Improved Stereoselectivity in Intramolecular $S_N2'$ Cyclization through Use of Mechanistic Principles

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Abstract: Valine and alanine were converted into the corresponding $\alpha$-hydroxy-$\beta$-amino acids through intramolecular $S_N2'$ cyclization. The novel cyclization protocol relied upon the use of $N$-benzyl-protected carbamates derived from $\alpha$-amino acids. The derivatization of $\alpha$-amino acids continues to be a vibrant and fruitful area of chemical endeavor because of the high optical purity and varied reactivity of these starting materials. $\alpha$-Amino acids have been converted efficiently into enantiopure amino epoxides, amino alcohols, amino diols, and a wide range of unsaturated intermediates, as well as into $\beta$-amino acids. $\beta$-Amino acids are of great chemical significance, and the huge interest in this field has been reflected in the publication of a number of recent reviews on both the general chemical function and the synthesis of this class of compound. However, despite their abundance in important bioactive compounds such as Taxol, highly selective routes to $\alpha$-hydroxy-$\beta$-amino acids (ABHAs; e.g., 1 and 2, Figure 1) are much rarer, because the controlled generation of two or more stereogenic centers is required. We were able to show that the derivatization of diastereo- and enantiomerically pure oxazolidinones constitutes a powerful route to ABHAs.

![Figure 1](target.png)

Figure 1 Target compounds

This methodology is based on the conversion of $\alpha$-amino acids into oxazolidin-2-ones through cyclization of (4-hydroxybutenyl)carbamates, in which the hydroxy group (nucleofuge) has been activated as a sulfonate prior to an internal $S_N2'$ cyclization. This cyclization strategy has been highly effective for substrates derived from $\alpha$-amino acids containing bulky side chains, but has, sadly, been of low utility in substrates possessing smaller side chains (valine and alanine). The objective of the work reported here has been to extend this methodology to allow stereoselective synthesis of ABHAs possessing smaller side chains. We will also discuss the mechanistic features of the cyclization transition state as elucidated during this work.

Synthesis of the substrates began with chemoselective reduction of $N$-Boc-$N$-Bn-protected $\alpha$-amino esters $3a$ and $3b$ with lithium aluminum hydride (Scheme 1). Swern oxidation of the resulting (2-hydroxyethyl)carbamates $4a$ and $4b$ furnished chiral aldehydes, which underwent an E-selective Horner–Wadsworth–Emmons reaction that afforded allylic carbamates $5a$ and $5b$. Finally, chemoselective reduction of the ester moiety with diisobutylaluminum hydride generated the cyclization precursors, allylic alcohols $6a$ and $6b$ (Scheme 1).

![Scheme 1](reagents.png)

Scheme 1 Reagents and conditions: (i) ref. 4; (ii) (a) Swern oxidation; (b) (EtO)$_2$P(O)CH$_2$CO$_2$Et (2 equiv), NaH (2 equiv), dry THF, 0 °C to r.t., 82% yield; (iii) DIBAL-H (3.0 equiv), THF, −78 °C, 85% yield.

Under our previously reported conditions, namely the use of trifluoromethanesulfonic anhydride in pyridine at −78 °C, allylic alcohols $6c$ and $6f$ ($R^2 = H$) gave the corresponding oxazolidinones $7$ in 1:2 and 1:5 cis/trans selectivities, respectively (Table 1, entries 1 and 4). However, when the steric bulk at nitrogen was increased by N-methylation ($6d$ and $6g$, $R^2 = Me$), the cyclization proceeded slightly more selectively, to afford the oxazolidi-
none products 7 in improved cis/trans ratios (Table 1, entries 2 and 5). We subsequently investigated the effect of the more sterically demanding N-benzyl substituent (6e and 6h, R² = Bn) upon the selectivity (Table 1 and 6). Triflation/cyclization of alanine derivative 6e and valine derivative 6h led to a dramatic improvement in the selectivities, with the corresponding trans-oxazolidinones 7 forming in 15:1 and an excellent 99:1 dr, respectively (Table 1, entries 3 and 6).

Previous, our consideration of the mechanism of the cyclization, as well as molecular modeling studies led us to conclude that minimization of A(1,3) strain by eclipsing of C(2)H and C(4)H is a probable cause for the observed trans selectivity in the case of substrates possessing bulky R¹ substituents. However, we noted that for efficient A(1,3) strain control, a substituent bulkier than a proton is generally required in the 2-position (Figure 2) to achieve good selectivity, and this seems to be the grounds for low selectivity when R¹ is small. However, as our results verify, when R² becomes an alkyl group, an extra interaction occurs, which destabilizes the transition state leading to the cis product. This interaction may be described as a syn-pentane interaction between the N–R² bond and the olefin. This new interaction is expected to stabilize B over A, even when R¹ is small enough to allow for significant C(3)–C(4) bond rotation in the absence of other factors.¹⁰

The conversion of the oxazolidinone products into the corresponding ABHAs was next undertaken (Scheme 2). Dihydroxylation of the vinyl substituent on 7a and 7b is achieved with osmium tetroxide followed by cleavage in the presence of periodate, and subsequent oxidation with potassium permanganate yielded acids 8a and 8b (Scheme 2). The oxazolidinone ring within these products was easily cleaved, without epimerization at the C(5)-position, by reflux in aqueous potassium hydroxide, to give N-benzyl-protected ABHAs 9a and 9b in 85% yield. Finally, the amino group was deprotected by hydrogenolysis to give (2R,3S)-1² and (2R,3S)-2¹¹ in 90% yield (Scheme 2).

The relative stereochemistry within the target molecules 1 and 2 was determined by 2D-NOESY experiments on oxazolidinone 7a and 7b, both of which showed a weak correlation between C(4)H and C(5)H. Vicinal coupling constants between C(4)H and C(5)H (J₁₅) are also consistent with this analysis (Figure 3).

To prove the enantiomeric purities of the product ABHAs, compounds (2R,3S)-1 and (2R,3S)-2 were converted first into the N-Boc-protected methyl ester derivatives 10 and 12,¹² and then into the Mosher’s esters 11 and 13 (Scheme 3).⁴ Analysis of the ¹⁹F NMR spectra of the Mosher’s esters and comparison with a sample synthesized from racemic α-methoxy-α-(trifluoromethyl)phenyl-
acetic acid (MTPA) showed that the enantiomeric ratio of the two ABHAs formed in this protocol were >99:1. The absolute configuration was inferred from the known absolute configuration of the starting α-amino acids.

In conclusion, we have synthesized two enantiopure ABHAs using a novel cyclization protocol relying upon the use of N-benzyl-protected carbamates derived from α-amino acids. Our study has not only brought about considerable new mechanistic understanding of this potentially highly useful system, but also extended the range of viable substrates to include branched and unbranched aliphatic side chains. We aim to apply these ideas to further development of this protocol by the synthesis of natural products, and by investigating its use in more complex systems.

All non-aqueous reactions were carried out under an inert N₂ atmosphere. Et₂N, DMSO, and CH₂Cl₂ were distilled from CaH₂. All reactions were monitored by TLC on commercially available glass-backed plates. Column chromatography was carried out on 230–400 mesh silica gel. The solvent was evaporated and the residue was chromatographed (silica gel, hexane–EtOAc, 6:1); this gave compound 5a as a solid. Yield: 2.4 g (81%); mp 72.6–73.4 °C; [α]D²⁰ +5.6 (c 2.0, CHCl₃).

IR (KBr): 3356, 2978, 1720 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.74–0.87 (m, 6 H), 1.28 (m, 2 H), 1.45 (m, 9 H), 2.04 (m, 1 H), 4.19 (m, 2 H), 4.27 (d, J = 15.1 Hz, 1 H), 4.47 (d, J = 15.1 Hz, 1 H), 5.78 (d, J = 15.7 Hz, 1 H), 6.85 (dd, J = 6.0, 15.8 Hz, 1 H), 7.20–7.32 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 14.2, 22.3, 22.4, 24.6, 28.4, 40.9, 60.4, 77.2, 80.3, 121.8, 128.0, 128.3, 147.4, 155.7, 166.2.


Ethyl (2E,4S)-4-[Benzyloxy-3-methylpent-2-enoyl]carbamate (5b)

Compound 5b was obtained by the same procedure as that used for compound 5a.

Oil; [α]D²⁰ −8.4 (c 1.0, CHCl₃).

IR (KBr): 3162, 2978, 1750 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.74–0.87 (m, 6 H), 1.28 (m, 2 H), 1.45 (m, 9 H), 2.04 (m, 1 H), 4.19 (m, 2 H), 4.27 (d, J = 15.1 Hz, 1 H), 4.47 (d, J = 15.1 Hz, 1 H), 5.78 (d, J = 15.7 Hz, 1 H), 6.85 (dd, J = 6.0, 15.8 Hz, 1 H), 7.20–7.32 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 14.2, 22.3, 22.4, 24.6, 28.4, 40.9, 60.4, 77.2, 80.3, 121.8, 128.0, 128.3, 147.4, 155.7, 166.2.


Ethyl (2E,4S)-4-[Benzyloxy-3-methylpent-2-enoyl]carbamate (5a)

A soln of NaH (0.7 g, 16.5 mmol) in THF (20 mL) was added to (EtO)₂P(O)CH₂CO₂Et (3.3 mL, 16.5 mmol) at 0 °C. The mixture was vigorously stirred until clear and then the corresponding aldehyde was slowly added at –40 °C. After 30 min, the resulting mixture was warmed to r.t. over 2 h. The mixture was quenched with sat. aq NaHCO₃ (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried (Na₂SO₄). The solvent was evaporated and the residue was chromatographed (silica gel, hexane–EtOAc, 6:1); this gave compound 5a as a solid. Yield: 2.4 g (81%); mp 72.6–73.4 °C; [α]D²⁰ +5.6 (c 2.0, CHCl₃).

IR (KBr): 3356, 2978, 1720 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.74–0.87 (m, 6 H), 1.28 (m, 2 H), 1.45 (m, 9 H), 2.04 (m, 1 H), 4.19 (m, 2 H), 4.27 (d, J = 15.1 Hz, 1 H), 4.47 (d, J = 15.1 Hz, 1 H), 5.78 (d, J = 15.7 Hz, 1 H), 6.85 (dd, J = 6.0, 15.8 Hz, 1 H), 7.20–7.32 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 14.2, 22.3, 22.4, 24.6, 28.4, 40.9, 60.4, 77.2, 80.3, 121.8, 128.0, 128.3, 147.4, 155.7, 166.2.


Ethyl (2E,4S)-4-[Benzyloxy-3-methylpent-2-enoyl]carbamate (5a)

Compound 5a was prepared as described in a literature procedure. 4

[α]D²⁰ −23.1 (c 1.0, CHCl₃).

IR (KBr): 3450, 3125, 1732 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.91 (m, 6 H), 1.42 (s, 9 H), 1.82 (m, 1 H), 3.53 (s, 1 H), 3.60 (m, 2 H), 4.08 (d, J = 9.2 Hz, 1 H), 4.83 (d, J = 9.2 Hz, 1 H), 7.26–7.49 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 18.5, 19.5, 28.4, 29.2, 58.0, 63.7, 72.6, 79.4, 128.1, 128.8, 135.3, 156.8.

tert-Butyl Benzyl[15,2E]-4-hydroxy-1-isopropylbut-2-enyl]carbamate (6a)

To a soln of allylic ester 5a (2.0 g, 5.5 mmol) in CH₂Cl₂ (27 mL) was added DIBAL-H (16.6 mmol, 3 equiv) at –78 °C and then the mixture was stirred for 2 h at the same temperature. The mixture was quenched with 10% NaOH (5 mL) and filtered. The filtrate was evaporated and chromatographed (silica gel, hexane–EtOAc, 2:1).

Yield: 1.5 g (85%); oil; [α]₂⁰D = –14.2 (c 1.0, CHCl₃).

IR (KBr): 3165, 1735, 1447 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.09 (d, J = 13.2 Hz, 3 H), 3.74 (m, 1 H), 4.05 (d, J = 15.2 Hz, 1 H), 4.80 (d, J = 15.2 Hz, 1 H), 4.91 (m, 1 H), 5.43 (m, 1 H), 5.82 (m, 2 H), 7.28–7.38 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 13.7, 45.7, 53.2, 78.1, 120.0, 127.9, 128.8, 131.2, 133.6, 136.0, 157.7.

Anal. Calcd for C₁₉H₂₇NO₄: C, 68.44; H, 8.16; N, 4.20. Found: C, 73.42; H, 7.80; N, 5.72.

(4S,5S)-3-Benzyl-4-isopropyl-5-vinlyoxazolidine-2-carboxylic Acid (8a)

To a stirred soln of 7a (0.4 g, 1.6 mmol) and NMO (0.4 g, 3.3 mmol) in acetone–H₂O (10:1, 11 mL) at r.t. was added aq OsO₄ (cat.). The mixture was stirred at r.t. overnight and quenched with aq 10% Na₂SO₄. The mixture was washed with CH₂Cl₂ (3 × 5 mL). The organic phase was dried and concentrated under reduced pressure to give the corresponding diol, which was used in the next step without further purification.

To a soln of the diol (1.4 mmol) in EtOH–H₂O (2:1, 2.1 mL) was added NaOH (1.0 mmol) at r.t. After stirring for 2 h, the reaction mixture was evaporated and filtered with EtOAc. The residue was oxidized with K₂MnO₄ (0.4 g, 2.8 mmol) and K₂CO₃ (0.4 g, 2.8 mmol) in THF–H₂O (2:1, 6 mL). After 30 min, the reaction was quenched by the addition of 5% citric acid (6 mL), and then extracted with EtOAc (4 × 10 mL). The organic layer was concentrated and the residue was chromatographed (silica gel, CH₂Cl₂–MeOH, 5:1).

Yield: 0.28 g (74%); oil; [α]₂⁰D = –46.0 (c 1.0, MeOH).

IR (KBr): 3155, 2910, 1714, 1595 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.92 (dd, J = 6.9, 16.9 Hz, 6 H), 2.09 (m, 1 H), 3.61 (t, J = 7.4 Hz, 1 H), 4.17 (d, J = 3.4 Hz, 1 H), 4.07 (d, J = 15.4 Hz, 1 H), 4.62 (d, J = 3.6 Hz, 1 H), 4.88 (d, J = 15.2 Hz, 1 H), 7.14–7.38 (m, 5 H).

13C NMR (125 MHz, CDCl₃): δ = 14.6, 17.4, 27.9, 46.2, 62.7, 70.9, 127.8, 128.1, 128.9, 135.0, 157.4, 172.5.

Anal. Calcd for C₁₉H₂₇NO₄: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.85; H, 6.50; N, 5.34.

(4S,5R)-3-Benzyl-4-isopropyl-2-oxooxazolidine-5-carboxylic Acid (8b)

Compound 8b was obtained by the same procedure used for 8a.

IR (KBr): 3122, 2940, 1721 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.36 (d, J = 3.7 Hz, 3 H), 3.78 (t, J = 7.4 Hz, 1 H), 4.17 (d, J = 9.2 Hz, 1 H), 4.50 (d, J = 3.7 Hz, 1 H), 4.75 (d, J = 9.2 Hz, 1 H), 7.26–7.37 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 19.1, 46.4, 54.7, 128.4, 128.5, 129.3, 135.5, 157.4, 171.7.

Anal. Calcd for C₁₉H₂₇NO₄: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.25; H, 5.58; N, 5.94.

(2R,3S)-3-Benzylamino)-2-hydroxy-4-methylpentanoic Acid (9a)

To a soln of 8a (0.5 g, 1.9 mmol) in EtOH (2 mL) was added 4 M KOH (4 mL), and the mixture was stirred for 4 h at 60 °C. The mixture was washed with Et₂O (20 mL) and the aqueous layer was acidified (pH 2) and extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried (Na₂SO₄). The solvent was evaporated and the residue was chromatographed (silica gel, CH₂Cl₂–aceton, 1:1).

Yield: 0.38 g (85%); solid; mp 214–216 °C; [α]₂⁰D = –2.6 (c 1.0, MeOH).

IR (KBr): 3432, 3010, 1724, 1595 cm⁻¹.
(2R,3S)-3-Benzylamino-2-hydroxybutanoic Acid (9b)

Compound 9b was obtained by the same procedure used for 9a. Solid; mp 250–252 °C; [α]_D^20 +3.3 (c 0.5, MeOH).

IR (KBr): 3410, 2930, 1640 cm⁻¹.

1H NMR (300 MHz, D₂O): δ 3.37–3.48 (m, 4 H), 4.88 (d, J = 15.2 Hz, 1 H), 7.14–7.38 (m, 5 H).

13C NMR (125 MHz, D₂O): δ 63.12; H, 7.21; N, 6.71.

Yield: 10 mg (90%); mp 208–209 °C; [α]_D^20 −11.5 (c 0.5, MeOH).

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References


