2-Thiazolyl α-Amino Ketones: A New Class of Reactive Intermediates for the Stereocontrolled Synthesis of Unusual Amino Acids[1]

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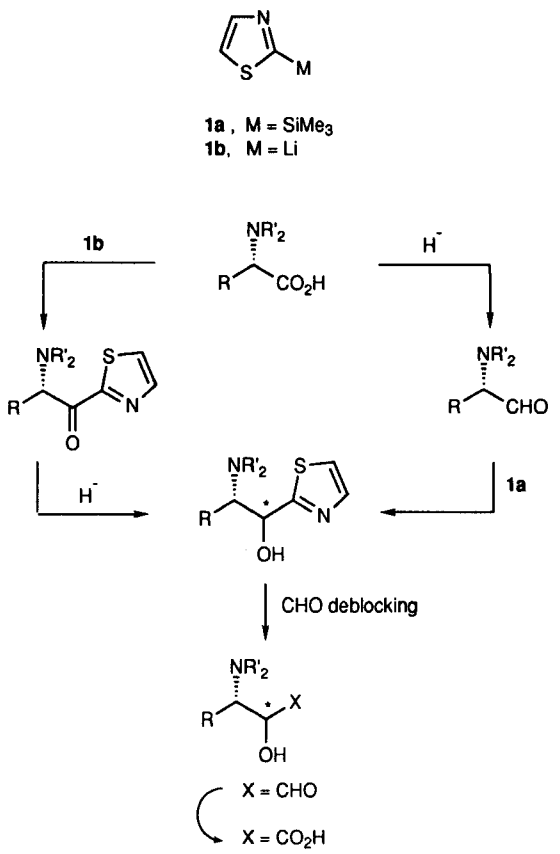
The thiazole-based one carbon homologation of four α-amino acids (L-phenylalanine, L-leucine, L-threonine, and L-serine) to the corresponding α-hydroxy β-amino aldehydes and acids in both configurations at C_α, is described. The methodology involves the following key operations: (i) the conversion of an α-amino ester to a 2-thiazolyl α-amino ketone; (ii) the stereocontrolled reduction of a ketone carbonyl to either syn or anti α,β-amino alcohols; (iii) the aldehyde release from the thiazole ring; (iv) the oxidation of the aldehyde to a carboxylic acid. The methodology was only partially applied to L-phenylglycine because of some limitations in operation (i).

Among the so-called unusual or non-protein amino acids,[2,3] those incorporating the 1,2-amino hydroxy unit are receiving much attention due to their presence in biologically important compounds such as the potent anticancers taxol and taxotere,[4,5] numerous protease inhibitors such as pepstatine,[6] bestatine,[7] and amastatine,[8] and various hydroxyethylene dipeptide isosteres[9] active against renin as well as the human immunodeficiency virus type-1 (HIV-1),[10] the virus responsible for AIDS. As most of these amino acids are available in small quantities from natural sources, they are synthetic targets of great interest. Moreover, structural modifications of these natural products are required to test for increased biological activity and for structure–activity studies.

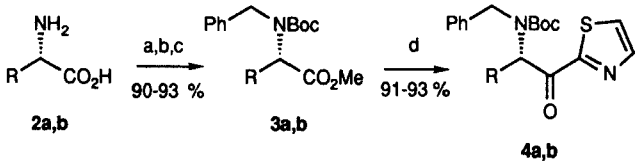
Various synthetic strategies have been developed toward amino hydroxy units.[2,11] One of these involves the diastereoselective nucleophilic addition of organometallic reagents to α-amino aldehydes,[12] a class of reactive intermediates readily available from α-amino acids.[13] Also the reduction of α-amino ketones has been recently described by us[14] and others.[15] An even more important synthetic operation appears to be the construction of building blocks wherein an amino hydroxy unit is adjacent to a formyl or carboxy group.[16] To this aim, we have exploited the thiazole–aldehyde synthesis[1] as a route to α-hydroxy β-amino aldehydes.[17] Key operations in this methodology are the stereoselective addition of 2-(trimethylsilyl)thiazole (2-TST, **1a**) to chiral α-amino aldehydes and the unmasking of the formyl group from the thiazole ring (Scheme 1). In this strategy, the access to carboxylic acids is secured by the numerous oxidative methods for the formyl to carboxy group transformation. Some limitations arising from the chemical and configurational instability of amino aldehydes led us to explore alternative approaches. We report here the results[14] of a new route wherein 2-thiazolyl amino ketones are employed as reactive intermediates to epimeric amino alcohols via stereoselective reduction of the ketone carbonyl.



Scheme 1

Thiazolylation of Amino Acids:

Following earlier work from this laboratory[18] on the facile substitution of α-alkoxy esters with 2-lithiothiazole (2-LTT, **1b**) (Gilman-type ketone synthesis)[19] we decided to employ this procedure for the preparation of 2-thiazolyl amino ketones from α-amino esters. A preliminary, yet important operation was the protection of the amino group with two different protective groups which could be selectively removed. Thus, L-phenylalanine **(2a)** and L-leucine **(2b)** were first converted into the corresponding methyl esters and then protected as the *N*-benzyl *N*-*tert*-butoxycarbonyl (*N*-Bn-*N*-Boc) derivatives **3a,b** by condensation with benzaldehyde, reduction of the resultant imine, and reaction with *tert*-butoxy anhydride. The thiazolylation of these esters occurred readily by treatment with 2-LTT **(1b)** at low temperature to give the ketones **4a,b** in very good overall yield. The ketone **4a** proved to be 95% enantiomerically pure based on the Mosher esters of the alcohols derived from it (vide infra). Neither compounds **4a,b** showed any appreciable decomposition or change of their physical properties (optical rotation and NMR spectra) upon storage in a refrigerator for several days.

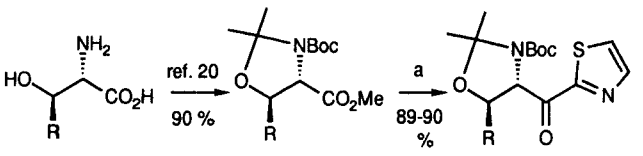


2a,b 3a,b 4a,b

2-4	R
a	$PhCH_2$
b	*i*-Bu

(a) $SOCl_2$/MeOH, r.t., 48 h. (b) 1. PhCHO/Et_3N/$MgSO_4$/CH_2Cl_2, r.t.,18 h; 2. $NaBH_4$/MeOH, 0 °C, 30 min. (c) $(Boc)_2O$/dioxane, r.t., 18 h. (d) 2-LTT (**1b**)/Et_2O, -78 °C, 30 min, then, -65 °C, 4 h.

The differential diprotection of the amino group of L-serine (**5a**) and L-threonine (**5b**) was easily achieved by taking advantage of the adjacent hydroxy group. The methyl esters of these amino acids were converted into the *N-tert*-butoxycarbonyl-*N,O*-isopropylidene derivatives **6a,b** by literature procedures[20] and then reacted with 2-LTT (**1b**) to give the ketones **7a,b** in good overall yields. Compound **7b** appeared to be diastereomerically pure by ^{1}H NMR. Both **7a** and **b** were stable upon storage in a refrigerator for several days.



5a,b 6a,b 7a,b

5-7	R
a	H
b	Me

(a) 2-LTT (**1b**)/Et_2O, -78 °C, 30 min, then -65 °C, 4 h.

It is worth pointing out that getting an efficient nucleophilic substitution of the above amino esters by 2-LTT (**1b**) to give high yields of amino ketones was crucial to the continuation of the planned methodology. In some cases, the Gilman-type ketone synthesis[19] is accompanied by side reactions or does not lead to the ketone at all. For example, such an unfortunate event appears to occur when 2-lithiofuran is used as a nucleophile.[21]

Stereoselective Reduction of Amino Ketones:

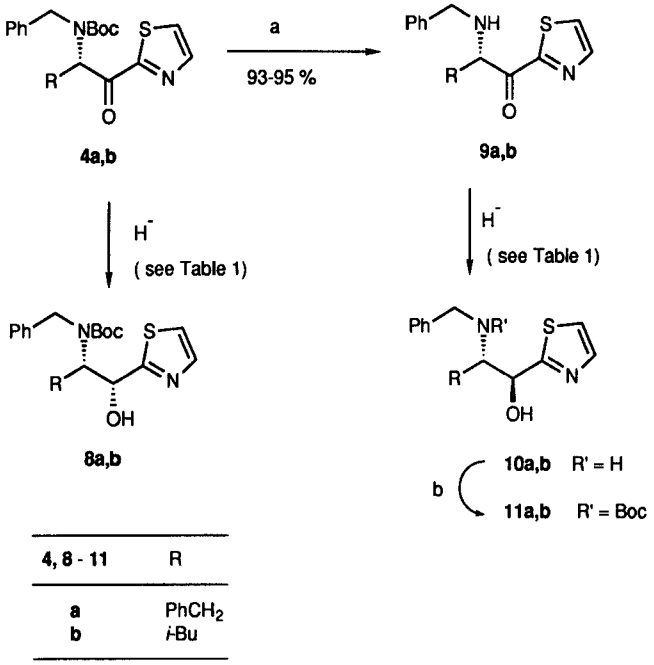
Tunable stereoselectivity by different protection of the amino group is a well established concept associated with addition[22] and cycloaddition[23] reactions to α-amino aldehydes. We observed the reversal of diastereoselectivity in the addition of 2-TST (**1a**) to mono- and diprotected amino aldehydes derived from serine and phenylalanine.[17] The rationalization for the opposite stereochemical course was that *N*-diprotected derivatives afforded anti amino alcohols via a non-chelation controlled addition (Felkin–Ahn model)[24] whereas *N*-monoprotected compounds produced syn isomers via a chelate-controlled addition caused by intramolecular hydrogen bonding (Cram chelate model).[25,26] The results of this *N*-protecting group tuning to the stereocontrolled reduction of 2-thiazolyl amino ketones are reported below. Based on the above models, stereochemical outcomes opposite to those of the addition of 2-TST (**1a**) to aldehydes were expected, i.e. the formation of anti amino alcohols from monoprotected amino ketones and syn isomers from the diprotected derivatives.

The $NaBH_4$ reduction of the *N*-Bn-*N*-Boc phenylalanine derived ketone **4a** (Scheme 2 and Table 1) afforded the expected syn amino alcohol **8a** in excellent yield and diastereoselectivity. This result is readily explained by assuming an external hydride delivery to the less hindered face of the carbonyl of **4a** existing in a non-chelated conformation **A** (Felkin–Ahn–Houk model)[24,27] (Figure 1). The removal of the *N*-Boc protecting group in **4a** gave

Biographical Sketch

Professor Alessandro Dondoni studied chemistry at the University of Bologna where he received the Doctorate Degree in Industrial Chemistry in 1960. He worked in the same place (1961) in the group of Professor A. Mangini, and then at the Illinois Institute of Technology in Chicago (1962–1963) with Professor S. I. Miller. In 1964 he was appointed Assistant Professor at the University of Bologna where he earned the habilitation in Physical Organic Chemistry in 1969. In 1970 he became Associate Professor at the University of Ferrara where he was promoted to the rank of Professor in 1975 and appointed to the chair of Organic Chemistry. Initial work was in reaction mechanisms in sulfur and heterocyclic chemistry. His present research interests are in new synthetic methods, asymmetric and diastereoselective synthesis, and use of heterocycles as synthetic auxiliaries. He has held visitor professorships at the University of Rennes, Hamburg, and Osaka (JSPS award).

the *N*-Bn monoprotected amino ketone **9a** whose reduction with the same metal hydride afforded the anti amino alcohol **10a** as a major product according to the Cram chelate model[25] **B** (Figure 1). In this case however the rather modest diastereoselectivity (ds 80%) was substantially increased (ds 92%) by the use of diisobutylaluminum hydride (DIBAH), thus suggesting a more favorable five-membered ring chelate structure through the participation of the metal. The coordinating ability of the metal hydride reducing agent is well known to affect profoundly the sense of the stereoselectivity of carbonyl reduction.[28]



4, 8 - 11	R
a	$PhCH_2$
b	*i*-Bu

(a) TFA-H_2O (95 : 5), r. t., 30 min. (b) $(Boc)_2O$/dioxane, r.t., 18 h.

Scheme 2

Table 1. Reduction of Ketones **4a,b** and **9a,b**

R	Ketone	Metal Hydride	Alcohol (yield %)[c]	ds (%)
$PhCH_2$	**4a**	$NaBH_4$[a]	**8a** (95)	≥ 95
$PhCH_2$	**9a**	$NaBH_4$[a]	**10a** (95)	80
$PhCH_2$	**9a**	DIBAH[b]	**10a** (90)	92
i-Bu	**4b**	$NaBH_4$[a]	**8b** (92)	≥ 95
i-Bu	**9b**	$NaBH_4$[a]	**10b** (95)	60
i-Bu	**9b**	DIBAH–$ZnCl_2$[b]	**10b** (89)	90

[a] – 80 °C, MeOH.
[b] – 78 °C, THF.
[c] Overall yield

Similar results were obtained in the reduction of the differentially protected leucine derived ketones **4b** and **9b** (Scheme 2 and Table 1). The configurations of syn amino alcohols **8a,b** and anti isomers **10a,b** were assigned by NMR analysis of the corresponding oxazolidinones threo-**12a,b** ($J_{4,5}$ = 4.0–4.2 Hz) and erythro-**13a,b** ($J_{4,5}$ = 7.9–8.1 Hz) showing consistent coupling constant values in distinct ranges as reported.[17] The enantiomeric purity of amino alcohols **8a** and **10a** (phenylalanine series), and consequently of the corresponding ketone precursors **4a** and **9a**, was established to be 95% by NMR analysis of the corresponding Mosher esters. Unfortunately the enantiomeric purity of **8b** and **10b** (leucine series) could not be determined similarly since these alcohols were resistant to esterification with the Mosher acids.

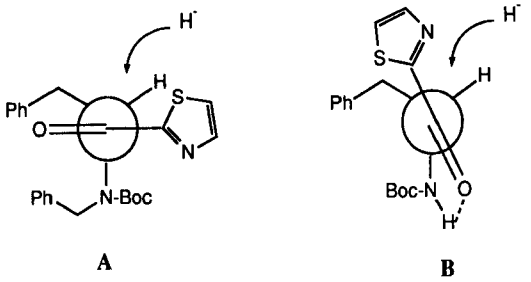
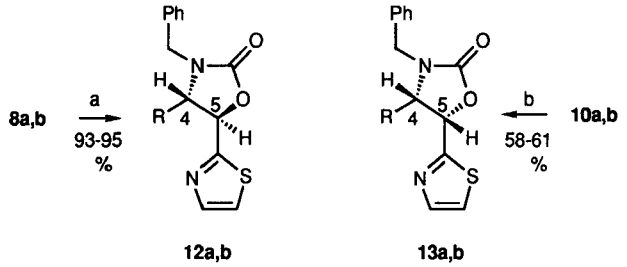


Figure 1



12, 13	R
a	$PhCH_2$
b	$i\text{-}C_4H_9$

(a) NaH/THF, reflux, 30 min. (b) $(Im)_2CO$/THF, r.t., 18 h.

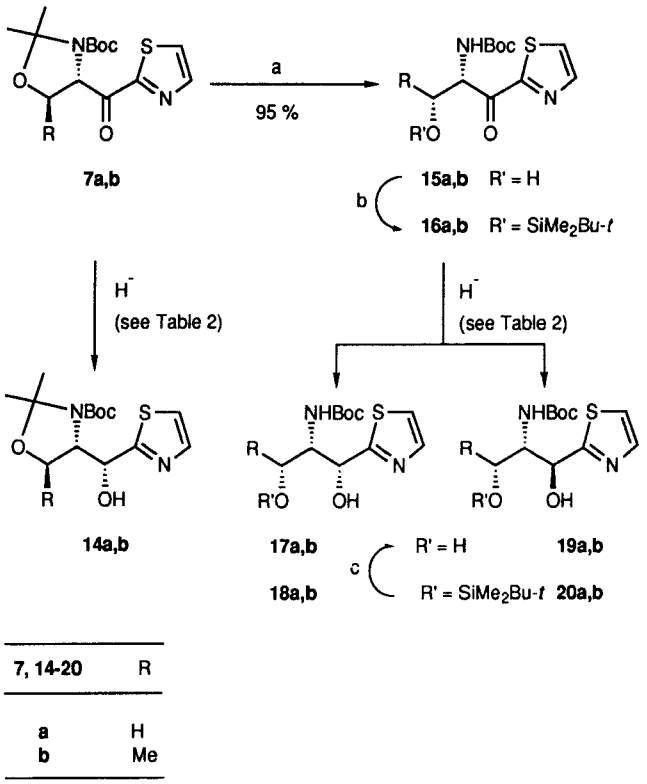
We next examined the reduction of the L-serine and L-threonine derived ketones (Scheme 3). Excellent levels of the expected syn selectivity (ds 95%) were obtained in the $NaBH_4$ reduction of the diprotected amino ketones **7a,b** to give the amino alcohols **14a,b** (Table 2). Then, structural modifications of these amino ketones and changes of the metal hydride reducing agent were studied in order to find a reversed diastereoselectivity of synthetic value. Attempts to remove selectively the *N*-Boc in **7a,b** failed due to the concomitant cleavage of the *N,O*-isopropylidene protecting group under the required harsh acid conditions (40% TFA in CH_2Cl_2).[29] On the other hand, deacetonization of **7a,b** to the corresponding *N*-Boc amino alcohols **15a,b** was readily carried out using dilute TFA (4%) in CH_2Cl_2. The reduction of **15a** with DIBAH, i.e. the metal hydride favoring high levels of anti selectivity in the reduction of phenylalanine and leucine derived ketones (see Table 1), afforded, in this case, the all syn *N*-Boc 2-amino 1,3-diol **17a** as the major isomer (ds

Table 2. Reduction of Ketones **7a,b**, **15a,b** and **16a,b**

R	Ketone	Metal Hydride	Alcohol (yield %)[d]	ds (%)
H	**7a**	$NaBH_4$[a]	**14a** (95)	≥ 95
H	**15a**	DIBAH[b]	**17a** (95)	80
H	**15a**	TETABH[c]	**17a** (90)	70
H	**16a**	$NaBH_4$[a]	**17a** (90)[e]	70
H	**16a**	DIBAH[b]	**17a** (87)[e]	65
H	**16a**	DIBAH–$ZnCl_2$[b]	**19a** (89)[e]	70
H	**16a**	$Zn(BH_4)_2$[b]	**19a** (89)[e]	80
Me	**7b**	$NaBH_4$[a]	**14b** (95)	≥ 95
Me	**15b**	TETABH[c]	**19b** (95)	85
Me	**16b**	DIBAH[b]	**19b** (90)[e]	90
Me	**16b**	L-Selectride[b]	**19b** (92)[e]	≥ 95

[a] −60 °C, MeOH.
[b] −78 °C, THF.
[c] −40 °C, MeCN, AcOH.
[d] Overall yield.
[e] Obtained by desiliylation of the corresponding *O*-silyl ether.

80%). This result is consistent with an external hydride delivery to a six-membered metal chelate structure involving the hydroxy and carbonyl groups.[30] The same sense of diastereoselectivity was maintained using tetramethylammonium triacetoxyborohydride, $Me_4NBH(OAc)_3$, a well known metal hydride reducing agent of β-hydroxy ketones operating via chelate structures involving a boron–oxygen bond.[31] Hence, the reduction of **15a** to syn 1,3-diol **17a** under the influence of the stereodirecting effect of the α-NHBoc group can be rationalized to occur via internal hydride delivery in a chair-like transition state **C** (Evans model)[31] (Figure 2). However, intramolecular activation of the carbonyl by tricoordinate boron followed by external hydride delivery cannot be ruled out. Hence we examined the reduction of the ketone **16a** obtained by protection of the hydroxy group of **15a** as *tert*-butyldimethylsilyl ether. Using either $NaBH_4$ or DIBAH, the syn amino alcohol **18a** was still the major product, although in low excess, whereas with DIBAH–$ZnCl_2$ or $Zn(BH_4)_2$ the stereoselectivity was reversed in favor of the anti isomer **20a** (ds 70–80%). This indicates that hydride delivery is taking place on Zn-mediated[28] chelate structures of the amino ketone **16a** involving the carbonyl and the amino group.



7, 14-20	R
a	H
b	Me

(a) TFA-CH_2Cl_2 (0.5 M), r.t., 15 min. (b) $CF_3SO_3SiMe_2Bu$-*t*/Et_3N/DMAP/DMF, r.t., 1 h. (c) Bu_4NF xH_2O/THF, r.t., 1 h.

Scheme 3

High levels of anti selectivity were more easily achieved in the case of the threonine derived ketone. The reduction of the β-hydroxy ketone **15b** with $Me_4NBH(OAc)_3$ afforded the anti amino alcohol **19b**. This result indicates that the hydroxy-directed selectivity according to the Evans-

Table 3. Physical and Spectroscopic Data of Amino Esters **3a,b** and Amino Ketones **4a,b**, **7a,b**[a]

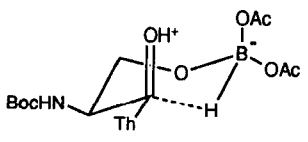
Product	mp/(°C)	$[\alpha]_D^{20}$ (*c*, $CHCL_3$)	^1H NMR (DMSO-d_6, 300 MHz) (°C) δ, *J* (Hz)
3a	syrup	−110.0 (1.5)	(120 °C): 1.36 (s, 9 H), 3.03 (dd, 1 H, *J* = 9.3, 15.2), 3.23 (dd, 1 H, *J* = 6.8, 15.2), 3.56 (s, 3 H), 4.06 (d, 1 H, *J* = 16.1), 4.34 (d, 1 H, *J* = 16.1), 4.45 (dd, 1 H, *J* = 6.8, 9.3), 7.10–7.32 (m, 10 H)
3b	syrup	−58.5 (1.3)	(120 °C): 0.76 (d, 3 H, *J* = 6.3), 0.82 (d, 3 H, *J* = 0.82), 1.40 (s, 9 H), 1.41–1.65 (m, 2 H), 1.70–1.82 (m, 1 H), 3.58 (s, 3 H), 4.36 (d, 1 H, *J* = 2.0), 4.37 (d, 1 H, *J* = 10.6), 4.46 (d, 1 H, *J* = 10.6), 7.18–7.32 (m, 5 H)
4a	syrup	−94.5 (1.2)	(100 °C): 1.29 (s, 9 H), 2.98 (dd, 1 H, *J* = 7.7, 14.3), 3.43 (dd, 1 H, *J* = 7.5, 14.3), 4.44 (d, 1 H, *J* = 16.5), 4.56 (dd, 1 H, *J* = 16.5), 5.56 (dd, 1 H, *J* = 7.5, 7.7), 7.08–7.24 (m, 10 H), 8.04 (d, 1 H, *J* = 3.2), 8.08 (d, 1 H, *J* = 3.2)
4b	syrup	−93.4 (1.4)	(120 °C): 0.74 (d, 3 H, *J* = 6.7), 0.87 (d, 3 H, *J* = 6.7), 1.36 (s, 9 H), 1.42–1.63 (m, 2 H), 1.87–1.98 (m, 1 H), 4.51 (d, 1 H, *J* = 16.1), 4.56 (d, 1 H, *J* = 16.1), 5.43 (dd, 1 H, *J* = 5.9, 7.0), 7.14–7.28 (m, 6 H), 8.08 (bs, 1 H)
7a	118–120	−72.5 (0.9)	(120 °C): 1.32 (s, 9 H), 1.53 (s, 3 H), 1.62 (s, 3 H), 4.02 (dd, 1 H, *J* = 3.2, 9.1), 4.38 (dd, 1 H, *J* = 7.7, 9.1), 5.57 (dd, 1 H, *J* = 3.2, 7.7), 8.15 (d, 1 H, *J* = 3.1), 8.21 (d, 1 H, *J* = 3.1).
7b	60–62	−42.7 (0.6)	(120 °C): 1.27 (s, 9 H), 1.39 (d, 3 H, *J* = 6.1), 1.61 (s, 3 H), 1.62 (s, 3 H), 4.21 (dq, 1 H, *J* = 6.1, 6.8), 5.25 (d, 1 H, *J* = 6.8), 8.14 (d, 1 H, *J* = 3.1), 8.19 d, 1 H, *J* = 3.1)

[a] Satisfactory microanalyses obtained: C, N, N ± 0.3.

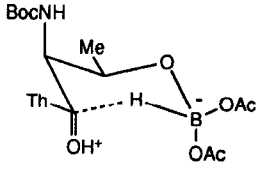
Table 4. Physical and Spectroscopic Data of Thiazolyl Derivatives **8a,b–13a,b**[a]

Product	mp (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^1H NMR ($CDCl_3$, 300 MHz) δ, *J* (Hz)	^{13}C NMR (75.5 MHz) δ
8a	syrup	+18.1 (1.1)	1.44 (s, 9H), 2.73 (dd, 1H, *J* = 6.4, 13.8), 3.43 (dd, 1H, *J* = 9.7, 13.8), 3.52 (d, 1H, *J* = 15.1), 3.91 (ddd, 1H, *J* = 4.0, 6.4, 9.7), 4.26 (d, 1H, *J* = 15.1), 4.95 (dd, 1H, *J* = 4.0, 8.8), 6.95–7.09 (m, 4H), 7.10–7.30 (m, 7H), 7.22 (bs, 1H, ex D_2O), 7.63 (d, 1H, *J* = 3.2)	28.09, 35.24, 55.26, 67.01, 73.25, 81.72, 118.85, 126.82, 127.72, 128.55, 128.80, 129.70, 137.90, 138.49, 143.03, 158.46, 177.32
8b	syrup	+87.5 (1.2)	0.66 (d, 3H, *J* = 6.7), 0.73 (d, 3H, *J* = 6.3), 1.18–1.31 (m, 1H), 1.32–1.61 (m, 10H), 1.98–2.20 (m, 1H), 3.55 (d, 1H, *J* = 14.7), 3.71–3.89 (m, 1H), 4.41 (d, 1H, *J* = 14.7), 5.05 (d, 1H, *J* = 3.7), 7.04–7.13 (m, 2H), 7.14–7.38 (m, 4H), 7.70 (d, 1H, *J* = 3.2)[b]	20.90, 22.07, 23.89, 27.39, 37.06, 43.97, 62.41, 73.38, 80.72, 118.24, 126.97, 127.79, 127.99, 137.58, 142.25, 157.67, 176.52
9a[c]	syrup		2.2 (bs. 1H, ex D_2O), 3.01 (dd, 1H), *J* = 7.4, 13.7), 3.22 (dd, 1H, *J* = 5.7, 13.7), 3.64 (d, 1H, *J*=13.3), 3.79, (d, 1H, *J* = 13.3), 4.76 (dd, 1H, *J* = 5.7, 7.4), 7.11–28 (m, 10H), 7.68 (d, 1H, *J* = 3.2), 7.96 (d, 1H, *J* = 3.2)	39.29, 51.78, 64.45, 126.59, 126.79, 127.26, 128.43, 128.56, 129.79, 139.81, 145.30, 157.86, 166.18, 195.70
9b[c]	syrup		0.91 (d, 6H, *J* = 6.6), 1.40–1.52 (m, 1H), 1.59 (ddd, 1H, *J* = 6.1, 8.9, 12.2), 1.83–1.98 (m, 1H), 2.04 (bs, 1H, ex D_2O), 3.70 (d, 1H, *J* = 13.3), 3.61 (d, 1H, *J* = 13.3), 4.45 (dd, 1H, *J* = 5.1; 8.9), 7.11–7.30 (m, 5H), 7.63 (d, 1H, *J* = 3.2), 7.98 (d, 1H, *J* = 3.2)	21.53, 22.81, 24.80, 42.32, 51.98, 61.89, 126.32, 127.12, 128.47; 128.99, 140.53, 145.19, 166.63, 197.98
10a[c]	syrup		1.25 (bs, 1H, ex D_2O), 2.57–2.62 (m, 2H), 3.3 (bs, 1H, ex D_2O), 3.40 (ddd, 1H, *J* = 4.0, 6.5, 7.5), 3.68 (d, 1H, *J* = 13.3), 3.78 (d, 1H, *J* = 13.3), 5.11 (d, 1H, *J* = 4.0), 7.05–7.15 (m, 4H), 7.16–7.39 (m, 6H), 7.30 (d, 1H, *J* = 3.3), 7.78 (d, 1H, *J* = 3.3)	34.80, 51.47, 62.64, 70.82, 118.89, 126.86, 127.46, 128.29, 128.71, 129.07, 129.51, 138.59, 139.96, 142.96, 173.02
10b	syrup		0.71 (d, 3H, *J* = 6.8), 0.81 (d, 3H, *J* = 6.3), 0.90–1.10 (m, 1H), 1.20–1.32 (m, 1H), 1.46–1.61 (m, 1H), 2.31 (bs, 1H, ex D_2O), 3.14 (ddd, 1H, *J* = 3.8, 5.0, 8.6), 3.82 (d, 1H, *J* = 14.1), 3.87 (d, 1H, *J* = 14.1), 4.25 (bs, 1H, ex D_2O), 5.08 (d, 1H, *J* = 3.8), 7.14–7.38 (m, 6H), 7.72 (d, 1H, *J* = 3.2)	21.77, 22.85, 24.61, 38.30, 51.75, 59.74, 71.37, 118.76, 127.59, 128.53, 128.91, 140.42, 142.85, 137.14
11a	syrup	+20.4 (1.2)	1.46 (s, 9H), 2.58 (dd, 1H, *J* = 3.9, 14.4), 3.41 (dd, 1H, *J* = 11.0, 14.4), 3.49 (d, 1H, *J* = 15.7), 4.18 (dd, 1H, *J* = 3.9, 11.0), 4.28 (d, 1H, *J* = 15.7), 5.27 (bs, 1H), 6.65 (bs, 1H, ex D_2O), 7.03–7.11 (m, 4H), 7.12–7.29 (m, 6H), 7.30 (d, 1H, *J* = 3.2), 7.79 (d, 1H, *J* = 3.2)	28.09, 30.85, 55.54, 69.72, 76.15, 81.45, 119.44, 126.55, 127.47, 127.81, 128.64, 128.73, 129.55, 138.17, 139.29, 143.02, 158.32, 174.18.
11b	syrup	+27.4 (1.5)	0.64 (d, 3H, *J* = 6.0), 0.72 (d, 3H, *J* = 6.0), 1.14–1.36 (m, 2H), 1.46 (s, 9H), 1.82–1.99 (m, 1H), 3.98–4.10 (m, 1H), 4.32 (d, 1H, *J* = 14.7), 4.57 (d, 1H, *J* = 14.7), 5.15–5.24 (m, 1H), 6.11 (bs, 1H, ex D_2O), 7.20–7.30 (m, 2H), 7.30–7.37 (m, 3H), 7.32 (d, 1H, *J* = 3.1), 7.71 (d, 1H, *J* = 3.1).	21.79, 23.11, 24.79, 28.28, 34.60, 54.29, 64.45, 76.37, 81.27, 119.09, 127.44, 128.27, 128.60, 138.62, 142.57, 157.81, 174.02.
12a	125–126	−30.9 (1.6)	3.02 (dd, 1H, *J* = 6.7, 14.2), 3.11 (dd, 1H, *J* = 6.0, 14.2), 4.01 (d, 1H, *J* = 15.2), 4.15 (ddd, 1H, *J* = 4.0, 6.0, 6.7), 4.88 (d, 1H, *J* = 15.2), 5.41 (d, 1H, *J* = 4.0), 7.01–7.09 (m, 2H), 7.11–7.18 (m, 2H), 7.21–7.36 (m, 7H), 7.70 (d, 1H, *J* = 3.2)	38.04, 46.57, 61.18, 76.25, 120.33, 127.59, 128.23, 128.97, 129.19, 129.66, 135.48, 135.62, 143.47, 157.17, 168.36.
12b	78–79	−78.2 (0.8)	0.71 (d, 3H, *J* = 6.2), 0.89 (d, 3H, *J* = 6.7), 1.49–1.82 (m, 3H), 3.79 (ddd, 1H, *J* = 4.2, 5.2, 8.5), 4.10 (d, 1H, *J* = 15.2), 4.79, (d, 1H, *J* = 15.2), 5.39 (d, 1H, *J* = 4.2), 7.11–7.31 (m, 5H), 7.34 (d, 1H, *J* = 3.2), 7.72 (d, 1H, *J* = 3.2)	21.38, 23.29, 23.95, 40.93, 46.13, 59.38, 120.41, 128.20, 129.05, 135.85, 143.52, 157.03, 169.06
13a	syrup	+2.5 (0.7)	2.61 (m, 2H), 3.60 (d, 1H, *J* = 15.2), 4.25 (ddd, 1H, *J* = 6.4, 7.1, 8.1), 4.80 (d, 1H, *J* = 15.2), 5.78 (d, 1H, *J* = 8.1), 6.80–7.10 (m, 4H), 7.14–7.32 (m, 6H), 7.38 (d, 1H, *J* = 3.2), 7.68 (d, 1H, *J* = 3.2)	35.47, 47.02, 58.88, 76.27, 120.08, 128.24, 128.32, 128.99, 129.17, 135.86, 136.81, 143.58, 157.36, 165.43
13b	syrup	+30.1 (1.1)	0.57 (d, 3H, *J* = 6.3), 0.62 (d, 3H, *J* = 6.3), 1.05 (ddd, 1H, *J* = 3.7, 10.0, 13.2), 1.16–1.38 (m, 2H), 3.92 (ddd, 1H, *J* = 3.4, 7.9, 10.3), 4.05 (d, 1H, 15.2), 4.85 (d, 1H, *J* = 15.2), 5.80 (d, 1H, *J* = 7.9), 7.10–7.34 (m, 5H), 7.38 (d, 1H, *J* = 3.2), 7.78 (d, 1H, *J* = 3.2)	21.31, 22.97, 23.91, 36.46, 46.35, 56.56, 120.33, 128.44, 129.06, 129.18, 135.90, 143.21, 157.79, 165.99

[a] Satisfactory microanalyses obtained: C, H, N ± 0.3.
[b] Obtained in $CDCl_3 + D_2O$.
[c] Not analytically pure.



C



D

Figure 2

type[31] chair-like transition state **D** (Figure 2) operates in this case. Were the stereodirecting effects of the α-NHBoc and β-OH bearing stereocenters operating at comparable extents and in opposite directions, a lower diastereoselectivity would have been observed. Furthermore, the reduction of the silyl ether **16b** with either DIBAH or lithium tri-*sec*-butylborohydride{LiB[$CH(CH_3)C_2H_5$]$_3$H (L-Selectride)} produced the anti amino alcohol **20b** with good

Table 5. Physical and Spectroscopic Data of Thiazolyl Derivatives **14a,b–22a,b**[a]

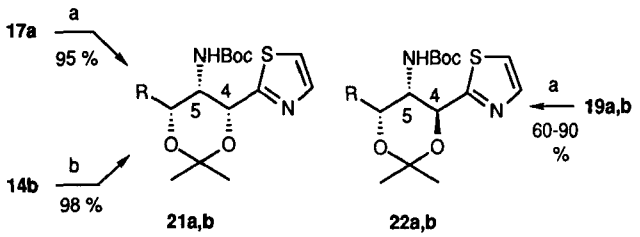
Product	mp (°C)	$[\alpha]_D^{20}$ (c, $CHCl_3$)	^1H NMR ($CDCl_3$, 300 MHz) δ, J(HZ)	^{13}C NMR (75.5 MHz) δ
14a	86–87	+1.56 (0.8)	1.51, (s, 9 H), 1.53 (s, 3 H), 1.61 (s, 3 H), 3.87 (dd, 1 H, J = 6.0, 8.8), 4.23 (ddd, 1 H, J = 1.5, 6.0, 9.1), 4.38 (dd, 1 H, J = 1.4, 8.8), 5.06 (dd, 1 H, J = 4.5, 9.1), 5.89 (d, 1 H, J = 4.5, ex D_2O), 7.32 (d, 1 H, J = 3.2), 7.74 (d, 1 H, J = 3.2)	23.72, 26.84, 28.05, 62.53, 64.48, 75.12, 82.09, 94.75, 119.63, 142.97, 156.20, 174.11.
14b	syrup	−22.9 (0.9)	0.99 (bs, 3 H), 1.48 (d, 3 H, J = 6.2), 1.59 (s, 9 H), 1.66 (s, 3 H), 3.95 (dd, 1 H, J = 5.5, 7.6), 4.45 (dq, 1 H, J = 5.5, 6.2), 5.21 (d, 1 H, J = 7.6), 6.25 (bs, 1 H, ex D_2O), 7.38 (d, 1 H, J = 3.2), 7.75 (d, 1 H, J = 3.2)	20.09, 26.66, 28.11, 28.41, 68.73, 72.47, 75.25, 81.95, 94.71, 119.86, 142.69, 172.88, 173.02.
15a	105–106	+2.9 (0.7)	1.48 (s, 9 H), 2.98 (bs, 1 H, ex D_2O), 4.10 (dd, 1 H, J = 5.8, 11.7), 4.20 (dd, 1 H, J = 5.1, 11.7), 5.42–5.52 (m, 1 H), 5.82 (d, 1 H, J = 7.3), 7.72 (d, 1 H, J = 3.2), 8.04 (d, 1 H, J = 3.2)	28.16, 59.23, 63.59, 80.20, 126.95, 145.14, 155.83, 164.72, 190.72.
15b	96–98	+24.3 (0.7)	1.35 (d, 3 H, J = 6.3), 1.45 (s, 9 H), 2.38 (bs, 1 H, ex D_2O), 4.48–4.61 (m, 1 H), 5.38 (d, 1 H, J = 3.5), 5.64 (d, 1 H), J = 3.2), 7.73 (d, 1 H, J = 3.2), 8.06 (d, 1 H, J = 3.2)	20.22, 28.15, 61.80, 68.03, 79.97, 126.88, 145.05, 156.16, 165.16, 191.02.
16a	syrup	−2.3 (1.4)	−0.83 (s, 3 H), −0.92 (s, 3 H), 0.78 (s, 9 H), 1.47 (s, 9 H), 4.03 (dd, 1 H, J = 2.8, 10.1), 4.41 (dd, 1 H, J = 2.6, 10.1), 5.45 (ddd, 1 H, J = 2.6, 2.8, 8.0), 5.65 (d, 1 H, J = 8.0), 7.69 (d, 1 H, J = 3.2), 8.02 (d, 1 H, J = 3.2)	−6.27, −6.14, 17.80, 25.38, 28.09, 59.07, 64.34, 79.83, 126.53. 145.21, 155.85, 166.45, 190.51.
16b	syrup	+45.9 (0.8)	−0.37 (s, 3 H), −0.14 (s, 3 H), 0.74 (s, 9 H), 1.30 (d, 3 H, J = 6.1), 1.44 (s, 9 H), 4.76 (dq, 1 H, J = 1.8, 6.1), 5.29 (dd, 1 H, J = 1.8, 9.8), 5.44 (d, 1 H, J = 9.8), 7.66 (d, 1 H, J = 3.1), 8.0 (d, 1 H, J = 3.1)	−5.90, −4.98, 17.54, 20.79, 25.34, 28.11, 62.76, 69.03, 79.75, 126.62, 145.22, 156.71, 165.93, 190.92
17a	156–158	−2.1° (0.2)	1.38 (s, 9 H), 3.65 (dd, 1 H, J = 6.3, 11.7), 3.79 (dd, 1 H, J = 4.1, 11.7), 4.00 (dddd, 1 H, J = 3.8, 4.1, 6.3, 8.1), 5.30 (d, 1 H, J = 3.8), 5.52 (d, 1 H, J = 8.1), 7.29 (d, 1 H, J = 3.2), 7.70 (d, 1 H, J = 3.2)[b]	27.95, 56.45, 62.20, 71.69, 80.07, 119.45, 142.53, 163.18, 174.35[b]
17b	syrup	+8.3 (1.2)	1.21 (d, 3 H, J = 6.3), 1.38 (s, 9 H), 3.78–3.87 (m, 1 H), 4.17 (dq, 1 H, J = 4.3, 6.3), 5.27 (d, 1 H, J = 4.3), 5.44 (d, 1 H, J = 9.5), 7.31 (d, 1 H, J = 3.2), 7.61 (d, 1 H, J = 3.2)[b]	19.52, 27.77, 59.43, 67.96, 74.53, 79.84, 119.34, 142.04, 157.30, 172.62[b].
19a	syrup	−72.7 (0.5)	1.32 (s, 9 H), 3.70 (dd, 1 H, J = 4.5, 11.7), 3.95–4.12 (m, 2 H), 5.12 (d, 1 H, J = 3.4), 7.30 (d, 1 H, J = 3.2), 7.68 (d, 1 H, J = 3.2)[b]	27.88, 56.34, 62.13, 75.79, 80.47, 119.66, 142.57, 158.05, 175.55[b]
19b	syrup	−115.3 (0.8)	1.27 (d, 1 H, J = 6.2), 1.41 (s, 9 H), 3.97 (ddd, 1 H, J = 1.8, 2.2, 6.9), 4.36 (dq, 1 H, J = 1.8, 6.2), 5.10 (d, 1 H, J = 2.2), 5.35 (d, 1 H, J = 6.9), 5.60 (bs, 1 H, ex D_2O), 6.12 (d, 1 H, J = 7.1 ex D_2O), 7.31 (d, 1 H, J = 3.2), 7.75 (d, 1 H, J = 3.2).	20.75, 27.90, 60.13, 66.76, 77.65, 80.66, 119.68, 142.68, 159.09, 176.38.
21a	100–101	−2.3 (1.5)	1.29 (s, 9 H), 1.49 (s, 3 H), 1.52 (s, 3 H), 3.82 (dd, 1 H, J = 1.8, 12.0) 4.01 (dddd, 1 H, J = 1.7, 1.8, 2.0, 10.1), 4.22 (dd, 1 H, J = 1.7, 12.0), 5.33 (d, 1 H, J = 10.1), 5.45 (d, 1 H, J = 2.0), 7.23 (d, 1 H, J = 3.2), 7.73 (d, 1 H, J = 3.2)	17.60, 27.25, 28.52, 46.97, 63.97, 71.91, 78.80, 99.69, 118.52, 142.14, 154.75, 168.13.
21b	105–106	−5.2 (0.6)	1.21 (d, 3 H, J = 6.3), 1.32 (s, 9 H), 1.55 (s, 3 H), 1.61 (s, 3 H), 3.92 (ddd, 1 H, J = 1.3, 1.9, 10.6), 4.27 (dq, 1 H, J = 1.3, 6.3), 5.12 (d, 1 H, J = 10.6), 5.42 (d, 1 H, J = 1.9), 7.30 (d, 1 H, J = 3.2), 7.80 (d, 1 H, J = 3.2)	16.52, 18.24, 27.24, 28.73, 50.49, 67.33, 72.87, 78.66, 99.88, 118.46, 142.06, 155.37, 168.29.
22a	syrup	+2.8 (1.0)	1.33 (s, 9 H), 1.50 (s, 3 H), 1.55 (s, 3 H), 3.64–3.82 (m, 2 H), 4.11 (dd, 1 H, J = 3.8, 10.1), 4.85 (d, 1 H, J = 6.2, ex D_2O), 5.01 (d, 1 H, J = 9.5), 7.34 (d, 1 H, J = 3.2), 7.69 (d, 1 H, J = 3.2)	19.23, 27.93, 28.36, 50.51, 63.08, 73.21, 79.89, 99.85, 119.99, 142.41, 155.52, 169.99.
22b	syrup	+45.1 (0.7)	1.15 (d, 3 H, J = 6.3), 1.21 (s, 3 H), 1.37 (s, 9 H), 1.39 (s, 3 H), 4.27 (ddd, 1 H, J = 3.5, 5.1, 10.1), 4.38 (dq, 1 H, J = 3.5, 6.3), 4.87 (d, 1 H, J = 5.1), 5.06 (d, 1 H, J = 10.1, ex D_2O), 7.31 (d, 1 H, J = 3.1), 7.69 (d, 1 H, J = 3.1).	15.94, 23.80, 26.83, 28.08, 53.01, 65.29, 74.20, 79.65, 101.34, 120.32, 142.57, 156.13, 170.42.

[a] Satisfactory microanalyses obtained: C, H, N ± 0.3.
[b] Obtained in $CDCl_3 + D_2O$

levels of asymmetric induction. This suggests that the contribution of a metal-mediated Cram-type cyclic transition state (Figure 1) is significant in these cases as well.

The stereochemistry of the above serine and threonine derived amino alcohols **17a** and **14b** (syn series) and **19a,b** (anti series) was established following their conversion into the isopropylidene derivatives **21a,b** and **22a,b** and analysis of their NMR spectra. In agreement with the Rychnovsky–Evans generalization,[32] the carbon resonances for the two acetonide methyl groups of the threonine derived syn isomer **21b** (chair conformation) were quite distinct from one another at δ = 18 and 29, whereas those of the anti isomer **22b** (twisted boat conformation) were poorly separated in the range δ = 24–27 ppm; moreover, the ^1H NMR spectrum of **21b** showed $J_{4,5}$ values smaller (2.0 Hz) than **22b** (5.0 Hz).

The serine derived compounds **21a** and **22a** could not be characterized by the above criterion based on carbon resonances of acetonide methyl groups since these compounds showed values at $\delta = 18$ and 29 in agreement with a chair-conformation in both cases. However, the ^{1}H NMR spectra displayed significant differences of coupling constants, i.e. $J_{4,5} = 2.0$ Hz for **21a** and $J_{4,5} = 9.5$ Hz for **22a**. Finally, the syn alcohol **8b** compared quite well (^{1}H NMR and optical rotation) with the minor isomer obtained via the amino aldehyde route,[17] i.e. by addition of 2-TST (**1a**) to the Garner *N*-Boc L-serinal acetonide.[19]



21, 22	R
a	H
b	Me

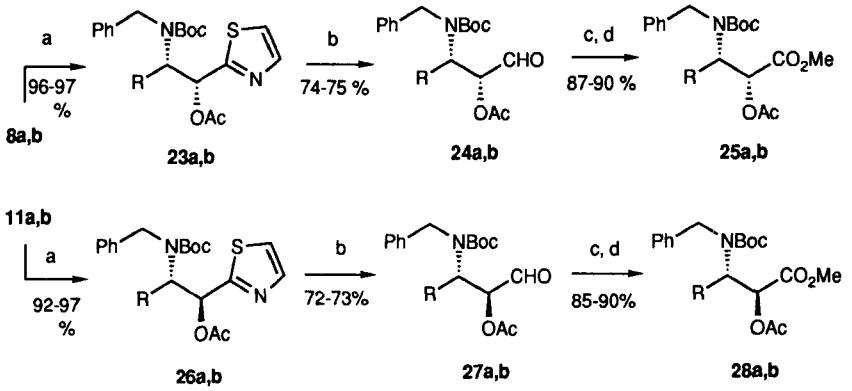
(a) DMP/CSA/acetone, r.t.,1 h. (b) TFA-CH_2Cl_2 (0.5 M), r.t., 5 min.

Unmasking α-Hydroxy β-Amino Aldehydes and Acids:

Having established stereocontrolled routes to chiral α-hydroxy-β-amino-2-alkylthiazoles from α-amino acids, the remaining step was the efficient conversion of these intermediates into aldehydes and acids. The reaction sequence employed with the phenylalanine and leucine derived alcohols **8a,b** (syn series) and **11a,b** (anti series (Scheme 4), involved the protection of the hydroxy group as an acetyl ester, the liberation of the aldehyde using the conventional one-pot protocol,[33] and oxidation with neutral $KMnO_4$ to a carboxylic acid. The latter compounds were isolated (35–52 %) and characterized as the methyl esters **25a,b** and **28a,b**. In a similar way, the serine and threonine derived compounds **14a,b** (syn series) and **20a,b** (anti series) were elaborated into the corresponding esters **31a,b** and **34a,b** (22–51 %) (Scheme 5). It is worth noting that while the conversion of **14a,b** to the *O*-acetyl derivatives **29a,b** was straightforward, the transformation of **20a,b** to the similarly protected anti isomers **32a,b** required a three-step sequence which was carried out in one pot, i.e. acetylation, desilylation, and acetonization.

Homologation of Phenylglycine:

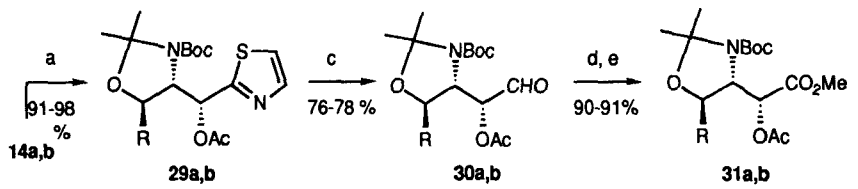
The homologation of L-phenylglycine (**2c**) was examined as a possible route to (2*R*)-*N*-Boc-phenylisoserine (**36a**) and the *N*-Bz isomer **36b**, the side-chains of taxotere and taxol respectively.[4] The syn relationship between the amino and hydroxy groups in these compounds and the stereoselective reductions described above indicated that a 2-thiazolyl amino ketone **35** having temporary diprotection on nitrogen, had to be used. Thus, the amino acid **2c** was transformed into the *N*-Bn-*N*-Boc methyl ester **37** which was treated with 2-LTT (**1b**) under the usual conditions (Et_2O, −78 °C). Quite surprisingly, the expected substitution reaction did not proceed in this case, even by increasing the temperature to −50 °C, the limit of stability of **1b**. A similar behaviour was observed with the *N*,*N*-Boc_2 methyl ester **37b**. These results show that *N*-diprotected phenylglycine methyl esters are inert toward thiazolylation, very likely because of the steric inhibition of the substituents on nitrogen which are pushed toward the carbomethoxy group by the proximal phenyl ring. On the other hand, the monoprotected *N*-Boc methyl ester **37c** (Scheme 6) reacted promptly with



23-28	R
a	$PhCH_2$
b	*i*-Bu

(a) $(Ac)_2O$/DMAP/pyridine, r.t., 6 h. (b) 1. $CF_3SO_3CH_3$ / MeCN, r.t., 10 min; 2. $NaBH_4$ / MeOH, 0 °C, addition time, then, r.t., 10 min; 3. $HgCl_2$/MeCN-H_2O (10 : 1), r.t., 15 min. (c) $KMnO_4$ / *t*-BuOH / phosphate buffer (pH 7), r.t., 20 min. (d) CH_2N_2/Et_2O, 0 °C, 20 min.

Scheme 4

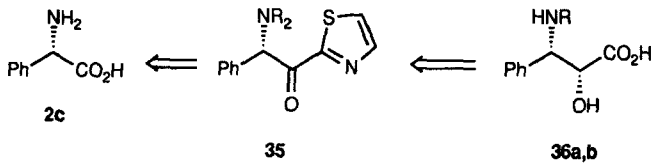


29 - 34	R
a	H
b	Me

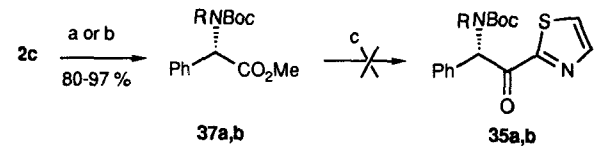
(a) $(Ac)_2O$/DMAP/pyridine, r.t., 6 h. (b) 1. $(Ac)_2O$/DMAP/pyridine, r.t., 4 h; 2. $Bu_4NF\,xH_2O$/THF, r.t., 1 h; 3. DMP/CSA, 80 °C, 18 h. (c) 1. $CF_3SO_3CH_3$/MeCN, r.t., 10 min; 2. $NaBH_4$/MeOH, 0 °C, addition time, then, r.t., 10 min; 3. $HgCl_2$/MeCN-H_2O (10 : 1), r.t., 15 min. (d) $KMnO_4$/*t*-BuOH/phosphate buffer (pH 7), r.t., 20 min. (c) CH_2N_2/Et_2O, 0 °C, 20 min.

Scheme 5

2-LTT (**1b**) to give the ketone **35c** in excellent yield (98 %). The $NaBH_4$ reduction of this compound afforded the expected anti amino alcohol **38** (ds 90 %) which was characterized as the corresponding isoxazolidinone **42** ($J_{4,5}$ = 8.4 Hz). After protection of **38** as the *O*-acetyl

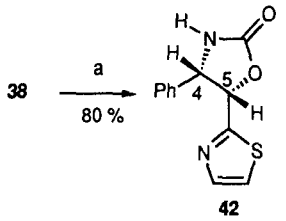


36	R
a	COBu-*t*
b	COPh



35, 37	R
a	Bn
b	COBu-*t*

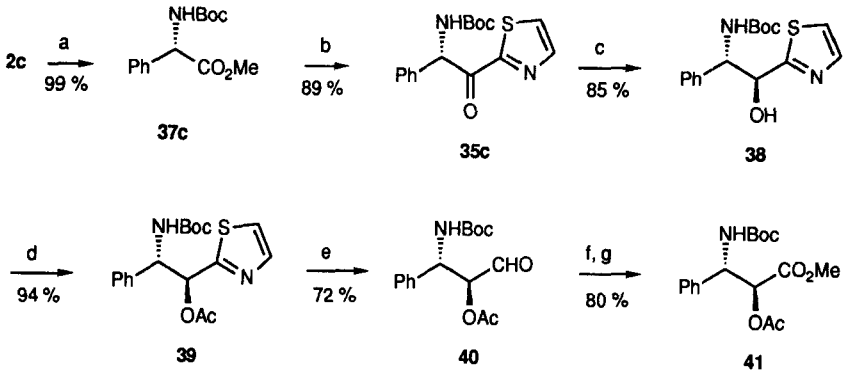
(a) 1. PhCHO/NaOH/MeOH, r.t., 18 h. 2. $NaBH_4$, 0 °C, 30 min; 3. $(Boc)_2O$/NaOH/dioxane, r.t., 18 h; 4. CH_2N_2/Et_2O, 0 °C, 20 min. (b) 1. $(Boc)_2O$/dioxane/NaOH, r.t., 18 h; 2. CH_2N_2/Et_2O, 0 °C, 20 min; 3. $(Boc)_2O$/DMAP/THF, 80 °C, 6 h. (c) 2-LTT (**1b**)/Et_2O, -78 °C, 30 min, then, -50 °C, 4 h.



(a) 1. TFA-CH_2Cl_2 (40 %), r.t., 15 min; 2. $(Im)_2CO/Et_3N$/THF, r.t., 18 h.

derivative **39**, the aldehyde **40** was released and oxidized to carboxylic acid which was isolated as the ester **41**. Hence the route via 2-thiazolyl amino ketone appeared to be unsuitable for the synthesis of taxol and taxotere (2*R*)-phenylisoserine side-chains **36a,b** from phenylglycine. The synthesis of these amino acids via the complementary amino aldehyde route involving phenylglycinal and 2-TST (**1a**) will be reported elsewhere.[34]

A thiazole-based homologation of four α-amino acids to synthetically interesting α-hydroxy β-amino aldehydes and acids has been described. This new synthetic route is centred on the use of 2-thiazolyl α-amino ketones as reactive intermediates. It is noteworthy that the stereocontrolled reduction of the carbonyl of these intermediates affords alcohols with opposite configuration to that arising in the addition of the silyl thiazole **1a** to amino aldehydes under the same chelating or non-chelating conditions. The complementarity of the amino aldehyde and amino ketone routes (see Scheme 1) is also evident when considering some limitations of the latter route which became apparent from the work on phenylglycine. Whether the extent of substitution on nitrogen of α-amino esters is a general limitation of this methodology is a point of interest for further work.



(a) 1. $(Boc)_2O$/NaOH/dioxane, r.t., 18 h; 2. CH_2N_2/Et_2O, 0 °C, 20 min. (b) 2-LTT (**1b**)/Et_2O, -78 °C, 1 h. (c) $NaBH_4$/MeOH, -80 °C, 30 min. (d) $(Ac)_2O$/DMAP/pyridine, r.t., 6 h. (e) 1. $CF_3SO_3CH_3$/MeCN, r.t. 10 min; 2. $NaBH_4$/MeOH, 0 °C, addition time, then, r.t., 10 min; 3. $HgCl_2$/MeCN-H_2O (10 : 1), r.t., 15 min. (f) $KMnO_4$/*t*-BuOH/phosphate buffer (pH 7), r.t., 20 min. (g) CH_2N_2/Et_2O, 0 °C, 20 min.

Scheme 6

Table 6. Physical and Spectroscopic Data of *O*-Acetyl Esters **23, 26, 29, 32, a, b** and Methyl Esters **25, 28, 31, 34, a, b**[a]

Product	mp/(°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^1H NMR (DMSO-d_6, 300 MHz) (°C) δ, *J* (Hz).
23a	syrup	−14.6 (0.9)	(120 °C): 1.39 (s, 9 H), 1.92 (s, 3 H), 2.71 (dd, 1 H, *J* = 4.9, 13.9), 3.06 (dd, 1 H, *J* = 9.9, 13.9), 4.14 (d, 1 H, *J* = 15.6), 4.36 (d, 1 H, *J* = 15.6), 4.60–4.74 (m, 1 H), 6.26 (d, 1 H, *J* = 8.3), 6.97–7.04 (m, 2 H), 7.10–7.25 (m, 8 H), 7.69 (d, 1 H, *J* = 3.2), 7.80 (d, 1 H, *J* = 3.2)
23b	syrup	+17.3 (0.9)	(140 °C): 0.63 (d, 3 H, *J* = 6.4), 0.68 (d, 3 H, *J* = 6.4), 1.04–1.16 (m, 1 H), 1.20–1.34 (m, 1 H), 1.42 (s, 9 H), 1.58–1.71 (m, 1 H), 1.98 (s, 3 H), 4.39 (d, 1 H, *J* = 15.8), 4.48 (d, 1 H, *J* = 15.8), 4.48–4.59 (m, 1 H), 6.11 (d, 1 H, *J* = 8.4), 7.18–7.37 (m, 5 H), 7.66 (d, 1 H, *J* = 3.2), 7.78 (d, 1 H, *J* = 3.2)
26a	99–100	−12.1 (0.6)	(120 °C): 1.35 (s, 9 H), 1.94 (s, 3 H), 3.05 (dd, 1 H, *J* = 5.9, 15.1), 3.13 (dd, 1 H, *J* = 8.4, 15.1), 4.02 (d, 1 H, *J* = 15.9), 4.12 (d, 1 H, *J* = 15.9), 4.50–4.62 (m, 1 H), 6.40 (d, 1 H, *J* = 7.4), 6.87–6.96 (m, 2 H), 7.04–7.10 (m, 2 H), 7.11–7.26 (m, 6 H), 7.63 (d, 1 H, *J* = 3.2), 7.75 (d, 1 H, *J* = 3.2)
26b	103–104	−20.4 (0.5)	(120 °C): 0.68 (d, 3 H, *J* = 6.0), 0.78 (d, 3 H, *J* = 6.0), 1.30–1.45 (m, 2 H), 1.38 (s, 9 H), 1.64–1.80 (m, 1 H), 2.01 (s, 3 H), 4.22 (d, 1 H, *J* = 16.4), 4.31 (d, 1 H, *J* = 16.4), 4.42–4.52 (m, 1 H), 6.19 (d, 1 H, *J* = 6.7), 7.18–7.30 (m, 5 H), 7.63 (d, 1 H, *J* = 3.2), 7.78 (d, 1 H, *J* = 3.2)
29a	74–76	−16.1 (0.9)	(100 °C): 1.21 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 9 H), 2.10 (s, 3 H), 4.01 (dd, 1 H, *J* = 6.0, 9.7), 4.14 (dd, 1 H, *J* = 1.6, 9.7), 4.37 (ddd, 1 H, *J* = 1.6, 6.0, 6.6), 6.30 (d, 1 H, *J* = 6.6), 7.69 (d, 1 H, *J* = 3.1), 7.80 (d, 1 H, *J* = 3.1)
29b	83–84	−48.0 (0.9)	(120 °C): 0.97 (s, 3 H), 1.34 (d, 3 H, *J* = 6.9), 1.51 (s, 12 H), 2.11 (s, H), 3.99 (dd, 1 H, *J* = 4.9, 6.1), 4.49 (dq, 1 H, *J* = 4.9, 6.9), 6.60 (d, 1 H, *J* = 6.1), 7.71 (d, 1 H, *J* = 3.1), 7.83 (d, 1 H, *J* = 3.1)
32a	109–111	−35.2 (1.6)	(100 °C): 1.42 (s, 9 H), 1.48 (s, 3 H), 1.51 (s, 3 H), 2.17 (s, 3 H), 3.98 (dd, 1 H, *J* = 6.9, 9.4), 4.05 (dd, 1 H, *J* = 2.8, 9.4), 4.45 (ddd, 1 H, *J* = 2.8, 3.1, 6.9), 6.46 (d, 1 H, *J* = 3.1), 7.69 (d, 1 H, *J* = 3.2), 7.81 (d, 1 H, *J* = 3.2)
32b	syrup	−42.0 (1.9)	(120 °C): 0.91 (d, 3 H, *J* = 6.9), 1.47 (s, 12 H), 1.59 (s, 3 H), 2.19 (s, 3 H), 4.09 (dd, 1 H, *J* = 3.0, 5.4), 4.35 (dq, 1 H, *J* = 5.4, 6.9), 6.69 (d, 1 H, *J* = 3.0), 7.69 (d, 1 H, *J* = 3.1), 7.84 (d, 1 H, *J* = 3.1)
25a	73–74	−55.3 (0.6)	(120 °C): 1.33 (s, 9 H), 2.0 (s, 3 H), 2.91 (dd, 1 H, *J* = 6.9, 14.3), 3.05 (dd, 1 H, *J* = 8.6, 14.3), 3.62 (s, 3 H), 4.29 (d, 1 H, *J* = 15.8), 4.41 (d, 1 H, *J* = 15.8), 4.70 (ddd, 1 H, *J* = 6.5, 6.9, 8.6), 5.05 (d, 1 H, *J* = 6.5), 7.05–7.31 (m, 10 H).
25b	syrup	−29.8 (0.6)	(120 °C): 0.72 (d, 3 H, *J* = 6.5), 0.82 (d, 3 H, *J* = 6.5), 1.11–1.31 (m, 2 H), 1.38 (s, 9 H), 1.57–1.70 (m, 1 H), 2.00 (s, 3 H), 3.68 (s, 3 H), 4.39 (d, 1 H, *J* = 15.1), 4.45 (d, 1 H, *J* = 15.1), 4.48–4.58 (m, 1 H), 4.97 (d, 1 H, *J* = 6.5), 7.17–7.26 (m, 1 H), 7.27–7.35 (m, 4 H)
28a	75–76	−9.2 (0.6)	(120 °C): 1.37 (s, 9 H), 1.90 (s, 3 H), 2.98 (dd, 1 H, *J* = 7.4, 14.9), 3.10 (dd, 1 H, *J* = 9.3, 14.9), 3.55 (s, 3 H), 4.24 (d, 1 H, *J* = 16.7), 4.28 (d, 1 H, *J* = 16.7), 4.54 (ddd, 1 H, *J* = 5.7, 7.4, 9.3), 5.25 (d, 1 H, *J* = 5.7), 7.02–7.32 (m, 10 H)
28b	71–72	−3.4 (0.6)	(120 °C): 0.73 (d, 3 H, *J* = 6.3), 0.81 (d, 3 H, *J* = 6.3), 1.11–1.35 (m, 2 H), 1.40 (s, 9 H), 1.65–1.82 (m, 1 H), 1.93 (s, 3 H), 3.69 (s, 3 H), 4.35 (d, 1 H, *J* = 16.0), 4.41 (d, 1 H, *J* = 16.0), 4.41–4.52 (m, 1 H), 5.09 (d, 1 H, *J* = 6.2), 7.15–7.40 (m, 5 H)
31a	syrup	−64.2 (0.6)	(120 °C): 1.61 (s, 3 H), 1.64 (s, 9 H), 1.68 (s, 3 H), 2.06 (s, 3 H), 3.62 (s, 3 H), 3.92–4.06 (m, 2 H), 4.17–4.30 (m, 1 H), 5.15 (d, 1 H, *J* = 4.6)
31b	syrup	−70.3 (1.1)	(120 °C): 1.33 (d, 3 H, *J* = 6.2), 1.37 (s, 3 H), 1.46 (s, 9 H), 1.54 (s, 3 H), 2.10 (s, 3 H), 3.70 (s, 3 H), 3.87 (dd, 1 H, *J* = 4.0, 5.8), 4.21 (dq, 1 H, *J* = 5.8, 6.1), 5.42 (d, 1 H, *J* = 4.0)
34a	syrup	−20.2 (1.1)	(120 °C): 1.41 (s, 9 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 2.06 (s, 3 H), 3.67 (s, 3 H), 3.87 (dd, 1 H, *J* = 4.0, 9.2), 3.95 (dd, 1 H, *J* = 6.9, 7.2), 4.25 (ddd, 1 H, *J* = 4.0, 4.6, 6.9), 5.26 (d, 1 H, *J* = 4.6)
34b	syrup	−26.3 (1.5)	(120 °C): 1.19 (d, 3 H, *J* = 6.3), 1.45 (s, 9 H), 1.49 (s, 3 H), 1.52 (s, 3 H), 2.01 (s, 3 H), 3.72 (s, 3 H), 3.88 (dd, 1 H, *J* = 3.6, 5.9), 4.23 (dq, 1 H, *J* = 5.9, 6.3), 5.68 (d, 1 H, *J* = 3.6)

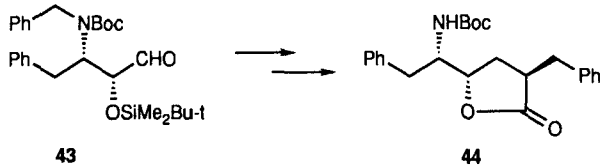
[a] Satisfactory microanalyses obtained for these compounds and also for compounds **24b, 27b, 30a, b, 33b**: C, H, N ± 0.3.

Table 7. Physical and Spectroscopic Data of Phenylglycine Derivatives[a]

Product	mp/(°C)	$[\alpha]_{20}^{D}$ (c, $CHCl_3$)	^1H NMR ($CDCl_3$, 300 MHz), δ, J (Hz).	^{13}C NMR ($CDCl_3$, 75.5 MHz), δ
35c	100–102	+63.9 (1.5)	1.36 (s, 9H), 6.41 (d, 1H, J = 6.0), 7.18 (bs, 1H), 7.26–7.38 (m, 3H), 7.41–7.51 (m, 2H), 8.09–8.17 (m, 2H)[b]	
37a	syrup	+1.5 (1.1)	1.40 (s, 9H), 3.69 (s, 3H), 4.25 (d, 1H, J = 16.4), 4.52 (d, 1H, J = 16.4), 5.59 (s, 1H), 7.0–7.08 (m, 2H), 7.10–7.21 (m, 3H), 7.22–7.35 (m, 5H)[b]	
37b	50–51	+2.3 (1.4)	1.45 (s, 18H), 3.77 (s, 3H), 6.05 (s, 1H), 7.29–7.38 (m, 2H), 7.42–7.49 (m, 3H)	27.62, 52.07, 61.04, 83.03, 127.73, 127.87, 128.69, 135.49, 152.04, 169.35.
37c	112–113	+135.7 (0.8)	1.42 (s, 9H), 3.71 (s, 3H), 5.32 (d, 1H, J = 7.2), 5.55 (d, 1H, J = 7.2), 7.29–7.40 (m, 5H)	28.16, 52.51, 57.39, 80.05, 127.20, 128.47, 128.93, 137.01, 154.91, 171.75.
38	180–181	−3.5 (1.2)	1.41 (s, 9H), 3.96 (d, 1H, J = 6.3, ex D_2O), 5.06–5.21 (m, 1H), 5.30 (dd, 1H, J = 3.5, 6.3), 5.73–5.91 (m, 1H), 7.09–7.18 (m, 2H), 7.20–7.28 (m, 4H), 7.69 (d, 1H, J = 3.2)	28.16, 60.11, 74.05, 80.03, 119.43, 127.52, 127.78, 128.35, 137.72, 142.22, 155.77, 171.02.
39	110–111	−5.8 (0.4)	1.44 (s, 9H), 2.12 (s, 3H), 5.29–5.47 (m, 1H), 6.31 (d, 1H, J = 4.8), 6.32–6.48 (m, 1H), 7.11–7.19 (m, 2H), 7.20–7.30 (m, 4H), 7.81 (d, 1H, J = 3.2)	20.69, 28.20, 57.35, 72.98, 79.73, 119.99, 127.03, 127.77, 128.44, 137.91, 142.98, 162.46, 165.12, 169.83.
41	syrup	+24.8 (0.5)	1.39 (s, 9H), 1.99 (s, 3H), 3.62 (s, 3H), 5.06 (dd, 1H, J = 6.5, 8.4), 5.31 (d, 1H, J = 6.2), 6.97–7.12 (m, 1H), 7.22–7.40 (m, 5H)[b]	
42	150–151	+25.7 (0.4)	5.30 (d, 1H, J = 8.4), 6.27 (d, 1H, J = 8.4), 6.34 (bs, 1H), 7.04–7.13 (m, 3H), 7.14–7.22 (m, 3H), 7.54 (d, 1H, J = 3.2)	60.29, 79.83, 119.94, 126.86, 128.50, 128.68, 135.39, 142.49, 158.61, 164.97.

[a] Satisfactory microanalyses obtained: C, H, N ± 0.3
[b] Obtained in DMSO-d_6 at 120 °C.

The service of the thiazole ring as a convenient masked formyl group is appreciated for its easy installation in different substrates and tolerance of various synthetic elaborations. Hence, the target α-hydroxy β-amino acids are approached through aldehydes whose availability, however, should not be overestimated. For example, the protected α-hydroxy β-amino aldehyde **43** derived from L-phenylalanine proved to be a convenient intermediate[10b,35] toward the Phe–Phe hydroxyethylene isostere **44**, a modified dipeptide employed as a constituent of potent HIV-1 inhibitors.[36]



43 **44**

Experimental Section:[37]

All air- and moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[38] and freshly distilled prior to use. Flash column chromatography[39] was performed on Silica gel 60 (230–400 mesh, Merck). Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations, were measured at 20 ± 2 °C for solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer in $CDCl_3$ solution r.t., unless otherwise specified.

All starting α-amino acids were commercially available. 2-Bromothiazole was conveniently prepared from 2-aminothiazole (Fluka) as described.[1a]

***N*-Benzyl-*N*-*tert*-butoxycarbonylphenylalanine Methyl Ester (3a):**

Thionyl chloride (1.92 g, 16.18 mmol) was added dropwise to a suspension of L-phenylalanine **(2a)** (1.91 g, 11.59 mmol) in MeOH (10 mL) at 0 °C. The bath was removed and the solution was stirred at r.t. for 48 h, and concentrated. The residue material was triturated with Et_2O, filtered, washed with cold (0 °C) Et_2O and concentrated to give 2.5 g of ester hydrochloride. A mixture of this ester (11.59 mmol), Et_3N (1.41 g, 13.91 mmol), $MgSO_4$ (3 g), PhCHO (1.48 g, 13.91 mmol) and CH_2Cl_2 (100 mL) was stirred at r.t. for 18 h, then filtered through Celite and concentrated. The residue was dissolved in MeOH (100 mL) cooled (0 °C) then $NaBH_4$ (0.88 g, 23.18 mmol) was added. The solution was stirred at 0 °C for 30 min, then diluted with acetone (10 mL) and concentrated. The crude product was washed with sat. aq $NaHCO_3$ (50 mL) extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in dioxane (20 mL) and $(Boc)_2O$ (3.03 g, 13.91 mmol) was added and the mixture stirred at r.t. for 18 h, then concentrated. Flash chromatography (silica gel, 90:10 hexane/Et_2O) of the crude product gave 3.85 g (90%) of the ester **3a**.

***N*-Benzyl-*N*-*tert*-butoxycarbonylleucine Methyl Ester (3b):**

Compound **3b** (3.43 g, 93%) was obtained from **2b** (1.45 g, 11.01 mmol) by the procedure described for **3a**.

2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylphenylalanyl)-1,3-thiazole (4a):

To a cold (−78 °C) stirred solution of BuLi (6.60 mL, 10.55 mmol of 1.6 M solution in hexane) in Et_2O (30 mL), was added, dropwise, a solution of 2-bromothiazole (1.60 g, 9.74 mmol) in the same solvent (30 mL). After the yellow solution had been stirred at −78 °C for 30 min, a solution of the ester **3a** (3.0 g, 8.12 mmol) in Et_2O (30 mL) was added slowly. The mixture was allowed to warm to −65 °C, stirred at this temperature for 4 h, and sat. aq $NaHCO_3$ (30 mL) was then added. The mixture was allowed to warm to r.t. over 20 min and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 80:20 hexane/Et_2O) of the residue material gave 3.12 g (91%) of the ketone **4a**.

2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylleucyl)-1,3-thiazole (4b):
The ester **3b** (3 g, 8.94 mmol) was processed as described above for **3a** to give, after flash chromatography (silica gel, 80:20 hexane/Et_2O), 3.23 g (93%) of the ketone **4b**.

(*S*)-2-[(*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)carbonyl]-1,3-thiazole (7a) and 2-{[(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-2,2,5-trimethyl-1,3-oxazolidin-4-yl]carbonyl}-1,3-thiazole (7b):
These ketones were prepared as described above for **4a** starting from the ester **6a** (3.0 g, 11.57 mmol) or **6b** (3.0 g, 10.97 mmol). Flash chromatography of the crude products (silica gel, 80:20 hexane/Et_2O), afforded pure ketone **7a** (3.25 g, 90%) or **7b** (3.18 g, 89%).

(1′*R*,2′*S*)-2-[2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-1-hydroxy-3-phenylpropyl]-1,3-thiazole (8a):
To a cold (−80°C) stirred solution of **4a** (1.0 g, 2.37 mmol) in MeOH (15 mL), $NaBH_4$ (0.18 g, 4.74 mmol) was added. The mixture was stirred for 30 min, diluted with acetone (5 mL), then concentrated. The residue was washed with sat. aq $NaHCO_3$ (15 mL), extracted with Et_2O (2 × 15 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the crude **8a** (silica gel, 95.5:4.5 CH_2Cl_2/EtOAc), gave 0.95 g (95%) of the pure alcohol **8a**.

(1′*R*,2′*S*)-2-[2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-1-hydroxy-4-methylpentyl]-1,3-thiazole (8b):
The ketone **4b** (1.0 g, 2.57 mmol) was processed as described above for the ketone **4a** to give after flash chromatography (silica gel, 98:2 CH_2Cl_2/acetone) 0.91 g (95%) of the alcohol **8b**.

***N*-Benzylphenylalanyl-1,3-thiazole (9a) and *N*-Benzylleucyl-1,3-thiazole (9b):**
A solution of the ketone **4a** (1.50 g, 3.55 mmol) or **4b** (1.80 g, 4.60 mmol) in a 95:5 mixture of TFA in H_2O (10 mL) was stirred at r.t. for 30 min, then neutralized with sat. aq $NaHCO_3$ and diluted with EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude ketone **9a** (1.08 g, 95%) or **9b** (1.24 g, 93%) (95% pure by ^1H NMR) was employed without purification.

(1′*S*,2′*S*)-2-[2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-1-hydroxy-3-phenylpropyl]-1,3-thiazole (11a):
A cold (−78°C) solution of crude **9a** (1.08 g, 3.35 mmol) in THF (15 mL) was treated under stirring with a 1.5 M solution of DIBAH in toluene (3.3 mL, 5.02 mmol). After 1 h stirring, the solution was diluted with EtOAc (5 mL), allowed to warm to r.t. over 5 min, and treated with 10% aq KOH (50 mL). The mixture was stirred at r.t. for 30 min, then diluted with EtOAc (15 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.99 g of a mixture of crude alcohols (see Table 1). This material was dissolved in dioxane (10 mL) and $(Boc)_2O$ (0.80 g, 3.66 mmol) was added and the mixture stirred at r.t., for 18 h, then concentrated. Flash chromatography of the mixture (silica gel, 95.5:4.5 CH_2Cl_2/EtOAc) afforded pure **11a** (0.80 g, 76%).

(1′*S*,2′*S*)-2-[2-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-1-hydroxy-4-methylpentyl]-1,3-thiazole (11b):
To a solution of crude **9b** (1.24 g, 4.31 mmol) in THF (15 mL) was added anhydrous zinc chloride (0.65 g, 4.74 mmol) in THF (15 mL). The mixture was stirred at r.t. for 1 h, then cooled (−78°C) and a solution of 1.5 M DIBAH in toluene (4.31 mL, 6.46 mmol) was added. After 1 h at −78°C, the same workup as for **11a** was carried out to give 1.11 g of a mixture of crude alcohols (see Table 1). This material was dissolved in dioxane (10 mL) and $(Boc)_2O$ (1.0 g, 4.59 mmol) was added and the mixture stirred at r.t. for 18 h, then concentrated. Flash chromatography of the residue (silica gel, 98:2 CH_2Cl_2/acetone) afforded pure **11b** (1.18 g, 77%).

(*R*)-2-{[(4*S*)-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-hydroxymethyl}-1,3-thiazole (14a):
To a cold (−60°C) solution of **7a** (1.0 g, 3.20 mmol) in MeOH (10 mL), $NaBH_4$ (0.24 g, 6.40 mmol) was added with stirring. The mixture was stirred for 2 h at −60°C, then diluted with acetone (10 mL) and concentrated. The residue was washed with sat. aq $NaHCO_3$ (10 mL), extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 90:10 CH_2Cl_2/acetone) of the residue gave 0.95 g (95%) of pure alcohol **14a**.

(*R*,*R*,*R*)-2-{[*N*-*tert*-Butoxycarbonyl-2,2,5-trimethyl-1,3-oxazolidin-4-yl]-hydroxymethyl}-1,3-thiazole (14b):
The ketone **7b** (1.0 g, 3.06 mmol) was processed as described above for **7a**, to give, after flash chromatography (silica gel, 60:40 hexane/Et_2O), 0.95 g (95%) of pure alcohol **14b**.

(1*R*,2*S*)-2-*tert*-Butoxycarbonylamino-1-(1,3-thiazol-2-yl)propane-1,3-diol (17a) and (1*R*,2*S*,3*R*)-2-*tert*-butoxycarbonylamino-1-(1,3-thiazol-2-yl)butane-1,3-diol (17b):
A solution of **14a** (0.15 g, 0.48 mmol) or **14b** (0.15 g, 0.46 mmol) and PPTS (15%) in MeOH (8 mL) was stirred at 80°C (bath temperature) for 18 h, then concentrated. Flash chromatography (silica gel, 35:1 Et_2O/MeOH) afforded pure **17a** (0.12 g, 90%) or **17b** (0.12 g, 89%).

(*S*)-2-(2-*tert*-Butoxycarbonylamino-3-hydroxypropionyl)-1,3-thiazole (15a):
To a stirred solution of **7a** (1.50 g, 4.80 mmol) in CH_2Cl_2 (10 mL) was added a 0.5 M solution of TFA in CH_2Cl_2 (150 mL). The mixture was stirred at r.t. for 15 min, then neutralized with sat. aq $NaHCO_3$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography of the crude product (silica gel, 30:70 hexane/Et_2O) afforded 1.24 g (95%) of **15a** as a white solid.

(*S*)-2-(2-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxypropionyl)-1,3-thiazole (16a):
Freshly prepared ketone **15a** (1.24 g, 4.55 mmol) was dissolved in DMF (5 mL). Then, Et_3N (0.83 mL, 5.93 mmol), DMAP (catalytic), and CF_3SO_3Si*t*-$BuMe_2$ (1.57 g, 5.93 mmol) were added in that order. The mixture was stirred at r.t. for 1 h, then concentrated. Flash chromatography (silica gel, 75:25 hexane/Et_2O) of the crude product afforded pure **16a** (1.72 g, 98%).

(2*S*,3*R*)-2-(2-*tert*-Butoxycarbonylamino-3-hydroxybutyryl)-1,3-thiazole (15b):
Compound **15b** was obtained from **7b** (1.5 g, 4.59 mmol) following the procedure described for **16a**. Flash chromatography (silica gel, 40:60 hexane/Et_2O) afforded pure **15b** (1.25 g, 95%) as a white solid.

(2*S*,3*R*)-2-(2-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxybutyryl)-1,3-thiazole (16b):
Compound **16b** (1.71 g, 98%) was obtained and purified as described above for **16a**, starting from **15b** (1.25 g, 4.36 mmol).

Amino Alcohol 19a from Ketone 16a:
To a cold (−78°C) stirred solution of **16a** (0.16 g, 0.41 mmol) in THF (2 mL), was added dropwise $Zn(BH_4)_2$ (0.83 mmol, 5.91 mL of a 0.14 M solution in Et_2O). The mixture was stirred at −78°C for 18 h, then brine (5 mL) was added. The mixture was allowed to warm to r.t. over 30 min, diluted with Et_2O (2 mL) and washed with 1 M NaOH (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give a mixture (0.16 g) of alcohols **20a** + **18a** (see Table 2), 89% pure by ^1H NMR. The mixture of these alcohols was dissolved in THF (1.5 mL), $Bu_4NF \cdot xH_2O$ (0.09 g, 0.35 mmol) was added, and the brown solution was stirred at r.t. for 30 min, then concentrated. Flash chromatography (silica gel, 35:1 Et_2O/MeOH) of the residue afforded **19a** (76 mg, 68%).

Amino Alcohols 17a and 19a from Ketone 15a:
To a solution of tetramethylammonium triacetoxyborohydride $[Me_4NBH(OAc)_3]$ (0.52 g, 1.98 mmol) in MeCN (1.3 mL), HOAc was added (1.3 mL). The mixture was stirred at r.t. for 30 min, cooled (−40°C), and a solution of freshly prepared **15a** (0.06 g, 0.22 mmol) in MeCN (0.5 mL) was added. The mixture was stirred at −40°C for 40 h, neutralized with 0.5 M sodium potassium

tartrate (3 mL), allowed to warm to r.t., then diluted with CH_2Cl_2 (3 mL) and washed with sat. aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give a mixture (57 mg, 95% pure by NMR) of the two diastereomers **19a** and **17a** (see Table 2).

Amino Alcohol 19b from Ketone 16b:
To a cold (−78 °C) stirred solution of **16b** (0.15 g, 0.37 mmol) in THF (2 mL), L-Selectride (0.74 mmol, 0.74 mL of 1 M solution in THF) was added slowly. The mixture was stirred at −78 °C for 1 h, then 1 M NaOH (5 mL) was added. After warming to r.t. and stirring for an additional 30 min, Et_2O (5 mL) was added. The phases were separated, the aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The resulting material (see Table 2), was dissolved in THF (15 mL) and $Bu_4NF \cdot xH_2O$ (0.11 g, 0.41 mmol) was added. The brown solution was stirred at r.t. for 30 min, then concentrated. Flash chromatogrphy (silica gel, 35:1 Et_2O/MeOH) afforded pure **19b** (94 mg, 88%).

Amino Alcohols 17b and 19b from Ketone 15b:
Freshly prepared **15b** (0.10 g, 0.35 mmol), was processed as described above for **15a** to give a mixture (95 mg, 95% pure by NMR) of alcohols **17b** and **19b** (see Table 2).

(4*S*,5*R*)-3,4-Dibenzyl-5-(1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (12a):
To a solution of **8a** (0.10 g, 0.23 mmol) in THF (5 mL), NaH (0.23 mmol) as a 60% dispersion in mineral oil (9.20 g) was added. The suspension was refluxed for 30 min, then diluted with MeOH (0.5 mL) and concentrated. Flash chromatography of the crude product (silica gel, 60:40 hexane/Et_2O) afforded pure **12a** (73 mg, 93%).

(4*S*,5*R*)-3-Benzyl-4-isobutyl-5-(1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (12b):
The reaction was carried out as described above for **12a**, starting from **8b** (0.10 g, 0.25 mmol). Flash chromatography (silica gel, 60:40 hexane/Et_2O) afforded pure **12b** (75 mg, 95%).

(*S*,*S*)-3,4-Dibenzyl-5-(1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (13a):
A solution of crude **10a** (0.1 g, 0.31 mmol) and carbonyldiimidazole (55.3 mg, 0.34 mmol) in THF (5 mL) was stirred at r.t. for 18 h, then concentrated. Flash chromatography of the crude product (silica gel, 60:40 hexane/Et_2O) afforded pure **13a** (65 mg, 61%).

(*S*,*S*)-3-Benzyl-4-isobutyl-5-(1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (13b):
This compound was obtained from **10b** (0.1 g, 0.35 mmol) by the same procedure described for **13a**. Flash chromatography of the crude product (silica gel, 60:40 hexane/Et_2O) afforded pure **13b** (64 mg, 58%).

(4*R*,5*S*)-5-*tert*-Butoxycarbonylamino-2,2-dimethyl-4-(1,3-thiazol-2-yl)-1,3-dioxane (21a):
A solution of **17a** (0.10 g, 0.36 mmol), DMP (0.44 mL, 3.60 mmol), CSA (catalytic) in acetone (6 mL) was stirred at r.t. for 1 h then concentrated. Flash chromatography (silica gel, 40:60 hexane/Et_2O) of the crude product afforded pure **21a** (0.11 g, 95%).

(4*R*,5*S*,6*R*)-5-*tert*-Butoxycarbonylamino-2,2,6-trimethyl-4-(1,3-thiazol-2-yl)-1,3-dioxane (21b):
To a stirred solution of **14b** (0.10 g, 0.30 mmol) in CH_2Cl_2 (1 mL) was added a 0.5 M solution of TFA in CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 5 min, then neutralized with sat. aq $NaHCO_3$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 40:60 hexane/Et_2O) afforded pure **21b** (96 mg, 98%).

(*S*,*S*)-5-*tert*-Butoxycarbonylamino-2,2-dimethyl-4-(1,3-thiazol-2-yl)-1,3-dioxane (22a):
This compound (52 mg, 90%) was obtained and purified as described above for **21a**, starting from **19a** (50 mg, 0.18 mmol).

(4*S*,5*S*,6*R*)-5-*tert*-Butoxycarbonylamino-2,2,6-trimethyl-4-(1,3-thiazol-2-yl)-1,3-dioxane (22b):
This compound (61 mg, 60%) was obtained as described above for **22a** starting from **19b** (90 mg, 0.31 mmol). The crude product proved by NMR to be a mixture of **22b** and a 2,3-oxazolidine isopropylidene which were separated (after acetylation of the resulting material) by flash chromatography (silica gel, 60:40 hexane/Et_2O).

(1*R*,2*S*)- and (*S*,*S*)-2-(*N*-*tert*-Butoxycarbonyl)benzylamino-3-phenyl-1-(1,3-thiazol-2-yl)propyl Acetates (23a) and (26a):
A solution of **8a** or **11a** (0.70 g, 1.65 mmol), $(Ac)_2O$ (0.23 mL, 2.47 mmol) and DMAP (catalytic) in pyridine (3 mL), was stirred at r.t. for 6 h, then concentrated. Flash chromatography of crude products (silica gel, 60:40 hexane/Et_2O), afforded pure **23a** (0.74 g, 96%) and **26a** (0.75 g, 97%).

(1*R*,2*S*)- and (*S*,*S*)-2-(*N*-*tert*-Butoxycarbonyl)benzylamino-4-methyl-1-(1,3-thiazol-2-yl)pentyl Acetates (23b) and (26b).
These compounds were obtained from **8b** (0.70 g, 1.79 mmol) and **11b** (0.80 g, 2.05 mmol) according to the procedure described for **23a**. Flash chromatography of crude products (silica gel, 70:30 hexane/Et_2O) gave pure **23b** (0.75 g, 97%) and **26b** (0.81 g, 92%).

(2*R*,3*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzylamino-4-phenylbutanal (24a):
A mixture of the thiazole derivative **23a** (0.50 g, 1.07 mmol), activated 4Å powdered molecular sieves (2.14 g) and MeCN (11 mL) was stirred at r.t. for 10 min, and then methyl triflate (0.16 mL, 1.39 mmol) was added. The suspension was stirred for 40 min and then concentrated to dryness. The residue was suspended in MeOH (11 mL), cooled (0 °C) and treated with $NaBH_4$ (89.4 mg, 3.35 mmol). The mixture was stirred at r.t. for an additional 10 min, diluted with acetone (11 mL), filtered through Celite and concentrated. The residue was dissolved in 10:1 MeCN/H_2O (8 mL) and the solution treated with $HgCl_2$ (0.29 g, 1.07 mmol) in 3 mL of the same solvent mixture. The mixture was stirred for 15 min, then filtered through Celite and concentrated (bath temperature not exceeding 40 °C). The residue was dissolved in CH_2Cl_2 (15 mL), washed with 20% KI (15 mL) and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and quickly filtered through a pad of Florisil to afford the crude aldehyde as a clear yellow syrup (0.33 g, 74%) which was 90% pure by ^1H NMR spectroscopy. The purification of the aldehyde by flash chromatography led to extensive decomposition. The crude aldehyde was utilized for the oxidation without purification.

^1H NMR (DMSO-d_6, 120 °C): δ = 1.31 (s, 9H), 2.01 (s, 3H), 2.99–3.15 (m, 2H), 4.25 (d, 1H, J = 16.5 Hz), 4.39 (d, 1H, J = 16.5), 4.76–4.88 (m, 1H), 5.15 (d, 1H, J = 6.1), 6.95–7.35 (m, 10H), 9.44 (s, 1H).

(*S*,*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzylamino-4-phenylbutanal (27a):
The deblocking procedure was carried out as described above for **23a**, starting from **26a** (0.30 g, 0.64 mmol), to give a crude clear yellow syrup (0.19 g, 72%) which was 90% pure by ^1H NMR spectroscopy. Since the purification of the aldehyde by flash chromatography led to extensive decomposition, crude compound was utilized for the oxidation without purification.

^1H NMR (DMSO-d_6, 120 °C): δ = 1.38 (s, 9H), 1.95 (s, 3H), 2.90–3.15 (m, 2H), 4.24 (d, 1H, J = 16.5 Hz), 4.32 (d, 1H, J = 16.5 Hz), 4.45–4.56 (m, 1H), 5.17 (d, 1H, J = 5.7 Hz), 7.08–7.35 (m, 10H), 9.32 (s, 1H).

(2*R*,3*S*)- and (*S*,*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzylamino-5-methylhexanal (24b) and (27b):
The thiazole derivatives **23b** and **26b** (0.50 g, 1.15 mmol), were processed as described above for **23a** (*N*-methylation, reduction, hydrolysis), to give crude **24b** (0.31 g, 75%) and **27b** (0.30 g, 73%), which were 95% pure by ^1H NMR spectroscopy. Analytically pure samples were obtained by flash chromatography (silica gel, 98:2 CH_2Cl_2/acetone). **24b**: syrup; $[\alpha]_D^{20}$ −24.3° (c = 0.5, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 0.78 (d, 3 H, J = 6.6 Hz), 0.85 (d, 3 H, J = 6.6 Hz), 1.26–1.50 (m, 2 H), 1.38 (s, 9 H), 1.62–1.74 (m, 1 H), 2.02 (s, 3 H), 4.36 (d, 1 H, J = 16.1 Hz), 4.44 (d, 1 H, J = 16.1 Hz), 4.61 (ddd, 1 H, J = 4.8, 6.4, 9.6 Hz), 5.1 (d, 1 H, J = 6.2 Hz), 7.17–7.32 (m, 5 H), 9.51 (s, 1 H).

27b: syrup; $[\alpha]_D^{20}$ – 8.3° (c = 1.2, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 0.76 (d, 3 H, J = 6.3 Hz), 0.83 (d, 3 H, J = 6.2 Hz), 1.27–1.50 (m, 2 H), 1.41 (s, 9 H), 1.68–1.79 (m, 1 H), 2.0 (s, 3 H), 4.37 (d, 1 H, J = 16.2 Hz), 4.36–4.44 (m, 1 H), 5.07 (dd, 1 H, J = 1.1, 5.6 Hz), 7.18–7.34 (m, 5 H), 9.4 (d, 1 H, J = 1.1 Hz).

The crude aldehydes were utilized for the oxidation without purification.

Methyl (2*R*,3*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzylamino-4-phenylbutyrate (25a):
A solution of crude **24a** (0.20 g, 0.49 mmol) in *t*-BuOH (2.8 mL) was suspended in aq potassium phosphate buffer (pH 7) (1.9 mL). To the resulting mixture was added, with vigorous stirring, aq 1 M $KMnO_4$ (2.8 mL). The mixture was stirred at r.t. for 20 min, then quenched with sat. aq $Na_2S_2O_5$ and the resulting pH was adjusted to 3 with cold (0°C) 1 M HCl. The mixture was extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated. The crude acid was dissolved in Et_2O (2 mL), cooled (0 °C) and treated with cold (– 5 °C) ethereal diazomethane,[40] to give a clear yellow solution. After 20 min at 0 °C, the solution was concentrated. Flash chromatography (silica gel, 70:30 hexane/Et_2O) of the crude product afforded pure ester **25a** (0.18 g, 87 %).

Methyl (*S*,*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzylamino-4-phenylbutyrate (28a):
The crude aldehyde **27a** (0.19 g) was processed as described above for the aldehyde **25a**, to afford, after flash chromatography of the crude product (silica gel, 80:20 hexane/Et_2O), the pure ester **28a** (0.17 g, 85 %).

Methyl (2*R*,3*S*)- and (*S*,*S*)-2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl)benzyl-amino-5-methylhexanoate (25b) and (28b):
Crude aldehydes **24b** and **27b** (0.20 g) were processed as described above for the aldehyde **25a**, to afford after flash chromatography (silica gel, 80:20 hexane/Et_2O), the pure esters **25b** (0.16 g, 90 %) and **28b** (0.16 g, 89 %).

(*R*)-2-{[(4*S*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]acetoxymethyl}-1,3-thiazole (29a):
A solution of **14a** (0.70 g, 2.23 mmol), $(Ac)_2O$ (0.42 mL, 4.26 mmol), DMAP (catalytic) in pyridine (5 mL) was stirred at r.t. for 6 h, then concentrated. Flash chromatography (silica gel, 40:60 hexane/Et_2O) of the crude product afforded pure **29a** (0.72 g, 91 %).

(*R*)-2-{[(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-2,2,5-trimethyl-1,3-oxazolidin-4-yl]acetoxymethyl}-1,3-thiazole (29b):
Compound **29b** (0.77 g, 98 %) was obtained and purified as described above for **29a** starting from **14b** (0.70 g, 2.13 mmol).

(*S*)-2-{[(4*S*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]acetoxymethyl}-1,3-thiazole (32a):
A solution of crude **20a** + **18a** obtained from **16a** (1.2 g, 3.10 mmol) as described above (see preparation of **19a**), $(Ac)_2O$ (0.52 mL, 5.50 mmol), DMAP (catalytic) in pyridine (5 mL), was stirred at r.t. for 4 h, then concentrated. The residue was washed with sat. aq $NaHCO_3$ (30 mL), extracted with Et_2O (2 × 30 mL), dried (Na_2SO_4) and concentrated. The crude product was dissolved in THF (10 mL) and then treated with $Bu_4NF \cdot xH_2O$ (0.89 g, 3.40 mmol). The brown solution was stirred at r.t. for 1 h, then concentrated. The residue was filtered through a short column of silica gel with Et_2O, then dissolved in 2,2-dimethoxypropane (3.42 mL, 27.8 mmol), in the presence of a catalytic amount of camphorsulfonic acid. The mixture was stirred at 80 °C for 18 h, then concentrated. Flash chromatography (silica gel, 40:60 hexane/Et_2O) of the residue afforded **32a** (0.57 g, 52 %).

(*S*)-2-{[(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-2,2,5-trimethyl-1,3-oxazolidin-4-yl]acetoxymethyl}-1,3-thiazole (32b):
Compound **32b** (0.70 g, 69 %) was obtained and purified as described above for **32a**, starting from **16b** (1.1 g, 2.75 mmol), which was reduced with L-Selectride as **19b**.

(*R*)-2-Acetoxy-2-[(4*S*)-*N*-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]ethanal (30a):
The elaboration of **29a** (0.50 g, 1.40 mmol) by the deblocking procedure described above for **23a** (*N*-methylation, reduction, hydrolysis), gave the crude aldehyde **30a** (0.32 g, 78 %) which was 95 % pure by ^{1}H NMR. An analytically pure sample of **30a** was obtained by flash chromatography (silica gel, 20:1 CH_2Cl_2/EtOAc): mp 77–78 °C; $[\alpha]_D^{20}$ – 63.9° (c = 0.8, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 1.45 (bs, 12 H), 1.53 (s, 3 H), 2.11 (s, 3 H), 3.92 (dd, 1 H, J = 2.3, 9.7 Hz), 4.08 (dd, 1 H, J = 6.3, 9.7 Hz), 4.35 (ddd, 1 H, J = 2.3, 5.2, 6.3 Hz), 5.18 (d, 1 H, J = 5.2 Hz), 9.53 (s, 1 H).

The crude aldehyde was utilized for the oxidation without purification.

(*S*)-2-Acetoxy-2-[(4*S*)-*N*-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]ethanal (33a):
The deblocking procedure was carried out as described above for **23a** starting from **32a** (0.50 g, 1.40 mmol), to give a clear crude yellow syrup (0.30 g, 71 %) which was 89 % pure by ^{1}H NMR. The purification of the aldehyde by flash chromatography led to extensive decomposition. The crude compound was utilized for the oxidation without purification.

^{1}H NMR (DMSO-d_6, 100 °C): δ = 1.42 (s, 9 H), 1.48 (s, 3 H), 1.55 (s, 3 H), 2.15 (s, 3 H), 3.86 (dd, 1 H, J = 2.0, 9.8 Hz), 3.99 (dd, 1 H, J = 6.2, 9.8 Hz), 4.30 (ddd, 1 H, J = 2.0, 6.2, 6.3 Hz), 5.14 (d, 1 H, J = 6.3 Hz), 9.49 (s, 1 H).

(*R*)- and (*S*)-2-Acetoxy-2-[(4*S*,5*R*)-*N*-*tert*-butoxycarbonyl-2,2,5-trimethyloxazolidin-4-yl]ethanal (30b) and (33b):
O-Acetyl derivatives **29b** and **32b** (0.50 g, 1.35 mmol) were processed as described above for **23a** to give **30b** (0.32 g, 76 %, 93 % pure by ^{1}H NMR) and **33b** (0.31 g, 73 %, 95 % pure by ^{1}H NMR). Analytically pure samples of these compounds were obtained by flash chromatography (silica gel, 30:1 CH_2Cl_2/EtOAc).

30b: mp 54–55 °C; $[\alpha]_D^{20}$ = – 34.0° (c = 0.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.38 (d, 3 H, J = 6.1 Hz), 1.46 (s, 9 H), 1.49 (s, 3 H), 1.58 (s, 3 H), 2.19 (s, 3 H), 3.83 (dd, 1 H, J = 1.4, 8.5 Hz), 3.94 (dq, 1 H, J = 6.1, 8.5 Hz), 4.90 (d, 1 H, J = 1.4 Hz), 9.40 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 18.16, 20.41, 24.72, 27.94, 28.19, 63.55, 72.30, 74.30, 80.85, 94.14, 152.54, 170.39, 188.22.

33b: syrup; $[\alpha]_D^{20}$ – 52.3° (c = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.29 (d, 3 H, J = 6.3 Hz), 1.47 (s, 9 H), 1.50 (s, 3 H), 1.61 (s, 3 H), 2.21 (s, 3 H), 3.91–4.10 (m, 1 H), 4.15–4.27 (m, 1 H), 5.62 (d, 1 H, J = 4.2 Hz), 9.55 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 20.34, 26.36, 27.53, 28.10, 29.51, 62.50, 71.80, 81.11, 94.14, 169.89, 196.21, 196.65.

The crude aldehydes were utilized for the oxidation without purification.

Methyl (*R*)- and (*S*)-2-Acetoxy-2-[(4*S*)-*N*-*tert*-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]acetate (31a) and (34a):
These compounds were obtained from the crude aldehydes **30a** and **33a** (0.20 g) by the procedure described for **25a**. Flash chromatography (silica gel, 60:40 hexane/Et_2O) gave pure **31a** (0.20 g, 91 %) and **34a** (0.17 g, 80 %).

Methyl (*R*)- and (*S*)-2-Acetoxy-2-[(4*S*,5*R*)-*N*-*tert*-butoxycarbonyl-2,2,5-trimethyloxazolidin-4-yl]acetate (31b) and (34b):
These compounds were obtained from crude **30b** and **33b** (0.25 g) by the procedure described for **25a**. Flash chromatography of the crude esters (silica gel, 70:30 hexane/Et_2O) afforded pure **31b** (0.24 g, 90 %) and **34b** (0.25 g, 92 %).

Methyl (*S*)-2-(*N*-*tert*-Butoxycarbonyl)benzylamino-2-phenylacetate (37a):
A solution of **2c** (0.25 g, 1.65 mmol), PhCHO (0.21 g, 1.98 mmol), NaOH (1 mL) in MeOH (5 mL) was stirred at r.t. for 18 h, then cooled (0 °C) and $NaBH_4$ (0.13 g, 3.31 mmol) was added. After 30 min at 0 °C, the solution was diluted with acetone (1 mL) and concentrated (bath temperature: 30 °C) to nearly dryness. The residue was dissolved in dioxane (2 mL), and NaOH (1 mL) and $(Boc)_2O$ (0.54 g, 2.48 mmol) were added. The mixture was stirred at r.t. for 18 h, concentrated to half its original volume, cooled in ice and acidified to pH 2–3 by slow addition of cold (0 °C) 1 M $KHSO_4$. The resulting mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O (2 mL), cooled (0 °C) and treated with sufficient ethereal CH_2N_2 to afford a clear yellow solution. After 20 min at 0 °C, the excess diazomethane was destroyed with AcOH and the resulting solution was diluted with sat. aq $NaHCO_3$ (10 mL), extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 96:4 toluene/Et_2O) gave pure **37a** (0.47 g, 80%).

Methyl (*S*)-2-*tert*-Butoxycarbonylamino-2-phenylacetate (37c):
A solution of $(Boc)_2O$ (2.16 g, 9.22 mmol) in dioxane (8 mL) was added to an ice-cold solution of **2c** (1.0 g, 6.61 mmol) in NaOH (4 mL) with stirring. After 5 min at 5 °C, the mixture was warmed to r.t., stirred at this temperature for 18 h, then concentrated to half its original volume, cooled (0 °C) and acidified to pH 2–3 by slow addition of cold (0 °C) 1 M $KHSO_4$. The mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The resulting material was treated with cold (−5 °C) ethereal CH_2N_2, as for **37a**, to afford pure **37c** (1.64 g, 99%).

Methyl (*S*)-2-[*N*,*N*-Bis(tert-butoxycarbonyl)amino]-2-phenylacetate (37b):
A solution of **37c** (0.25 g, 0.94 mmol), $(Boc)_2O$ (0.31 g, 1.41 mmol) and DMAP (catalytic) in THF (5 mL), was stirred at 80 °C for 6 h, then concentrated. Flash chromatography (silica gel, 80:20 hexane/Et_2O) gave pure **37b** (0.33 g, 97%).

(*S*)-2-(2-*tert*-Butoxycarbonylamino-2-phenylacetyl)-1,3-thiazole (35c):
To a cold (−78 °C), stirred solution of BuLi (8.29 mmol, 5.20 mL of a 1.6 M solution in hexane) in Et_2O (10 mL), was added, dropwise, a solution of 2-bromothiazole (1.35 g, 8.29 mmol) in the same solvent (10 mL). After the yellow solution had been stirred at −78 °C for 30 min, a solution of the ester **37c** (1.0 g, 3.77 mmol) in Et_2O (10 mL) was added slowly. The mixture was stirred at −70 °C for 1 h, then sat. aq $NaHCO_3$ (10 mL) was added. The mixture was allowed to warm to r.t. over 30 min and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 60:40 hexane/Et_2O) gave **35c** (1.07 g, 89%).

(*S*,*S*)-2-*tert*-Butoxycarbonylamino-2-phenyl-1-(1,3-thiazol-2-yl)ethanol (38):
Ketone **35c** (0.90 g, 2.83 mmol) was reduced as described above for the ketone **4a**, to give after flash chromatography (silica gel, 55:45 hexane/EtOAc) pure **38** (0.77 g, 85%).

(*S*,*S*)-4-Phenyl-5-(1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (42):
A 40% solution of TFA in CH_2Cl_2 (10 mL) was added to the alcohol **38** with vigorous stirring. After 15 min at r.t., the mixture was concentrated. The resulting material was dissolved in THF (3 mL), and then Et_3N (0.03 mL) and carbonyldiimidazole (0.10 g, 0.62 mmol) were added in that order. The mixture was stirred at r.t. for 18 h, then concentrated. Flash chromatography (silica gel, 40:60 hexane/EtOAc) afforded pure **42** (61 mg, 80%).

(*S*,*S*)-2-*tert*-Butoxycarbonylamino-2-phenyl-1-(1,3-thiazol-2-yl)ethyl Acetate (39):
Alcohol **38** (0.50 g, 1.56 mmol) was acetylated as described above for the alcohol **8a**, to give after flash chromatography (silica gel, 75:25 hexane/EtOAc) pure **39** (0.53 g, 94%).

(*S*,*S*)-2-Acetoxy-3-*tert*-butoxycarbonylamino-3-phenylpropanal (40):
The deblocking procedure was carried out as described above for **23a** (*N*-methylation, reduction, hydrolysis) starting from the thiazole derivative **39** (0.31 g, 0.86 mmol). Filtration through Florisil of the brown residue afforded the crude aldehyde as a clear yellow syrup (0.19 g, 72%) which was 85% pure by ^1H NMR spectroscopy. The purification of the aldehyde by flash chromatography led to extensive decomposition. The crude aldehyde was utilized for the oxidation without purification.
^1H NMR (DMSO-d_6, 120 °C): δ = 1.39 (s, 9H), 1.99 (s, 3H), 5.09 (dd, 1H, J = 2.5, 6.2 Hz), 5.32 (d, 1H, J = 6.2 Hz), 5.64 (d, 1H, J = 2.5 Hz), 7.17–7.60 (m, 5H), 9.55 (s, 1H).

Methyl (*S*,*S*)-2-Acetoxy-3-*tert*-butoxycarbonylamino-3-phenylpropionate (41):
The compound was obtained from the crude aldehyde **40** (0.19 g) according to the procedure described for **25a**. Flash chromatography of the crude ester (silica gel, 60:40 hexane/Et_2O) afforded the pure product **41** (0.17 g, 80%).

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