°$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.34 (d, 3H, *J* 6.2 Hz), 1.47 (s, 9H), 1.49 (s, 3H), 3.58 (m, 1H), 4.0 (m, 1H), 4.26 (m, 1H), 5.50 (d, 1H, *J* 10.3 Hz), 9.65 (bs, 1H). For **12**: oil, $[\alpha]_D^{20} = +6.8°$ (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1720; ^1H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.14 (d, 3H, *J* 6.3 Hz), 1.41 (s, 9H), 1.49 (s, 3H), 1.51 (s, 3H), 3.97 (ddd, 1H, *J* 10.2, 2.2 and 1.6 Hz), 4.16 (dq, 1H, *J* 6.3 and 1.6 Hz), 4.61 (d, 1H, *J* 2.2 Hz), 5.17 (d, 1H, *J* 10.2 Hz). For **13**: oil, $[\alpha]_D^{20} = -20.3°$ (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1720; ^1H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.32 (d, 3H, *J* 6.1 Hz), 1.42 (s, 3H), 1.45 (s, 9H), 1.54 (s, 3H), 3.70 (m, 1H), 4.20 (m, 1H), 4.45 (m, 1H), 5.30 (d, 1H, *J* 10.2 Hz).

‡ All compounds exhibited satisfactory spectra (^1H and ^{13}C NMR, IR) and analytical data. Quoted yields refer to pure compounds isolated by chromatography.

O,N-protecting group arrangement of **5**. Thus, removal of the acetonide protecting group gave the β-hydroxy ketone **7** (95%) which treated with the Evans borohydride[12] $Me_4NBH(OAc)_3$ produced the 1,3-diol *anti*-**9** with a good level of diastereoselectivity (ds = 85%). The protection of the hydroxy group of **7** with the *tert*-butyldimethylsilyl group by treatment with *tert*-butyldimethylchlorosilane afforded the *O*-silyl derivative **8** (90%) which upon carbonyl reduction with $LiBH(Bu^s)_3$ (L-Selectride) in tetrahydrofuran (THF) and *in situ* desilylation with Bu^n_4NF produced *anti*-**9** as a single observable diastereoisomer by NMR spectroscopy (ds ≥ 95%) in 81% islolated yield. The reduction of **8** with diisobutylaluminium hydride (DIBAL-H) gave an identical high degree of *anti* diastereoselectivity. The relative configuration at C-1 and C-2 was confirmed by the ^1H and ^{13}C NMR spectra of the 1,3-dioxane derivative **10** (75%).§ In this case, the observed coupling constant between H-1 and H-2 (5.1 Hz) and the rather close signals for the two acetonide methyls (δ 23.80 and 26.82) indicated a *trans* diaxial relationship and a twisted boat conformation.[11] As for the addition of 2-trimethylsilylthiazole to *N*-monoprotected aldehydes,[1b] the sense of diastereofacial selectivity in the reduction of **8** to **9** is consistent with a chelation-controlled model arising from an intramolecular proton-bridge. Finally, the aldehyde **11**† (68%) was revealed from **10** by the usual unmasking protocol.[1]

The *O,N*-protected β-amino-α,γ-dihydroxy aldehydes **6** and **11** were smoothly converted by oxidation with potassium permanganate into the corresponding carboxylic acids **12**† and **13**.†

Application of this technology to the homologation of other α-amino acids into *syn* and *anti* α-hydroxy-β-amino aldehydes and acids now becomes of interest.

§ In the reaction of **9** with acetone (Scheme 1, ix) a minor compound arose (*ca.* 20%) from acetonide formation between the amidic and the primary hydroxy groups.

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