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# Preparation of α-Amino Acids by Oxidative Oxazoline–Oxazinone Rearrangement–Hydrogenation (OOOH). Scope and Limitations

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*Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday*

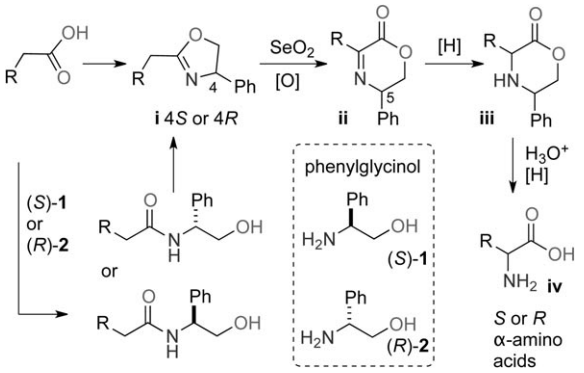
**Abstract:** The range and scope of the oxidative oxazoline–oxazinone rearrangement–hydrogenation sequence (OOOH)—a short, direct asymmetric synthesis of α-amino acids from carboxylic acids—was explored. The highest yet reported diastereoselectivity for hydrogenation of the oxazinone C=N bond (d.r. = > 80:1) is disclosed and rationalized with the aid of ab initio molecular calculations.

**Keywords:** amino acids · asymmetric synthesis · hydrogination · natural products · oxazolines

The oxidative oxazoline–oxazinone rearrangement–hydrogenation sequence (OOOH)[1] constitutes a short preparation of α-amino acids directly from carboxylic acids (Scheme 1): 1) conversion into the corresponding optically pure 4-phenyloxazoline **i** with (*S*) or (*R*)-phenylglycinol (*S*)-**1** or (*R*)-**2**, 2) $SeO_2$-promoted oxidation to the 3-substituted 5-phenyl-5,6-2*H*-1,4-dihydrooxazin-2-one **ii** (henceforth referred to as "oxazinone"), and 3) hydrogenation to morpholin-2-one **iii** and hydrogenolysis of the chiral auxiliary to give the corresponding α-amino acid **iv**.

Williams and Dellaria first reported use of 5-phenyl- and 5,6-diphenylmorpholin-2-ones (c.f. Scheme 1, **iii**) as nucleophilic chiral glycine equivalents for the synthesis of **iv**,[2] and Harwood and co-workers have described the hydrogenation–hydrogenolysis of electrophilic **ii** (R = alkyl) to **iv**.[3]

Oxazolines are readily obtained from alkanoic acids; thus, OOOH constitutes a direct functionalization of the latter into α-amino acids with high enantioselectivity. The OOOH sequence is particularly efficient and highly diastereoselective (up to 70:1[1,3,5]) for the preparation of β,β-disubstituted




Scheme 1. Synthesis of α-amino acids through the oxidative oxazoline-oxazinone-hydrogenation (OOOH) sequence.

α-amino acids that are not accessible by complementary methods for α-alkylation of nucleophilic chiral glycine equivalents,[2] or asymmetric alkylation of benzophenone imine-glycinates under phase-transfer conditions using cinchona-alkaloid-derived catalysts.[4] For example, we have exploited this sequence in the diastereoselective synthesis of the bulky side-chain amino acids (*S*)-*tert*-leucine (**3a**),[1a] (*S*)-*tert*-amylglycine (**3b**),[1c] and the highly cytotoxic marine-derived peptides milnamides A (**4**) and D (**5**),[5] which both contain a β-carboline-amino-acid residue derived from "tetramethyltryptophan" (**6**; Scheme 2).[6] Compound **6** is also found in the related peptides hemiasterlin (**7**)[7] and hemiasterlins A, B,[8a,b] and C.[8c] Hemiasterlins are potent antimitotic agents;[9] the synthetic analog HTI-286 (**8**)[9] was advanced as an anticancer investigational drug in open-label Phase I trials.[10] Finally, OOOH has been shown to be of

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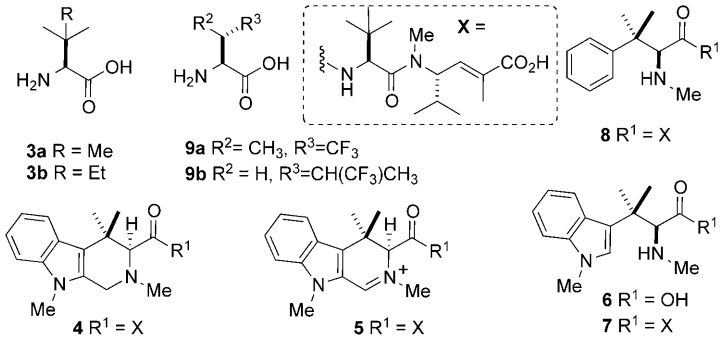


Scheme 2. *N,N′*-β,β-Tetramethyltryptophan peptides milnamides A (**1**), D (**2**), hemiasterlin (**3**) and branched fluorinated α-amino acids.

practical use in the preparation of homologous amino acids trifluoroleucine (**9a**) and trifluorovaline (**9b**),[1e] which find use in preparation of fluorinated proteins for $^1$H NMR spectroscopic structural biology studies.[11]

The tolerance of substituted oxazolines towards $SeO_2$ has only been briefly addressed.[1a–c] For example, primary 2-alkyloxazolines lacking β-substituents gave poor yields of oxazinones with $SeO_2$ (2-ethyl, <20%), but 2-benzyl- and 2-naphthylmethyl-oxazolines were efficiently converted (>90%) into their ring-expanded oxazinones.[1a,b] In order to more-fully investigate the scope and limitations of OOOH, we prepared a series of oxazolines **10** from their corresponding carboxamides **9** and carried out their oxidation with $SeO_2$ followed by two-step hydrogenolysis–hydrogenation reactions to afford the corresponding (*S*) or (*R*)-amino acids (Table 1). Arenylmethyl-substituted oxazolines, some containing C–H bonds that were potentially susceptible to benzylic hydroxylation, were chosen to test their compatibility with $SeO_2$. In addition, the first asymmetric syntheses of (*S*)- and (*R*)-*N*,β,β-trimethyltryptophan from the known *N*-methylindolyl-1-methylethyl-oxazolines[5] were achieved. Herein, we report that the OOOH sequence is broad in scope for the synthesis of β-branched α-amino acids with diastereoselectivities (up to d.r.>80:1) superior to those reported to date.[1,3,5] Semi-empirical calculations support a conformational model for the exceptionally high diastereoselective of the hydrogenation of α-(1-aryl-1-methylethyl) oxazinones.

## Results and Discussion

Methods have been described for one-step preparation of oxazolines from carboxylic acids,[12a] carboxylic esters[12b] or nitriles[12c–f] by Lewis-acid-catalyzed condensation with 1,2-aminoalkanols; however, the yields can be variable and often dependent on the structure of the carboxylic acids and aminoalkanols.

For uniformity, oxazolines **10a-e** used in this study, were prepared using the same two-step method previously used for **10f,g**.[5] Condensation of carboxylic acid chlorides with either (*S*)-**1** or (*R*)-**2** gave the corresponding carboxamides

Table 1. Preparation of oxazolines **10** from carboxamides **9**.

| Entry | Amide **9**[a] | Yield [%] | Oxazoline **10**[c] | Yield [%] |
|---|---|---|---|---|
| 1 | **9a** R = Et | 92 | **10a** | 95 |
| 2 | **9b** R = Ph | 89 | **10b** | 89 |
| 3 | (2′*S*,3*S*)-**9c**[b] | 80[b] | **10c** | 85 |
| 4 | **9d** | 86 | **10d** | 73 |
| 5 | **9e**[d] | 82 | **10e**[e] | 88 |

Reaction conditions: [a] $SOCl_2$ (5–10 equiv), benzene or $CHCl_3$, reflux. [b] prepared from (±)-3-phenylbutanoic acid, followed by chromatographic separation of diastereoisomeric amides. Yield based on 50% of carboxylic acid. C3 configuration was assigned by measurement of $[\alpha]_D$ of (+)-(*S*)-3-phenylbutanoic acid obtained by hydrolysis of faster-eluting (3*S*,1′*S*)-**9c** (see the Supporting Information). [c] Diethylaminosulfur trifluoride (DAST), −78°C, $CH_2Cl_2$.[13] [d] Prepared in two steps: 1) 3,3-dimethylglutaric anhydride, 1.2 equiv, toluene, RT to 60°C, 99%; 2) $CH_2N_2$ (excess), $Et_2O$. [e] prepared according to the procedure reported by Langlois et al., $POCl_3$, toluene, RT, see Ref. [15].

**9a–e** which were cyclo-dehydrated in the presence of DAST[13] to give oxazolines **10a–e** in good to excellent yields (73–95%, Table 1). Oxazolines **10a–e** were subjected to oxidation with $SeO_2$ under previously published conditions[15] to give the rearranged products, oxazinones **11a–e**, in very good yields (68–79%, Table 2). As noted before, the highest yields (Table 2, entry 6; also see previous work[5]) were obtained with oxazolines with *gem*-substituents at the β-position. Evidently, 2-arenyl and 2-arenylalkyl-substituted oxazolines are tolerant of the $SeO_2$-oxidation conditions (Table 2, entries 2–5 and 7).

Hydrogenation of the imine double-bond in **11a–e** proceeded in uniformly excellent yields, prevailing in the *cis*-substituted morpholinones **12a–e** (assigned by NOESY) in diastereomeric ratios in the range 8.7:1 to >80:1 (Table 2, entries 2, 4, and 6), favoring addition of $H_2$ *anti* to the C-5 phenyl group. Finally, morpholinones **12a–e** were subjected to hydrogenolysis under modified conditions[5] from those reported by Cox and Harwood[3a] to give the corresponding α-amino acids **13** in good to excellent yields (56–92%) after purification by ion-exchange column chromatography (AG-50W, $H^+$ form; elution with aqueous $NH_4OH$). In the case of **9d**, the acetoxy group was hydrolyzed under the reaction conditions to (*R*)-*para*-hydroxyphenylglycine (**13d**). The poor yield observed for hydrogenation of the glutaric-acid-derived morpholinone **12e** (20%; Table 2, entry 6) possibly

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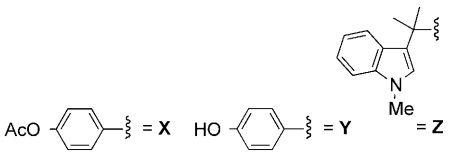
Table 2. $SeO_2$-promoted oxidation of oxazolines, diastereoselective hydrogenation to morpholinones **12** and hydrogenolysis to α-amino acids **13.**

| Entry | Oxazoline **10** | Oxazinone **11**[a] | Yield [%] | Morpholinone **12**[b] | Yield [%] | d.r. | α-Amino acid **13**[c] | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | **10a** R = Et | **11a** | 60 | **12a** | 90 | 8.7:1 | 2(*S*)-**13a** | 56 |
| 2 | **10b** R = Ph | **11b** | 72 | **12b** | 87 | >80:1 | 2(*S*)-**13b** | 84 |
| 3 | **10c** | **11c** | 79 | **12c** | 79 | 9:1 | 2(*R*)-**13c** | 92 |
| 4 | **10d** R = X | **11d** | 68 | **12d** | 85 | >80:1 | 2(*R*),3(*S*)-**13d** | 65 |
| 5 | **10g** R = Z | **11g** | –[d] | **12g** | 90 | 72:1[d,e] | 2(*R*)-**13g**[d] | – |
| 6 | **10e** | **11e** | 68 | **12e**[c] | 20 | >80:1 | – | – |
| 7 | **10f** R = Z | **11f** | 90[d] | **12f** | 98 | –[d,e] | 2(*S*)-**13f**[d] | 84 |

Reaction conditions: [a] $SeO_2$ (2.5 equiv), oxazoline (ca. 0.15 mmol), EtOAc or $CHCl_3$, reflux, 4 h. [c] $H_2$ (4 atm), $PtO_2$ (15 mol%), EtOAc or MeOH, 22–52 h. [c] Modified hydrogenolysis based on conditions reported by Harwood and co-workers, Ref. [3b]; $Pd(OH)_2/C$, $H_2$, 4 atm, 40:2.5:0.47 MeOH/$H_2O$/TFA, RT. [d] Ref. [5]. [e] MeOH used as solvent.




arises from side-reactions involving cyclization of the terminal carboxymethoxy group to the γ-lactam. (*S*)-*tert*-Amylglycine (**13a**; Table 2, entry 1) was obtained in comparable yield (50%, two steps from 5(*R*)-oxazinone **11a**) to that previously reported (56%)[1d] for the diastereoselective nucleophilic addition of tributyl(dimethylallyl)stannane to the corresponding parent 5(*S*)-oxazinone (**11d**, R = H) followed by hydrogenolysis. Finally, we noted that OOOH provides the first asymmetric synthesis of (*S*)-**13b**,[14] a valuable amino acid for the synthesis of the investigational anticancer drug HTI-286,[10] in good overall yield from 3,3-dimethyl-3-phenylpropanoic acid[16] (39%, five steps; Table 2, entry 2) with essentially complete stereocontrol.

The exceptionally high diastereoselectivities (d.r. > 80:1) observed in the hydrogenation of β-aryl-α,α-dimethyl-oxazinones (e.g. **11b,f,g**, d.r. > 80:1) compared to *tert*-alkyl oxazinones (e.g. **11a** d.r. 8.7:1) was unexpected. In order to better understand the origin of these unusually high diastereoselectivities we calculated the lowest-energy conformations of **11b** by DFT methods (B3LYP-6-31G(D), Spartan) and derived their conformational distributions (Figure 1). Only two conformers, **I** and **II**, were found, differing in energy by approximately 8.0 kcal mol$^{-1}$. In each, the oxazinone ring adopts a half-chair conformation with the C-5 phenyl group in a quasi-equatorial orientation. As suggested by Cox and Harwood,[3a] it is likely the C-3 *tert*-substituent plays the role of a "conformational lock"[3a] of the oxazinone ring during hydrogenation; however a significant conformational bias exists between rotamers about the C3–αC bond. The most-stable rotamer(**I**) places the less-bulky (smaller *A* value) β-phenyl group on the face of the C=N bond, *anti* to the C-5 phenyl group. This would favor approach to the catalyst and addition of $H_2$ from the face opposite to the C-5 phenyl group, consistent with the observed stereochemical outcome. Simultaneously, the larger *gem*-dimethyl groups are forced onto the other face, blocking the approach to the catalyst

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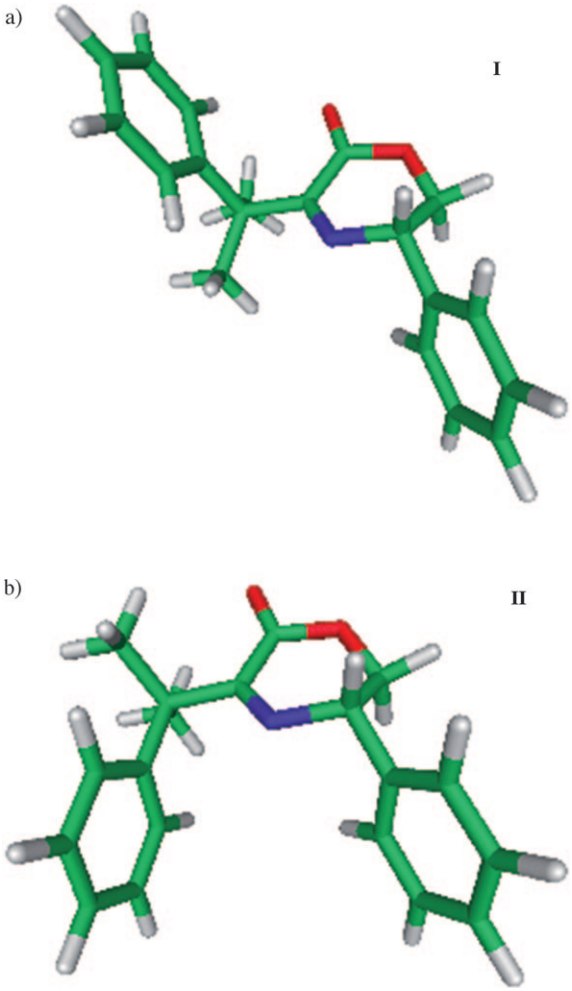


Figure 1. Minimized structures of **11b** (B3LYP 6-31G(D), Spartan), relative energies ($E°$) and Boltzmann populations (%). (a) **i**, $E°$ = 0 kcal mol$^{-1}$(96.3%). (b) **ii**, $E°$ = 8.06 kcal (3.7%).

and reinforcing the directing effect of the C-5 phenyl group. Similar conformational preferences of $CH_2COOMe$ and indol-3-yl groups—specifically, differential rotameric preferences for *gem*-dimethyl and sp$^2$ groups—led to comparable d.r. values for the hydrogenation of **11e–g** (d.r. > 80:1), much higher than those of **11a** (d.r. = 8.7) and other 2-*tert*-alkyloxazinones (d.r. = 13:1).[1a,d] The effect was diminished in the hydrogenation of **11c** (d.r. = 9:1) where the 1-phenylethyl substituent is secondary, but recovered in **11d** (d.r. > 80:1) where the all-sp$^2$, conjugated substituent and planarity of the C2–C3(=N) *para*-hydroxyphenyl array exposes the singular influence of the C-5 phenyl directing effect.[17]

In summary, an evaluation of the scope of the oxidative oxazoline–oxazinone hydrogenation (OOOH) sequence, exploiting 5-phenyl-substitued oxazinones **11** as electrophilic glycine equivalents, was carried out. The sequence was generally applicable, returning morpholinones **12** and their corresponding amino acids **13** with exceptionally high diastereoselectivities. The OOOH sequence affords a practical route to α-amino acids that are otherwise difficult to obtain by methods involving asymmetric synthesis or catalysis with chiral nucleophilic glycine equivalents. Molecular calculations reveal a possible origin of the unusually large d.r. values observed in the hydrogenation of certain oxazinones.

## Experimental Section

For complete procedures, details of sample preparation, and spectroscopic characterization ($^1$H and $^{13}$C NMR spectra) of **11a,c–e** **12a,c–e**, **13a,c,d,f,g** see the Supporting Information.

*General Procedure for Carboxamide Preparation*

Carboxylic acid was heated at reflux in a solution of $SOCl_2$ (5–10 equivalents) in benzene or $CHCl_3$, depending on solubility, for about 3 h. Solvent and excess $SOCl_2$ were removed under vacuum and the acyl chloride residue was dissolved in dry $CH_2Cl_2$ (to a concentration of 0.1–0.2 M) prior to the next step. Freshly prepared acyl chloride in dry $CH_2Cl_2$ was added slowly to a solution of one equivalent of phenylglycinol [(*S*)-**1** or (*R*)-(**2**)] in dry $CH_2Cl_2$ (ca. 0.1 M) at 0°, and the reaction mixture allowed to warm to RT Following work-up, the crude product was purified by flash chromatography (silica) to obtain the desired carboxamide **9**.

*N-((R)-2-Hydroxy-1-phenylethyl)-3-methyl-3-phenylbutanamide (**9b**)*

Colorless solid (89%); m.p.: 98–99°C; $[\alpha]_D^{23} = -32.6$ ($c$ = 2.78 g.100 mL$^{-1}$,$CHCl_3$); IR: $\tilde{\nu}$ = 3318(br s), 3029, 2964, 1644, 1538 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.41 (s, 3H), 1.45 (s, 3H), 2.52 (s, 2H), 3.01 (s, OH), 3.50 (d, $J$ = 4.4 Hz, 2H), 4.79–4.82 (m, 1H), 5.68 (d, $J$ = 4.8 Hz, 1H), 6.86–6.91 (m, 2H), 7.20–7.24 (m, 4H), 7.29–7.39 ppm (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 29.2 ($CH_3$), 29.3 ($CH_3$), 37.9 (C), 51.6 ($CH_2$), 55.9 (CH), 66.5 ($CH_2$), 126.0 (2xCH), 126.5 (CH), 126.8 (2xCH), 127.8 (CH), 128.8 (2xCH), 128.9 (2xCH), 139.1 (C), 148.1 (C), 171.9 ppm (C); HRMS: (DCI/$NH_3$) $m/z$ 298.1815 $[M+H]^+$, Calcd $C_{19}H_{24}NO_2$ 298.1807.

*(R)-4,5-Dihydro-2-(2-methyl-2-phenylpropyl)-4-phenyloxazole (**10b**)*

A solution of carboxamide **9b** (75 mg, 0.25 mmol) in dry $CH_2Cl_2$ (2.5 mL) was cooled to −78°C, then treated dropwise with DAST (36 μL, 0.28 mmol, 1.1 equiv).[13] After stirring at −78°C for 75 min, anhydrous potassium carbonate (52.3 mg, 0.38 mmol, 1.5 equiv) was added in one portion, and the mixture allowed to warm to RT over 4 h. Saturated aqueous $NaHCO_3$ (5 mL) was added in one portion with vigorous stirring, and the mixture partitioned against $CH_2Cl_2$ (3×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product (70.0 mg), which was purified by flash chromatography on silica gel (1:4 ethyl acetate/petroleum ether), to provide the desired oxazoline **10b** (61.9 mg, 89%) as an oil which slowly crystallized into a colorless solid. m.p.: 98–99°C; $[\alpha]_D^{23} = +11.3$ ($c$ = 7.91 g.100 mL$^{-1}$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.58 (s, 3H), 1.60 (s, 3H, $CH_3$), 2.76 (d, $J$ = 13.8 Hz, 1H), 2.86 (d, $J$ = 13.8 Hz, 1H), 3.88 (t, $J$ = 8.4 Hz, 1H), 4.47 (dd, $J$ = 8.4 and 10.2 Hz, 1H), 5.12 (dd, $J$ = 8.4 and 10.2 Hz, 1H), 6.99~7.02 (m, 2H), 7.26~7.52 ppm (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 29.2 ($CH_3$), 29.9 ($CH_3$), 38.0 (C), 42.8 ($CH_2$), 69.8 (CH), 74.7 ($CH_2$), 126.1 (2xCH), 126.3 (CH), 126.9 (2xCH), 127.6 (CH), 128.5(2xCH), 128.8 (2xCH), 142.7 (C), 148.4 (C), 167.1 ppm (C); IR (film): $\tilde{\nu}$ = 3060, 2964, 1658, 1602, 1496, 1446 cm$^{-1}$; GCMS (EI 70 eV): $m/z$ (%) 280 $[M+H]^+$ (100), 279 (54) $[M^+]$; HRMS (EI): $m/z$ calcd for $C_{19}H_{21}NO$: 279.1623 $[M^+]$; found: 279.1619.

*(R)-5,6-Dihydro-5-phenyl-3-(2-phenylpropan-2-yl)-1,4-oxazin-2-one (**11b**)*

Oxidative rearrangement of oxazoline **10a** was effected with $SeO_2$ (in refluxing EtOAc, 4.5 h) using the general procedure described above.[1e,5,18] The crude product was purified by preparative tlc (4:1 petroleum ether/ethyl acetate) to provide dihydrooxazinone **11b** as a white solid (72%). m.p. 130–133°C; $[\alpha]_D^{23} = -99.5$ ($c$ = 0.62 g.100 mL$^{-1}$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.67 (s, 3H), 1.78 (s, 3H), 4.12 (t, $J$ = 11.4 Hz, 1H), 4.51 (dd, $J$ = 4.5 and 11.4 Hz, 1H), 4.92 (dd, $J$ = 4.5 and 11.4 Hz,

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1H), 7.20~7.45 ppm (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=27.7 ($CH_3$), 28.2 ($CH_3$), 46.3 (C), 59.8 (CH), 71.3 ($CH_2$), 125.8 (2xCH), 126.7 (CH), 127.3 (2xCH), 128.5 (CH), 128.9 (2xCH), 129.2 (2xCH), 137.3 (C), 145.8 (C), 154.1 (C), 167.65 ppm (C); IR: $\tilde{\nu}$=3060, 2971, 1743, 1631 cm$^{-1}$; GCMS (EI 70 eV): *m*/*z* (%) 293 $[M]^+$ (36); HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NO_2$: 293.1416: $[M]^+$; found: 293.1409.

*General Procedure for the Hydrogenation of Oxazinones **11** to Morpholinones **12***

Hydrogenation of oxazinone **11** was carried out using a modification[5] of the conditions reported by Harwood et al.[3b] $PtO_2$ (15 mol%) was added to a solution of oxazinone **11** in MeOH or EtOAc. The reaction flask was purged three times with $H_2$ and shaken under $H_2$ (4 atm) for 22–52 h. After venting, the contents of the vessel were filtered through Celite, and the filter bed washed with EtOAc. Removal of the solvent gave a mixture of *cis/trans* diastereomers (d.r. 8:1 to >80:1). The predominant *cis* diastereomer (determined by NOESY experiments) was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) and characterized.

*(3S,5R)-5-phenyl-3-(2-phenyl-propan-2-yl)morpholin-2-one (**12b**)*

Hydrogenation time: 52 h (86.6%, d.r. >80:1); colorless oil; $[\alpha]_D^{23}=-97.3$ ($c$=0.37 g.100 mL$^{-1}$, $CHCl_3$); IR: $\tilde{\nu}$=1738 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.60 (s, 6H), 3.86 (t, $J$=10.2 Hz, 1H), 3.85–4.18 (m, 3H), 7.18~7.46 ppm (m, 10H); $^{13}$C NMR (100 MHz, [D$_6$]acetone): $\delta$=24.1 ($CH_3$), 27.6 ($CH_3$), 43.5 (C), 56.8 (CH), 67.5 (CH), 74.1 ($CH_2$), 126.7 (CH), 127.4 (2xCH), 127.8 (2xCH), 128.6 (2xCH), 128.7 (CH), 129.1 (2xCH), 139.7 (C), 147.1 (C), 168.5 ppm (C); HRMS (DCI/$NH_3$): *m*/*z* calcd for $C_{19}H_{22}NO_2$: 296.1650: $[M+H]^+$; found: 296.1661.

*General Procedure for Hydrogenolysis-Hydrolysis of Morphilinones **12** to Amino Acids **13***

A modification of the procedure reported by Cox and Harwood was used.[3a] Pearlman's catalyst ($Pd(OH)_2$ on C, 20% w/w) was added to a solution of morpholinone **12** in 40:2.5:0.47 MeOH/$H_2O$/TFA (ca. 0.4 M). The vessel was purged with $H_2$, then pressurized with $H_2$ to 4 atm (60 psi) and shaken for 24 h. After venting the vessel, the contents were filtered through Celite, and the filter bed washed with MeOH. The combined filtrates were reduced to dryness under reduced pressure and the residue taken up in water and loaded onto a short column of cation-exchange resin (AG 50W-X8, 50–100 mesh, $H^+$ form). After washing the column with water, amino acid **13** was eluted with 5% aqueous ammonia. The fractions containing the desired amino acid (ninhydrin positive) were combined, evaporated under reduced pressure and dried under high vacuum (2 days) to give pure **13**.

*(S)-2-Amino-3-methyl-3-phenylbutanoic acid (**13b**)*

Colorless solid (84%); $[\alpha]_D^{23}=+15$ ($c$=0.08 g.100 mL$^{-1}$, $H_2O$); $^1$H NMR (400 MHz, $D_2O$): $\delta$=1.42 (s, 3H), 1.50 (s, 3H), 3.90 (s, 1H), 7.35~7.52 ppm (m, 5H); $^{13}$C NMR (100 MHz, $D_2O$): $\delta$=21.7 ($CH_3$), 27.5 ($CH_3$), 39.3 (C), 64.1 (CH), 126.5 (2xCH), 127.6 (CH), 129.2 (CH), 144.3 (C), 172.8 ppm (C); HRMS (DCI/$NH_3$): *m*/*z* calcd for $C_{11}H_{16}NO_2$: 194.1181 $[M+H]^+$; found: 194.1177.

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