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Highly diastereoselective addition of Et_2AlCN to β-keto amides derived from (*S*)-4-isopropyl-2-oxazolidinone

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Abstract—The addition of Et_2AlCN in the presence of $ZnBr_2$ or Et_2AlCl to 1,3-dicarbonyl compounds derived from (*S*)-4-isopropyl-2-oxazolidinone, proceeds with high diastereoselectivity (94–98% de) and good chemical yields. This type of addition to chiral β-dicarbonyl substrates represents a new synthetic methodology leading to the formation of enantiomerically pure cyanohydrins.

1. Introduction

The cyanation reaction of carbonyl compounds is one of the most versatile procedures for the synthesis of cyanohydrins; a variety of nucleophilic cyanide reagents can already be employed.[1] The production of optically active cyanohydrins is of continuing interest to organic chemists due to the central role of these compounds in the enantioselective synthesis of several classes of valuable intermediates, including β-hydroxy-α-amino acids,[2] α-hydroxy-β-amino acids,[3] α-hydroxyketones,[4] β-hydroxy nitrones,[5] β-amino alcohols,[6] α-amino acids[7] and α-hydroxy acids.[8]

Among these methods, trimethylsilyl cyanide (TMSCN) and HCN are already widely used in innumerable additions to aldehydes,[9] imines (Strecker's reaction),[10] ketones[11] and nitrones.[12] However, in the absence of a catalyst, no reaction occurs between TMSCN and a carbonyl or imine compound; therefore, it is necessary to use several additives along with Lewis acids, both in catalytic and stoichiometric amounts to promote such additions.[13] On the other hand the highly diastereoselective reduction of α-methyl-β-keto amides has provided a useful alternative to asymmetric aldol reactions in organic synthesis.[14] However, to the best of our knowledge, the cyanation reaction of β-keto amides has not yet been described.

As part of our ongoing program directed towards the design of chiral β-substituted-γ-amino acids, we herein report the highly diastereoselective cyanation of β-keto amides with the Nagata's reagent. One of these cyanohydrins has been converted in a three-step procedure to (2*R*,3*R*)-4-acetylamino-2,3-dimethyl-3-hydroxybutyric acid **7**, as an example of a new γ-amino acid with a quaternary β-hydroxy-α,β-dimethylated substitution pattern.

2. Results and discussion

Initially, the reaction of propionimides **1** with lithium diisopropylamide (LDA) in THF at −78°C and the corresponding acid chlorides under previously described conditions,[14c] afforded the chiral β-keto amides **2a**–**g** with good yields and high diastereoselectivity (Table 1).

The addition reaction of Et_2AlCN to β-keto amides **2a**–**g** was carried out in dry toluene from −78 to 0°C, in either the absence or presence of Lewis acids, the results are shown in Table 2.

From the results summarized in Table 2, it can be seen that the reaction of **2a** and **2b** with Et_2AlCN in the absence of a Lewis acid, resulted only in the recovery of the starting material in the crude reaction (entries 1 and 2). The same result was also seen when the reaction of **2a** and **2b** was carried out in the presence of $ZnBr_2$

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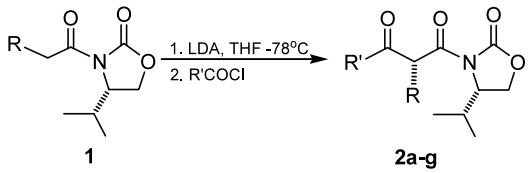
Table 1. Preparation of chiral β-keto amides **2a–g**



1 **2a-g**

Entry	**2**	R	R′	Yield (%)	De (%)[a]
1	**2a**	H	Me	22	–
2	**2b**	H	Ph	77	–
3	**2c**	Me	Me	75	98
4	**2d**	Me	Ph	79	96
5	**2e**	Me	*p*-Cl-Ph	88	98
6	**2f**	Me	*p*-MeO-Ph	71	98
7	**2g**	Me	*p*-Me-Ph	89	98

[a] Diastereomeric ration was measured by ^{1}H NMR at 400 MHz.

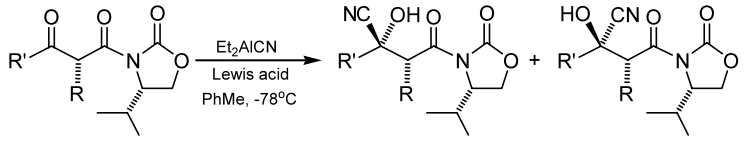
(entries 3 and 4). The lack of reactivity of these compounds can be attributed to the high stability of the enolic form generated.

However, the reaction of compound **2c** in the absence of a Lewis acid (entry 5) generated a mixture of **3c** and **4c** with a 50:50 ratio, whereas **2d**, under the same conditions (entry 6) provided **3d** and **4d** now with a diastereoselectivity of 80:20, in favor of the diastereomer **3d**.

The reaction of compounds **2c–d** with Et_2AlCN in the presence of $ZnBr_2$ (entries 7 and 8) or Et_2AlCl (entries 9 and 10) proceeded with high diastereoselectivity, with **3** as the major product. The high diastereoselectivity observed in **2c** and **2d** with either $ZnBr_2$ or Et_2AlCl can be attributed to the 1,3-dicarbonyl moiety of these compounds coordinating to the Lewis acid metals (Zn or Al) thus yielding a rigid chelate. Low temperature NMR studies have shown the ability of Et_2AlCl and $ZnBr_2$ to form six-membered ring chelates with oxazolidinone substrates.[15] Therefore, cyanide addition to the carbonyl group takes place from the side opposite to the α-methyl group, affording diastereomer **3** predominantly. The diastereomeric relation of **3** to **4** was determined by a 400 MHz ^{1}H NMR in the crude product by integration of some characteristic signals, eg. the α-methyl signal of **3c** and **4c** at 1.30 (d, $J=7.2$ Hz) and 1.42 (d, $J=7.2$ Hz), respectively. We also used the signal of the methyl groups bound to the quaternary centers at 1.58 and 1.70. For **3d** and **4d**, the diastereoselectivity relation was determined by the integration of the α-methyl signal at 1.06 (d, $J=6.8$ Hz) and 1.00 (d, $J=7.2$ Hz), respectively.

The use of other Lewis acids such as MgI_2 in the addition of Et_2AlCN was also evaluated (entries 11 and 12). However low yields and diastereoselectivities in the presence of MgI_2 were observed suggesting a weak chelate interaction between the Mg and the carbonyl oxygens or perhaps even the existence of an open transition state.[16] In the case of **2d**, (entry 12) although the chemical yield is lower, the magnitude of the diastereoselectivity observed is comparable to the case when the reaction was carried out in the absence of the Lewis acid (entry 6).

Table 2. Addition of Et_2AlCN to β-keto amides **2a–g**



2a-g **3a-g** **4a-g**

Entry	**2**	R	R′	Et_2AlCN (equiv.)	Lewis acid[a]	Yield (%)[c]	(**3**:**4**)[d]
1	**2a**	H	Me	2.0	–	[b]	–
2	**2b**	H	Ph	2.0	–	[b]	–
3	**2a**	H	Me	4.0	$ZnBr_2$	[b]	–
4	**2b**	H	Ph	4.0	$ZnBr_2$	[b]	–
5	**2c**	Me	Me	2.0	–	77	50:50
6	**2d**	Me	Ph	2.0	–	63	80:20
7	**2c**	Me	Me	4.0	$ZnBr_2$	77	94:6
8	**2d**	Me	Ph	4.0	$ZnBr_2$	82	98:2
9	**2c**	Me	Me	4.0	Et_2AlCl	77	94:6
10	**2d**	Me	Ph	4.0	Et_2AlCl	79	95:5
11	**2c**	Me	Me	4.0	MgI_2	33	80:20
12	**2d**	Me	Ph	4.0	MgI_2	23	78:22
13	**2e**	Me	*p*-Cl-C_6H_4	4.0	$ZnBr_2$	60	98:2
14	**2f**	Me	*p*-MeO-C_6H_4	8.0	$ZnBr_2$	27	98:2
15	**2g**	Me	*p*-Me-C_6H_4	8.0	$ZnBr_2$	65	98:2

[a] 1.2 equiv.
[b] The reaction did not proceed.
[c] Yield of major diastereomer.
[d] Determined by ^{1}H NMR at 400 MHz.

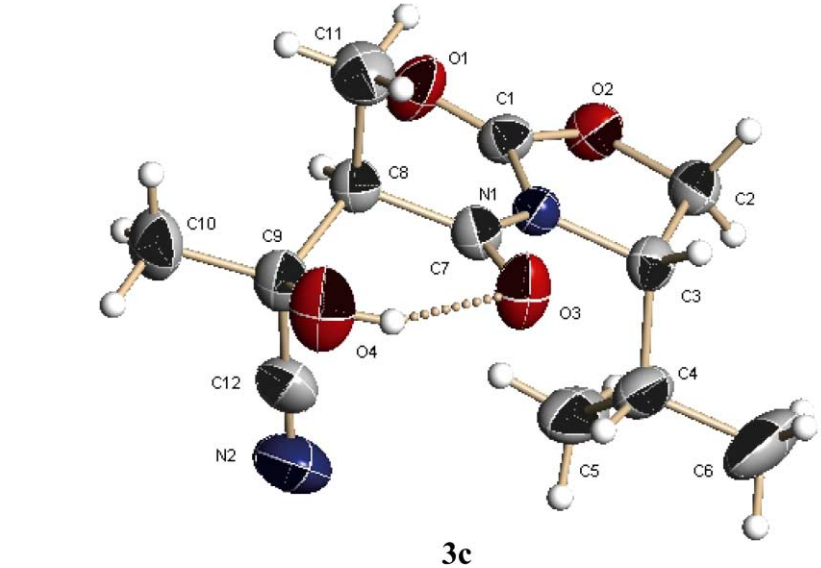
In order to investigate whether a stereoelectronic effect is operating in the addition reaction of Et_2AlCN, the β-keto amides **2e–g** substituted in the *para* position of the phenyl ring with chloro, methoxy and methyl groups were subjected to the addition of Et_2AlCN under the same reaction conditions. When compound **2e** (*p*-Cl) was treated with 4.0 equiv. of Et_2AlCN in the presence of $ZnBr_2$, a highly diastereoselective addition of CN^- to the carbonyl group was observed (entry 13) with only **3e** being detected by NMR.

In all the other cases, the presence of an electron-donating group (MeO and Me) on the aromatic ring, decreases the reactivity of the carbonyl group meaning that an excess of the Et_2AlCN reagent (8.0 equiv.) must be used in order to achieve some conversion of **2f** and **2g** (entries 14 and 15) to the corresponding cyanohydrins. However, under these conditions, using an excess of Nagata's reagent also induces the epimerization of the remaining starting material or the resulting cyanohydrin. In both cases, only **3f** and **3g** were detected by ^1H NMR.

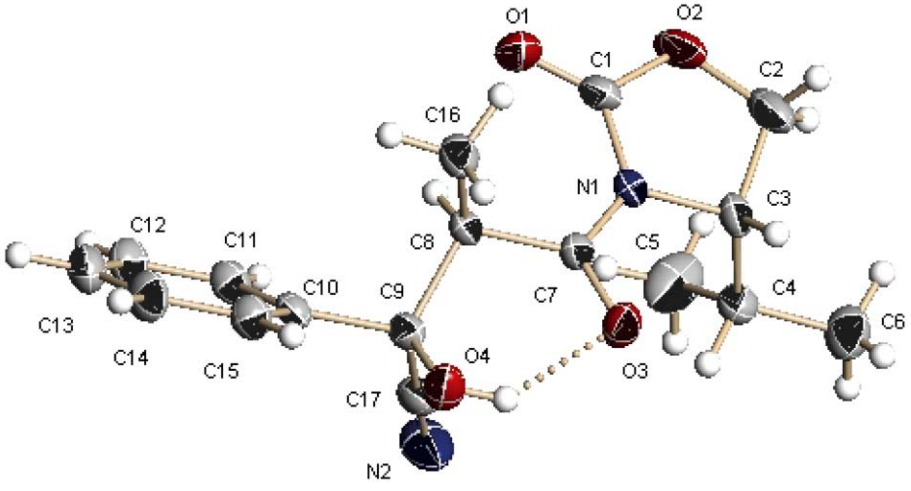
The configuration at the carbinol center for the cyanohydrins **3c** and **3d** was assigned by X-ray diffraction studies (Fig. 1).[17] On the basis of these, we assumed the same stereochemistry for all the cyanohydrins derived from the aromatic substrates.

In order to illustrate the usefulness of this method, compound **3c** was converted in a three-step procedure to the γ-amino acid **7** (Scheme 1). The reduction of the cyano group on **3c** was carried out by hydrogenolysis using Raney Ni in acetic anhydride at room temperature and atmospheric pressure, affording the *N*-acetyl derivative **5** in 95% yield.

Although we attempted to remove the chiral auxiliary directly from compound **5** to obtain the γ-amino acid **7** using the well established lithium peroxide protocol

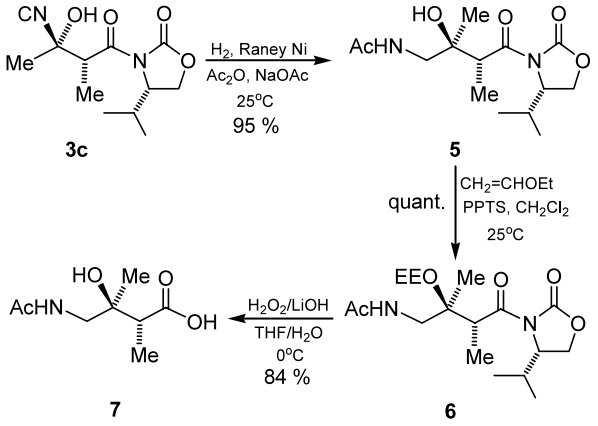


3c



3d

Figure 1. X-Ray crystal structure of **3c** and **3d**.



Scheme 1.

developed by Evans,[18] we observed under these basic conditions the decomposition of **5** by a retro aldol pathway, a process favoured by the presence of the tertiary OH group. In order to circumvent this problem, we therefore considered protection of the OH group under acid conditions. We introduced the 1-ethoxyethyl ether (EE) group in the presence of pyridinium *p*-toluensulfonate (PPTS), conditions that led to the formation of **6** in quantitative yield, which without further purification, was treated with lithium peroxide in aqueous THF, affording the γ-amino acid **7** in 84% yield, and 77% yield of the recovered chiral auxiliary.

In summary, we have demonstrated that diethylaluminum cyanide (Nagata's reagent) acts as an outstanding cyanating agent able to react with chiral β-keto amides to afford the corresponding cyanohydrins in good yield and high diastereoselectivity, which can be used in the synthesis of several other compounds of interest.

3. Experimental

The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of dry N_2. Solvents were purified and dried according to standard procedures. Flash chromatography was performed with silica gel 60 (230–400 mesh). Silica gel F_{254} plates were used for TLC monitoring. Melting points were determined in a Büchi B-540 apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer model 241 polarimeter (concentration in g/100 mL). Microanalyses were registered on a Elemental VARIO EL III. IR spectra were recorded on a Brucker vector 22 FT-IR. NMR spectra were recorded on an Inova Varian at 400 and 200 MHz for ^{1}H and 100 and 50 MHz for ^{13}C. The *J* values are given in Hertz.

3.1. Preparation of β-keto amides 2a–g

Compounds **1** and **2a–g** were synthesized and purified according to the protocol described by Evans et al.[14c]

3.1.1. (2*R*)-3-[2-Methyl-1,3-dioxo-3-(*p*-chlorophenyl)-propyl]-(*S*)-4-isopropyl-2-oxazolidinone 2e. To a cooled (−78°C) solution of diisopropylamine (0.54 mL, 3.89 mmol) in dry THF (15 mL) was added *n*-butyllithium (3.46 mL of a 1.17 M solution in hexane, 4.1 mmol). The mixture was stirred at −78°C for 30 min after which a solution of **1** (0.60 g, 3.28 mmol) in dry THF (10 mL) was added. The resulting solution was stirred for 45 min at −78°C and a solution of 4-chloro–benzoylchloride (0.82 mL, 6.5 mmol) in dry THF (25 mL) added dropwise via cannula. After being stirred at −78°C for 1.5 h, the reaction mixture was allowed to reach −10°C and quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane:ethyl acetate (85:15) as the eluent to give **2e** as a white solid 0.93 g, 88% yield. Mp: 89–90°C. $[\alpha]_D^{25}=-84.6$ (*c* 2.89, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (AA′BB′, $J=8.8$, 2H), 7.46 (AA′BB′, $J=8.8$, 2H), 5.28 (q, $J=7.2$, 1H), 4.51 (dt, $J=8.4$, 3.5, 1H), 4.30 (dd, $J=9.2$, 1H), 4.24 (dd, $J=9.2$, 3.2, 1H), 2.49–2.57 (m, 1H), 1.43 (d, $J=7.2$, 3H), 0.95 (d, $J=7.0$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 170.1, 154.4, 139.8, 134.1, 130.2, 129.2, 63.9, 58.9, 48.7, 28.6, 18.0, 14.8, 13.6. IR cm^{-1}: 2969.7, 1776.8, 1712.8, 1683.1, 1630.6. Anal. calcd for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.60; N, 4.33. Found: C, 60.10; H, 5.79; N, 4.39%.

3.1.2. (2*R*)-3-[2-Methyl-1,3-dioxo-3-(*p*-methoxyphenyl)-propyl]-(*S*)-4-isopropyl-2-oxazolidinone 2f. The reaction was carried out starting from **1** (0.50 g, 2.70 mmol) following the procedure described for the preparation of **2e**. The crude product was purified by column chromatography using hexane:ethyl acetate (80:20) as the eluent to give **2f** as a white solid 0.62 g, 71% yield. Mp: 97.7–99.9°C. $[\alpha]_D^{25}=-91.0$ (*c* 5.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (AA′BB′, $J=8.8$, 2H), 6.95 (AA′BB′, $J=8.8$, 2H), 5.33 (q, $J=7.2$, 1H), 4.50 (dt, $J=8.4$, 3.5, 1H), 4.29 (dd, $J=9.2$, 1H), 4.23 (dd, $J=9.2$, 3.0, 1H), 3.86 (s, 3H), 2.49–2.57 (m, 1H), 1.44 (d, $J=7.2$, 3H), 0.95 (d, $J=6.8$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 170.7, 163.8, 154.3, 131.1, 128.6, 114.1, 63.8, 58.8, 55.6, 48.4, 28.6, 18.0, 14.8, 13.9. IR cm^{-1}: 2967.0, 1777.2, 1709.5, 1671.6, 1601.3. Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.83; N, 4.31%.

3.1.3. (2*R*)-3-[2-Methyl-1,3-dioxo-3-(*p*-methylphenyl)-propyl]-(*S*)-4-isopropyl-2-oxazolidinone 2g. The reaction was carried out starting from **1** (0.35 g, 1.89 mmol) following the procedure for the preparation of **2e**. The crude product was purified by column chromatography using hexane:ethyl acetate (70:30) as the eluent to give **2g** as a white solid 0.51 g, 89% yield. Mp: 114–114.5°C. $[\alpha]_D^{25}=-89.2$ (*c* 2.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (AA′BB′, $J=8.4$, 2H), 7.27 (AA′BB′, $J=8.4$, 2H), 5.34 (q, $J=7.2$, 1H), 4.50 (dt, $J=8.4$, 3.5, 1H), 4.29 (dd, $J=9.2$, 1H), 4.23 (dd, $J=9.2$, 3.2, 1H), 2.49–2.57 (m, 1H), 2.41 (s, 3H), 1.44

(d, $J=7.2$, 3H), 0.95 (d, $J=7.2$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 170.7, 154.4, 144.1, 133.2, 129.6, 129.0, 63.9, 58.9, 48.7, 28.6, 21.8, 18.1, 14.9, 13.9. IR cm^{-1}: 2968.0, 1777.2, 1711.2, 1677.0, 1615.9. Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.56; H, 7.26; N, 4.61%.

3.2. General procedures for the addition of Et_2AlCN. Preparation of cyanohydrins 3c–g

3.2.1. Method A. To a stirred solution of 2.0 equiv. of a Et_2AlCN (1.0 M in toluene) in dry toluene at −78°C, was added dropwise 1.0 equiv. of a 0.1 M solution of β-keto amides **2a**–**g** in anhydrous toluene. The reaction was stirred at −78°C for 6 h, allowed to rise to −40°C and maintained at this temperature for 5 min. After this period of time, the reaction mixture was quenched by the addition of a mixture of 6 mL of methanol and 4 mL of concentrated HCl. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **3c**–**g** as oils. The crude cyanohydrins were analysed by 400 MHz ^{1}H and ^{13}C NMR.

3.2.2. Method B. A 0.1 M solution of 1.0 equiv. of β-keto amide **2a**–**g** and 1.2 equiv. of the corresponding Lewis acid ($ZnBr_2$, Et_2AlCl or MgI_2) in dry toluene under N_2 atmosphere was stirred for 1 h at room temperature. In a separate flask, a solution containing 4.0 equiv. of Et_2AlCN (1.0 M in toluene) was cooled to −78°C. The first solution was transferred to the Et_2AlCN solution. The reaction mixture was stirred at −78°C for 6 h, allowed to rise to −40°C and maintained at this temperature for 5 min. The reaction was then quenched by the addition of a mixture of 6 mL of methanol and 4 mL of concentrated HCl. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **3c**–**g** as oils. The crude cyanohydrins were analysed by 400 MHz ^{1}H and ^{13}C NMR.

3.2.3. (2*R*,3*S*)-3-[2-Methyl-3-cyano-3-hydroxy-1-oxobutyl]-(*S*)-4-isopropyl-2-oxazolidinone 3c. Obtained from **2c** (0.50 g, 2.20 mmol) following the method B with $ZnBr_2$ as the Lewis acid, and purified by trituration of the crude oil with a 90:10 mixture of hexane and isopropyl alcohol to give **3c** as a white solid 0.433 g 77% yield. Mp: 106–109°C. $[\alpha]_D^{25}=+62.5$ (c 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (s, 1H), 4.49 (dt, $J=8.4$, 3.6, 1H), 4.34 (dd, $J=9.2$, 1H), 4.29 (dd, $J=9.2$, 3.2, 1H), 4.20 (q, $J=7.0$, 1H), 2.43–2.50 (m, 1H), 1.58 (s, 3H), 1.30 (d, $J=7.2$, 3H), 0.95 (d, $J=7.0$, 3H), 0.94 (d, $J=7.0$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 153.8, 121.9, 69.3, 63.8, 59.1, 45.1, 28.7, 24.0, 18.1, 14.8, 11.3. IR cm^{-1}: 3438.8, 2965.6, 2359.6, 1778.9, 1698.1, 1387.8. Anal. calcd for $C_{12}H_{18}N_2O_4$:C, 56.68; H, 7.13; N, 11.02. Found: C, 56.68; H, 7.16; N, 11.23%.

3.2.4. (2*R*,3*R*)-3-[2-Methyl-3-cyano-3-hydroxy-1-oxo-3-phenylpropyl]-(*S*)-4-isopropyl-2-oxazolidinone 3d. Obtained from **2d** (0.445 g, 1.54 mmol) following the method B with $ZnBr_2$ as the Lewis acid, and purified by trituration of the crude oil with a 90:10 mixture of hexane and isopropyl alcohol to give **3d** as a white solid 0.40 g, 82% yield. Mp: 160–163°C. $[\alpha]_D^{25}=+35.5$ (c 2.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.61 (m, 2H), 7.36–7.45 (m, 3H), 5.46 (s, 1H), 4.52 (q, $J=7.0$, 1H), 4.51 (dd, $J=8.0$, 3.6, 1H), 4.33 (dd, $J=9.2$, 1H), 2.29 (dd, $J=9.2$, 3.6, 1H), 2.45–2.52 (m, 1H), 1.06 (d, $J=6.8$, 3H), 0.96 (d, $J=7.0$, 3H), 0.94 (d, $J=7.0$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 153.4, 136.6, 129.3, 128.9, 125.9, 121.3, 73.8, 63.7, 59.0, 47.1, 28.6, 18.1, 14.7, 11.3. IR cm^{-1}: 3411.3, 2966.7, 1781.6, 1673.2, 1377.6. Anal. calcd for $C_{17}H_{20}N_2O_4$, 64.54, H, 6.37, N, 8.86. Found: C, 64.52, H, 6.43, N, 8.93%.

3.2.5. (2*R*,3*R*)-3-[2-Methyl-3-cyano-3-hydroxy-1-oxo-3-(*p*-chlorophenylpropyl]-(*S*)-4-isopropyl-2-oxazolidinone 3e. The product was not isolated in a sufficiently pure form for either elemental analysis or for determining the specific rotation.

3.2.6. (2*R*,3*R*)-3-[2-Methyl-3-cyano-3-hydroxy-1-oxo-3-(*p*-methoxyphenylpropyl]-(*S*)-4-isopropyl-2-oxazolidinone 3f. The product was not isolated in a sufficiently pure form for either elemental analysis or for determining the specific rotation.

3.2.7. (2*R*,3*R*)-3-[2-Methyl-3-cyano-3-hydroxy-1-oxo-3-(*p*-methylphenylpropyl]-(*S*)-4-isopropyl-2-oxazolidinone 3g. The product was not isolated in a sufficiently pure form for either elemental analysis or for determining the specific rotation.

3.2.8. (2*R*,3*S*)-3-[4-*N*-Acetylamino-2,3-dimethyl-3-hydroxy-1-oxobutyl]-(*S*)-4-isopropyl-2-oxazolidinone. The catalyst for this reaction (Raney Ni) was washed with absolute ethanol (2×1 mL) and acetic anhydride (2×1 mL). A solution of **3c** (100 mg, 0.39 mmol), Raney Ni 0.12 mg, Ac_2O (0.5 mL) and NaOAc (0.59 mmol) was stirred for 48 h under hydrogen gas at room temperature. The mixture was filtered through a sintered glass filter and the precipitate successively washed with ethyl acetate (5.0 mL) and H_2O (5.0 mL). The filtrate was placed in a separatory funnel and the organic layer separated. The aqueous layer was further extracted with ethyl acetate (2×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure affording **5** as a colorless oil (95%). $[\alpha]_D^{25}=+19.7$ (c 3.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 4.44–4.47 (m, 1H), 4.30 (dd, $J=9.2$, 1H), 4.25 (dd, $J=9.2$, 2.8, 1H), 4.00 (q, $J=7.0$, 1H), 3.40 (dd, $J=14.0$, 6.4, 1H), 3.30 (dd, $J=14.0$, 5.4, 1H), 2.35–2.43 (m, 1H), 2.05 (s, 3H), 1.20 (d, $J=7.2$, 3H), 1.17 (s, 3H), 0.93 (d, $J=7.2$, 3H), 0.90 (d, $J=7.2$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 171.3, 155.2, 75.0, 63.8, 59.5, 48.5, 42.6, 28.9, 23.2, 20.6, 18.1, 14.9, 13.3. IR cm^{-1}: 3388.3, 2968.8, 1775.8, 1696, 1550.8, 1379.9. MS (EI): m/z 228 (45), 210 (5), 130 (95), 111 (22), 97 (18), 86 (47), 73 (76),

57 (100), 43 (65). Anal. calcd for $C_{14}H_{24}N_2O_4$ C, 55.98, H, 8.05, N, 9.32. Found: C, 55.88, H, 7.9, N, 9.15%.

3.2.9. (2*R*,3*S*)-4-Acetylamino-2,3-dimethyl-3-hydroxybutyric acid 7. A 0.05 M solution of substrate **5**, 0.22 g (0.73 mmol) in dry dichloromethane under nitrogen atmosphere was treated at 0°C with ethyl vinyl ether (2.0 equiv) followed by a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The resulting mixture was then stirred for 6 h at 0°C. The solvent was evaporated and the residue dissolved in ethyl acetate (10.0 mL), washed with saturated aqueous $NaHCO_3$ (5.0 mL) and brine (5.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure affording **6** as a yellow oil in a quantitative yield. Without any isolation, the oil dissolved in a mixture of THF/H_2O (3:1) to obtain a 0.05 M solution of substrate **6**, which was treated at 0°C with 4.0 equiv. of 30% H_2O_2 followed by 2.0 equiv. of LiOH. The resulting mixture was stirred for 9 h at 0°C and quenched with 10% aqueous HCl until reaching pH 2 and then extracted with dichloromethane (3×5.0 mL). The aqueous layer was evaporated under reduced pressure to afford 93 mg, 84% yield of the amino acid **7**, as a highly hygroscopic white solid. ^{1}H NMR (400 MHz, D_2O): δ 3.48 (AB, $J=11.0$, 2H), 3.30 (AB, $J=11.0$, 2H), 2.51 (q, $J=7.2$, 1H), 2.03 (s, 3H), 1.4 (s, 3H), 1.05 (d, $J=7.2$, 3H). ^{13}C NMR (100 MHz, D_2O): δ 183.5, 176.5, 78.8, 66.6, 49.6, 26.2, 14.6, 9.0. IR cm^{-1}: 3444.8, 1737.1. MS (EI): m/z (M^+-H_2O) = 171 (11), 130 (55), 116 (11), 112 (22), 98 (28), 86 (100), 72 (58), 57 (67), 43 (85). The product was not isolated in a sufficiently pure form for either elemental analysis or for determining the specific rotation.

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