A new methodology for the synthesis of β-amino acids

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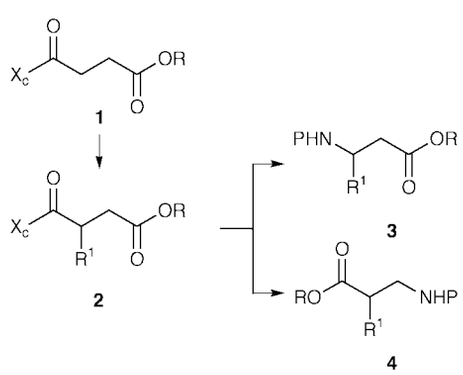
A differentially functionalized succinic acid unit **6** undergoes alkylation with excellent regio- and high stereocontrol at the carbon α to the imide to furnish the alkylated product **7** in 60–83% yield. Selective removal of the imide provides **8** in 80–90% yields. Curtius rearrangement of **8** with retention of stereochemistry provides *N*-protected β-amino acids (**9**) in 70–83% yields. Alternatively, selective deprotection of the ester group followed by Curtius rearrangement provides isomeric β-amino acids **14a**, **14b**, and **14e** in good yields. The methodology has been successfully applied to the synthesis of *N*-Boc-iturinic acid and 2-methyl-3-aminopropanoic acid, components of the antifungal peptide iturin and the cytotoxic depsipeptide cryptophycin respectively.

Naturally occurring β-amino acids are compounds with an interesting pharmacological profile.[1] They are also found as components in a wide variety of biologically active compounds[2] including peptides such as bestatin[3] and pepstatin.[4] The β-amino acids are useful precursors in the synthesis of β-lactams.[5] Recently, α-substituted β-amino acids have received greater scrutiny since they serve as important segments of bioactive molecules. For example, one of the promising antitumor agents in cancer chemotherapy, Paclitaxel®, contains an α-hydroxy β-amino acid side chain as its key pharmacophore.[6] Given the importance of the β-amino acids, development of a general methodology for their synthesis is important.

A variety of diastereoselective methods have been reported for the synthesis of β-amino acids.[7] These include the elegant chemistry from the Davies group[8] on the addition of chiral nitrogen nucleophiles to enoates and addition of achiral amines to chiral enoates by d'Angelo and co-workers.[9] Other diastereoselective methodologies for β-amino acids, which do not involve conjugate amine additions, have also been reported. Most notable of these are the Davis's chemistry[10] of chiral sulfinimines, Seebach's[11] hydropyrimidines, Juaristi's pyrimidinones,[12] and Konopelski's[13] dihydropyrimidinones. Wyatt and co-workers[14] have reported a new method for the synthesis of β-amino acids, which involves chiral enolate alkylation with 'NH_2CH_2' equivalents ($ZNHCH_2OAc$ or $BrCH_2COOR$). Recently, Evans and co-workers reported a protocol for β-amino acids, which also involves chiral enolate alkylation with $BrCH_2COOR$ followed by selective hydrolysis and Curtius rearrangement.[15]

Only a few reports of chiral Lewis acid catalyzed conjugate additions of amines to enoates have appeared. The first report was the work of Jørgensen[16] in which a chiral titanium Lewis acid was employed. Ishikawa has reported that *N*-benzylhydroxylamine adds to enoates with moderate selectivity using a chiral aluminium TADDOLate.[17] We have recently shown that 3,5-dimethylpyrazole derived enoates undergo conjugate amine addition with high enantioselectivity using substoichiometric amounts of chiral Lewis acids.[18] One of the most successful methodologies for the synthesis of functionalized β-amino acids with high selectivity is Sharpless's aminohydroxylation.[19] Other selected nonconjugate addition methodologies for the synthesis of β-amino acids (or derivatives) which utilize chiral Lewis acids are Corey's addition to imines,[20] and Yamamoto's[21] Diels–Alder reaction.

We have addressed in this paper the synthesis of β-amino acids in the context of a general methodology involving functionalization of linear dicarboxylic acid derivatives[22] in a regio- and stereoselective manner. The succinate unit is an ideal fragment[23] for the synthesis of β-amino acids if substituents can be introduced regio- and stereoselectively on the carbon framework and further selective conversion of one of the carboxy groups to an amino functionality can occur. Scheme 1



Scheme 1

illustrates our approach wherein the starting material is a readily available succinate unit **1**. This method is complementary to the recently published work from Evans' group.[15] The two carboxy groups are differentiated by forming an ester at one end and by attachment of a chiral auxiliary (oxazolidinone) to the other carboxy group. With the two ends differentiated, the first step is a regio- and stereoselective functionalization at the carbon α to the imide to furnish **2**. The second step involves the selective removal of either the imide or the ester functionality followed by a Curtius rearrangement of the free carboxy group with retention of stereochemistry (if applicable). Thus, intermediate **2** serves as a common precursor for two different β-amino acids **3** and **4**. The realization of the above strategy and its application in the synthesis of β-amino acid components of biologically active peptides iturin and cryptophycin are illustrated.

Our methodology begins with the attachment of the mono *tert*-butyl succinate[24] to an oxazolidinone **5** derived from D-diphenylalaninol by an anhydride method to provide **6** (Scheme 2).[25] The preparation[26] of **5** has been accomplished in our laboratory.[27] Treatment of **6** with one equivalent of NaHMDS in THF at −78 °C for 20 minutes followed by quenching with a reactive alkyl bromide furnished the mono alkylated compounds in good chemical yields and diastereo-

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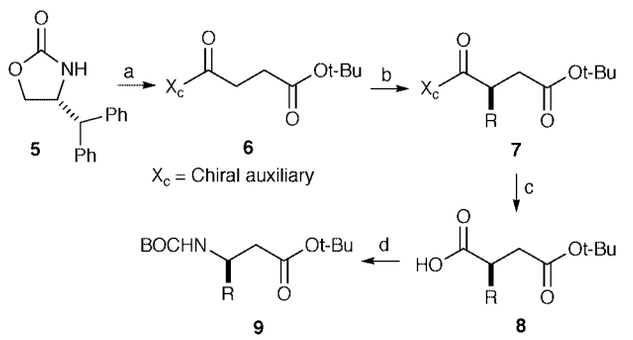
Table 1 Synthesis of *N*-protected β-amino acids

Entry	RBr	Yield **7** [%[a] (de)[b]]	Yield **8** (%)	Yield **9** (%)
a	$C_6H_5CH_2Br$	83 (92)	90	83
b	Allyl bromide	72 (92)	88	80
c	(*E*)-1-Bromoundec-3-ene	60 (>97)	87	70
d	Cinnamyl bromide	73 (84)	80	78
e	Methyl iodide	83 (81)		

[a] Yields are for column purified material. [b] de's were determined by ^{1}H NMR analysis of the crude alkylation products.

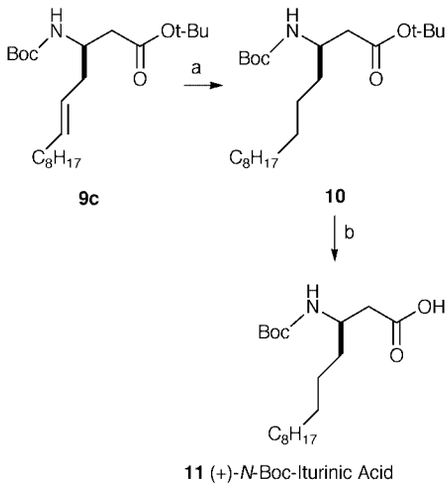


Scheme 2 *Reagents and conditions*: (a) DCC, CH_2Cl_2, HO_2CH_2-CCH_2CO_2t-Bu, LiCl, Et_3N, THF, rt, 86%; (b) (i) NaHMDS, THF, −78 °C, (ii) RBr, −78 °C, 1 h, warm to −48 °C, 3 h; (c) LiOH–H_2O_2, THF–H_2O, −5 to 0 °C; (d) (i) Et_3N, $ClCO_2Et$, acetone, 0 °C, 1 h, (ii) NaN_3, H_2O, acetone, 0 °C, 1 h, (iii) toluene, heat, 1 h, (iv) t-BuOH, heat, 24 h.

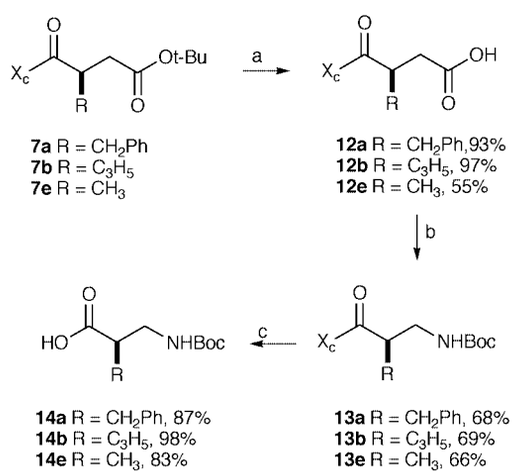
selectivity (Scheme 2, Table 1). Temperature and counterion play an important role in the generation of the enolate. When reactions were warmed to above −48 °C after sodium enolate generation, cleavage of the chiral auxiliary was observed. Similarly, lithium enolates were found to be unstable at −78 °C. The regioselectivity observed in enolate generation from **6** may be attributed to the increased acidity of these α-hydrogens adjacent to imide over the ester.[28] The next step involved the selective hydrolysis of the imide functionality. This could be accomplished by the treatment of **7** with LiOH–H_2O_2 in THF–H_2O at low temperatures to furnish **8**. The key step in our methodology was the one-pot conversion of the carboxy group to the protected amino group with retention of stereochemistry (**8**→**9**). This was carried out using a Curtius rearrangement[29] in moderate to good yields (Table 1).[30] The stereochemical outcome in this rearrangement is well precedented in the literature.[31] Thus, the synthesis of β-amino acids could be accomplished in four steps in good overall yields and high optical purity. The absolute stereochemistry of the newly formed chiral center was established by conversion to compounds of known configuration (*vide infra*).[32]

The utility of the new methodology is illustrated in the synthesis of *N*-Boc-iturinic acid (n-C_{14}),[33] the β-amino acid component of naturally occurring antifungal peptide iturin (Scheme 3). Catalytic hydrogenation of the β-amino acid **9c** furnished the saturated compound **10** in quantitative yield. Cleavage of the *tert*-butyl as well as the *N*-Boc functionalities using TFA followed by reprotection of the amino group provided (+)-*N*-Boc-iturinic acid.[34] This synthesis also establishes the absolute stereochemistry of the Curtius rearrangement products.

The intermediate **7** also serves as a useful precursor for the synthesis of isomeric β-amino acids (Scheme 4). Selective deprotection of the *tert*-butyl ester functionality was achieved in high yields using trifluoroacetic acid.[35] Curtius rearrangement followed by cleavage of the imide provided the isomeric β-amino acids in good yields (**12**→**14**). The amino acid **14e** is a component of cryptophycins, potent tumor-selective cyto-



Scheme 3 *Reagents and conditions*: (a) Pd/C, EtOH, H_2, 100%; (b) (i) TFA, CH_2Cl_2, rt, (ii) Boc_2O, Et_3N, rt, 73% (two steps).



Scheme 4 *Reagents and conditions*: (a) TFA, CH_2Cl_2, rt, 2 h; (b) (i) Et_3N, $ClCO_2Et$, acetone, 0 °C, 15 min, (ii) NaN_3, H_2O, acetone, 0 °C, 15 min, (iii) toluene, heat, 1 h, (iv) t-BuOH, heat 12 h; (c) LiO_2H, THF–H_2O, −5 to 0 °C.

toxins associated with the terrestrial blue–green algae *Nostoc* sp.[36,37]

In conclusion we have developed a new methodology for the preparation of a variety of β-amino acids in excellent optical purity. The application of the new protocol in the synthesis of β-amino acid segments of biologically active peptides was also illustrated. Extension of the new methodology in the synthesis of more complex targets is underway.

Experimental

General

NaHMDS (1 M solution in THF), allyl bromide, benzyl bromide were purchased from Aldrich. All bromides were purified over neutral alumina prior to use. Tetrahydrofuran was distilled from benzophenone–ketyl prior to use. Thin layer chromatographic analyses were performed on silica gel Whatmann-60 F glass plates and components were visualized by illumination with UV light or by staining with phosphomolybdic acid. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh). Melting points were determined using a Thomas Hoover capillary melting point apparatus, and are uncorrected. All glassware was oven and/or flame dried, assembled hot, and cooled under a stream of dry nitrogen or argon before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

^{1}H NMR were recorded on JEOL GSX-400 (400 MHz) and JEOL GSX-270 (270 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using TMS (0.00 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublet, m = multiplet, br = broad), coupling constant(s), integration and peak assignment. ^{13}C NMR were recorded on JEOL-GSX-400 (100 MHz) and JEOL GSX-270 (65 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. Optical rotations were recorded on a JASCO-DIP-370 instrument and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed on an in house Perkin-Elmer Series 2, CHNS/O, Analyzer 2400 or by MHW laboratories, Phoenix, AZ. A few of the elemental analyses are slightly outside the defined limits of the journal. This is most likely a result of inconsistent calibration of the in house instrument.

Preparation of succinate 6

Dicyclohexylcarbodiimide (8.28 g, 40.22 mmol) was added in portions to a solution of mono *tert*-butyl succinate (10.00 g, 57.71 mmol) in CH_2Cl_2 (250 mL) at room temperature. The reaction mixture was stirred for an additional 15 minutes. The precipitated solid was filtered and the filtrate was concentrated. The residue was diluted with hexane and passed through a short silica gel column. The eluent, after concentration under reduced pressure, afforded an anhydride (8.65 g) in 92% yield. To the anhydride (8.65 g, 26.21 mmol) in THF (60 mL) were added Et_3N (4.00 mL, 28.83 mmol), LiCl (1.13 g, 26.21 mmol) and 4-diphenylmethyloxazolidin-2-one **5** (5.96 g, 23.59 mmol) successively at −20 °C. The reaction mixture was then allowed to warm up gradually to room temperature. The progress of the reaction was monitored by TLC (~4 h). The volume of the reaction was reduced by evaporation of THF. The residue was diluted with CH_2Cl_2 (150 mL) and was washed with 3 M aqueous HCl followed by aqueous $NaHCO_3$ solution. The organic layer was washed with water followed by brine and dried over $MgSO_4$. Concentration in vacuum and chromatographic purification on silica gel using 5% EtOAc in hexane gave compound **6** (8.3 g, 86%).

Mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, $C(CH_3)_3$), 2.48 (m, 2H, CH_2), 2.93 (m, 1H, COCH), 3.13 (m, 1H, COCH), 4.37 (m, 2H, OCH_2), 4.66 (d, J = 5.4 Hz, 1H, Ph_2CH), 5.24 (ddd, J = 8.0, 5.1, 2.7 Hz, 1H, NCH), 7.01–7.30 (m, 10H, Ar); ^{13}C NMR (270 MHz, $CDCl_3$) δ 171.8, 171.6, 153.9, 139.6, 137.9, 129.4, 128.9, 128.7, 128.3, 127.8, 127.0, 80.5, 64.9, 56.2, 50.4, 30.9, 29.4, 28.0; $[a]_D^{25}$ −148.9 (*c* 1.5, CH_2Cl_2); Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.75; H, 6.84; N, 3.82%.

Typical procedure for NaHMDS alkylation

To a three-necked round-bottomed flask fitted with a thermometer and N_2 inlet, was added **6** (4.21 mmol) and dry THF (42 mL). The reaction was cooled to −78 °C and NaHMDS (1 M in THF, 4.63 mL, 4.63 mmol,) was added *via* syringe over 10 minutes. The reaction mixture was allowed to stir for an additional 20 minutes to ensure complete enolization and the alkyl bromide (6.32 mmol) in THF (3 mL) was added *via* syringe at −78 °C. The reaction was stirred at −78 °C for 1 h and then warmed to −48 °C and stirred at that temperature for an additional 3 h. After completion (TLC), the reaction was quenched with aqueous NH_4Cl solution. The reaction mixture was concentrated by evaporating THF under reduced pressure. The residue was diluted with CH_2Cl_2 (200 mL), washed successively with water, brine, dried over $MgSO_4$ and concentrated to give crude product. The product was chromatographed on silica gel using 5% EtOAc in hexanes as eluant to afford the alkylated products **7a**–**e**.

Alkylation with benzyl bromide to give 7a. Yield, 83%; mp 123–124 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36 (s, 9H, $C(CH_3)_3$), 2.13 (m, 2H, $PhCH_2$), 2.66 (dd, J = 16.8, 10.9 Hz, 1H, COCH), 2.89 (dd, J = 13.2, 3.7 Hz, 1H, COCH), 4.18 (m, 1H, NCOCH), 4.43 (m, 2H, OCH_2), 4.72 (d, J = 6.6 Hz, 1H, Ph_2CH), 5.38 (ddd, J = 8.8, 5.9, 1.5 Hz, 1H, NCH), 7.10–7.35 (m, 15H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 174.7, 171.3, 153.3, 138.5, 138.4, 138.3, 129.4, 129.3, 128.9, 128.6, 128.6, 128.5, 127.8, 127.0, 80.5, 65.2, 56.6, 51.4, 41.4, 37.5, 35.6, 28.0; $[a]_D^{25}$ −79.5 (*c* 1.5, CH_2Cl_2); Anal. Calcd for $C_{31}H_{33}NO_5$: C, 74.53; H, 6.66; N, 2.80. Found: C, 74.73; H, 6.95; N, 3.05%.

Alkylation with allyl bromide to give 7b. Yield, 72%; mp 79–80 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (s, 9H, $C(CH_3)_3$), 1.83 (m, 1H, allyl CH), 2.21 (m, 1H, allyl CH), 2.34 (dd, J = 17.6, 3.7 Hz, 1H, COCH), 2.66 (dd, J = 17.2, 11.7 Hz, 1H, COCH), 3.97 (m, 1H, NCOCH), 4.40 (m, 2H, OCH_2), 4.69 (d, J = 5.7 Hz, 1H, Ph_2CH), 5.01 (m, 2H, allyl), 5.34 (ddd, J = 8.8, 5.9, 2.9 Hz, 1H, NCH), 5.55 (m, 1H, allyl), 7.13–7.35 (m, 10H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 174.6, 171.3, 153.2, 139.5, 138.1, 134.5, 129.1, 128.8, 128.6, 128.4, 127.7, 126.9, 117.7, 80.5, 65.2, 56.5, 51.5, 38.6, 35.8, 35.7, 28.0; $[a]_D^{25}$ −118.7 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.33; H, 7.19; N, 3.62%.

Alkylation with (*E*)-undec-2-enyl bromide to give 7c. Yield, 60%; oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H, CH_2CH_3), 1.26–1.43 (m, 12H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$), 1.79 (m, 1H, allylic CH), 2.00 (m, 2H, allylic CH_2), 2.17 (m, 1H, allylic CH), 2.33 (dd, J = 16.9, 3.7 Hz, 1H, COCH), 3.63 (dd, J = 17.2, 11.7 Hz, 1H, COCH), 3.90 (m, 1H, NCOCH), 4.39 (m, 1H), 4.68 (d, J = 6.6 Hz, 1H, Ph_2CH), 5.19 (m, 1H, NCH), 5.36 (m, 2H, vinyl), 7.13–7.39 (m, 10H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 174.7, 171.4, 153.1, 139.5, 138.2, 134.0, 129.1, 128.8, 128.5, 128.4, 127.7, 126.9, 125.7, 80.3, 65.1, 56.4, 51.4, 39.0, 35.6, 34.5, 32.4, 31.8, 29.4, 29.3, 29.2, 27.9, 22.6, 14.0; $[a]_D^{25}$ −82.8 (*c* 1.3, CH_2Cl_2); Anal. Calcd for $C_{35}H_{47}NO_5$: C, 74.83; H, 8.43; N, 2.49. Found: C, 74.85; H, 8.38; N, 2.16%.

Alkylation with cinnamyl bromide to give 7d. Yield, 73%; mp 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 1.98 (m, 1H, allylic CH), 2.43 (m, 2H, allyl CH, COCH), 2.73 (dd, J = 17.7, 11.3 Hz, 1H, COCH), 4.06 (m, 1H, NCOCH), 4.43 (m, 2H, OCH_2), 4.73 (d, J = 6.5 Hz, 1H, Ph_2CH), 5.39 (ddd, J = 8.3, 6.5, 2.7 Hz, 1H, NCH), 6.06 (ddd, J = 15.6, 8.6, 6.9 Hz, 1H, vinyl CH), 6.40 (d, J = 16.1 Hz, 1H, vinyl CH), 7.17–7.39 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 171.4, 153.4, 139.6, 138.2, 137.0, 132.8, 129.2, 128.9, 128.6, 128.5, 127.8, 127.4, 127.0, 126.3, 126.2, 80.6, 65.4, 56.6, 51.6, 39.1, 35.9, 35.1, 28.1; $[a]_D^{25}$ −84.1 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.41; H, 6.71; N, 2.66. Found: C, 75.64; H, 7.01; N, 2.30%.

Alkylation with methyl iodide to give 7e. Yield, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 7.0 Hz, 3H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.24 (dd, J = 17.2, 4.3 Hz, 1H, COCH), 2.75 (dd, J = 17.2, 10.8 Hz, 1H, COCH), 3.39 (m, 1H, NCOCH), 4.38 (dd, J = 8.7, 2.7 Hz, 1H, OCH), 4.44 (dd, J = 9.1, 8.1 Hz, 1H, OCH), 4.70 (d, J = 6.5 Hz, 1H, Ph_2CH), 5.35 (ddd, J = 9.1, 5.9, 2.7 Hz, 1H, NCH), 7.13–7.34 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 171.2, 153.0, 139.4, 138.0, 129.2, 128.8, 128.5, 128.4, 127.7, 126.9, 80.5, 65.1, 56.3, 51.3, 38.3, 34.2, 28.0, 17.2; $[a]_D^{26}$ −101.1 (*c* 1.9, CH_2Cl_2); Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90. Found: C, 70.42; H, 6.81%.

Typical procedure for cleaving the chiral auxiliary

To a solution of **7a** (1.0 g, 2.00 mmol) in THF and H_2O (4 : 1,

20 mL) at 0 °C was added H_2O_2 (30% aqueous, 0.90 mL, 8.00 mmol) followed by aqueous LiOH solution (0.1 g 5 mL^{-1}, 3.84 mL, 3.20 mmol). The reaction mixture was stirred at 0 °C for 1 h and then an aqueous solution of Na_2SO_3 (1.0 g 6 mL^{-1}, 6.0 mL, 8.00 mmol) was added. After stirring for an additional 20 minutes, THF was evaporated under reduced pressure and the residue was diluted with CH_2Cl_2 (100 mL) and water. The organic layer was separated which contained the chiral auxiliary. The aqueous layer was acidified with 3 M aqueous HCl solution and was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water, brine and dried over $MgSO_4$. Concentration in vacuum yielded chemically pure acids **8a**–**d**. The chiral auxiliary **5** could be recovered in >95% yield and showed no loss of optical purity.

Acid 8a. Yield, 90%; mp 60–61 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.35 (dd, J = 16.7, 4.4 Hz, 1H, COCH), 2.55 (dd, J = 16.7, 8.8 Hz, 1H, COCH), 2.76 (dd, J = 15.4, 11.0 Hz, 1H, PhCH), 3.10 (m, 2H, PhCH and COCH), 7.17–7.33 (m, 5H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 180.7, 170.8, 138.0, 129.0, 128.5, 127.7, 81.0, 43.1, 37.3, 35.9, 27.9; $[\alpha]_D^{25}$ +8.4 (*c* 1.6, CH_2Cl_2); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.65; H, 7.67%.

Acid 8b. Yield, 88%; oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (s, 9H, $C(CH_3)_3$), 2.41 (m, 3H, allyl CH_2, COCH), 2.61 (dd, J = 16.9, 9.5 Hz, 1H, COCH), 2.90 (m, 1H, COCH), 5.12 (m, 2H, allyl CH), 5.73 (m, 1H, allyl CH); ^{13}C NMR (65 MHz, $CDCl_3$) δ 180.5, 170.9, 134.2, 117.9, 80.9, 40.9, 36.1, 35.5, 27.9; $[\alpha]_D^{25}$ +3.4 (*c* 1.4, CH_2Cl_2); Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 60.91; H, 8.25%.

Acid 8c. Yield, 87%; oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (t, J = 6.6 Hz, 3H, CH_3), 1.21–1.35 (m, 12H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$), 1.93 (m, 2H, allyl CH_2), 2.19 (m, 1H, CH_2CH), 2.33 (m, 2H, allyl CH_2), 2.53 (dd, J = 16.8, 8.7 Hz, 1H, COCH), 2.80 (m, 1H, COCH), 5.28 (m, 1H, vinyl CH), 5.40 (m, 1H, vinyl CH); ^{13}C NMR (65 MHz, $CDCl_3$) δ 180.8, 170.9, 134.3, 125.2, 80.7, 41.3, 35.9, 34.4, 32.4, 31.8, 29.3, 29.2, 29.1, 29.0, 27.8, 22.5, 13.9; $[\alpha]_D^{25}$ +1.8 (*c* 1.6, CH_2Cl_2); Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.08; H, 10.38%.

Acid 8d. Yield, 80%; mp 71–72 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 2.44 (m, 2H, allyl CH_2), 2.62 (m, 2H, $COCH_2$), 2.98 (m, 1H, COCH), 6.13 (dt, J = 15.4, 7.3 Hz, 1H, vinyl CH), 6.43 (d, J = 16.1 Hz, 1H, vinyl CH), 7.13–7.36 (m, 5H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 180.6, 170.9, 136.9, 133.0, 128.5, 127.3, 126.1, 125.8, 81.0, 41.2, 36.1, 34.7, 27.9; $[\alpha]_D^{25}$ +7.9 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 69.87; H, 7.47%.

Typical procedure for Curtius rearrangement

To a two-necked round-bottomed flask fitted with N_2 inlet was added acid **8a** (0.176 g, 0.67 mmol) in dry acetone (5 mL). The solution was cooled to 0 °C and Et_3N (0.111 mL, 0.80 mmol) and $ClCO_2Et$ (0.070 mL, 0.73 mmol) were added. The reaction mixture was stirred for 1 h. To this mixture was added NaN_3 (0.108 g, 1.67 mmol) in H_2O (3 mL) and stirred at 0 °C for another 1 h. The solvent was evaporated below room temperature either by air flow or by rotoevaporator. The residue was then extracted with toluene (3 × 20 mL). The organic layer was dried over $MgSO_4$ and heated carefully by using a distillation condenser. The volume was reduced to ~10 mL over a 1 h period. Addition of t-BuOH (5 mL) was carried out *via* syringe and the distillation condenser was replaced by a reflux condenser. The reaction was gently allowed to reflux for an additional 12 h. The solvent was evaporated and the residue was diluted with CH_2Cl_2 (50 mL) and was washed with 3 M aqueous HCl, water, brine, dried over $MgSO_4$, and concentrated. The oily material was chromatographed on silica gel using 2% EtOAc in hexane to yield *N*-Boc-amino acid esters **9a**–**d**.

Amino ester 9a. Yield, 83%; mp 84–85 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.30 (dd, J = 15.4, 5.9 Hz, 1H, COCH), 2.41 (dd, J = 15.4, 5.9 Hz, 1H, COCH), 2.82 (m, 2H, $PhCH_2$), 4.11 (m, 1H, NCH), 5.06 (m, 1H, NH), 7.17–7.32 (m, 5H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 170.9, 154.9, 137.8, 129.4, 128.3, 126.4, 80.8, 79.0, 48.9, 40.4, 38.8, 28.2, 27.9; $[\alpha]_D^{25}$ +10.0 (*c* 1.1, CH_2Cl_2); Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71. Found: C, 68.24; H, 8.71%.

Amino ester 9b. Yield, 80%; oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 2.29 (t, J = 6.6 Hz, 2H, allyl CH_2), 2.41 (d, J = 5.9 Hz, 2H, COCH), 3.95 (m, 1H, NCH), 4.9 (s, 1H, NH), 5.10 (m, 2H, vinyl CH), 5.78 (m, 1H, vinyl CH); ^{13}C NMR (65 MHz, $CDCl_3$) δ 170.7, 155.0, 134.0, 117.8, 80.6, 78.8, 47.2, 39.5, 38.8, 28.2, 27.8; $[\alpha]_D^{25}$ −10.09 (*c* 1.1, MeOH); Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54. Found: C, 62.71; H, 9.20%.

Amino ester 9c. Yield, 70%; oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 3H, CH_3), 1.28–1.43 (m, 12H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.00 (m, 2H, allyl CH_2), 2.22 (m, 2H, allyl CH_2), 2.42 (d, J = 5.9 Hz, 2H, COCH), 3.93 (m, 1H, NCH), 4.98 (s, 1H, NH), 5.37 (m, 1H, vinyl CH), 5.51 (m, 1H, vinyl CH); ^{13}C NMR (65 MHz, $CDCl_3$) δ 170.9, 155.1, 134.4, 125.1, 80.6, 78.9, 47.6, 39.5, 37.7, 32.5, 31.8, 29.4, 29.3, 29.2, 29.1, 28.3, 27.9, 22.6, 14.0; $[\alpha]_D^{25}$ −5.57 (*c* 0.7, MeOH); Anal. Calcd for $C_{23}H_{43}NO_4$: C, 69.48; H, 10.91. Found: C, 69.08; H, 10.59%.

Amino ester 9d. Yield, 78%; mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.47 (m, 4H, allyl CH_2, $COCH_2$), 4.06 (m, 1H, NCH), 5.07 (d, J = 8.3 Hz, 1H, NH), 6.16 (dt, J = 15.6, 7.2, 1H, vinyl CH), 6.43 (d, J = 15.6 Hz, 1H, vinyl CH), 7.20–7.36 (m, 5H, Ar); ^{13}C NMR (270 MHz, $CDCl_3$) δ 170.9, 155.1, 137.2, 133.0, 128.4, 127.2, 126.1, 125.7, 80.9, 79.2, 47.6, 39.6, 38.2, 28.3, 28.0; $[\alpha]_D^{25}$ +8.4 (*c* 1.0, MeOH); Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.37; H, 8.60; N, 3.22%.

(*R*)-*tert*-Butyl 3-[*N*-(*tert*-butyloxycarbonyl)amino]tetradecanoate 10

The (*R*)-*tert*-butyl 3-[*N*-(*tert*-butyloxycarbonyl)amino]tetradec-5-enoate **9c** (0.132 g, 0.33 mmol) in EtOH (5 mL) was hydrogenated using hydrogen (1 atm) and 10% Pd on activated carbon (0.015 g) as the catalyst. The reaction mixture was filtered through a small pad of Celite by diluting with $CHCl_3$ (20 mL). Concentration in vacuum and chromatography on silica gel gave **10** (0.127 g) in quantitative yield.

Oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$), 2.84 (m, 2H, $COCH_2$), 3.87 (m, 1H, NCH), 4.89 (m, 1H, NH); ^{13}C NMR (65 MHz, $CDCl_3$) δ 170.9, 155.2, 80.5, 78.7, 47.7, 40.4, 34.7, 31.7, 29.4, 29.3, 29.2, 29.1, 28.2, 27.9, 25.9, 22.5, 13.9; $[\alpha]_D^{25}$ +13.09 (*c* 1.1, CH_2Cl_2); Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.11; H, 11.36. Found: C, 68.68; H, 10.97%.

(*R*)-*N*-(*tert*-Butyloxycarbonyl)iturinic acid 11 †

Compound **10** (0.051 g, 0.127 mmol) was treated with CF_3COOH (0.10 mL, 1.28 mmol) in CH_2Cl_2 (5 mL) at room temperature and the reaction stirred for 12 h. The solvent was

† The IUPAC name for **11** is (3*R*)-3-[*N*-(*tert*-butyloxycarbonyl)amino]-tetradecanoate.

evaporated under reduced pressure. To the residue was added Et_3N (3 mL) followed by Boc_2O (0.030 g, 0.137 mmol) at room temperature and stirred for an additional 12 h. The excess Et_3N was removed by a steady air flow and the residue was treated with 3 M aqueous HCl and then diluted with CH_2Cl_2 (20 mL). The organic layer was washed with water, dried over $MgSO_4$, and concentrated. Column chromatography on silica gel using 2% EtOAc in hexane gave **11** (0.054 g) in 70% yield.

Mp 61 °C (lit.[33] 63–65 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H, CH_3), 1.25 (s, 18H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.51 (m, 2H, $NCHCH_2$), 2.55 (s, 2H, $COCH_2$), 3.89 (s, 1H, NCH), 4.89 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 155.6, 79.5, 47.5, 39.3, 34.6, 31.9, 29.6, 29.5, 29.3, 28.3, 26.1, 22.7, 14.1; $[\alpha]_D^{25}$ +5.3 (*c* 0.9, MeOH) (lit.[33] +5.3 (*c* 1.0, MeOH)).

Typical procedure for deprotection of the *tert*-butyl ester

To **7a** (0.725 g, 1.45 mmol) in CH_2Cl_2 (20 mL) was added CF_3COOH (1.12 mL, 14.50 mmol) at room temperature and the reaction mixture was stirred for 12 h. The solvent was evaporated under reduced pressure and the residue was chromatographed directly on silica gel using 10% EtOAc in hexane to afford oxazolidinone acid **10a**.

Acid 12a. Yield, 93%; mp 157–159 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.21 (dd, J = 17.4, 3.7 Hz, 1H, COCH), 2.34 (dd, J = 12.9, 10.2 Hz, 1H, COCH), 2.72 (dd, J = 16.9, 10.3 Hz, 1H, PhCH), 3.00 (dd, J = 13.4, 4.8 Hz, 1H, PhCH), 4.26 (m, 1H, NCH), 4.47 (br d, J = 8.3 Hz, 1H, Ph_2CH), 4.68 (m, 2H, OCH_2), 5.45 (m, 1H, NCH), 7.15–7.37 (m, 10H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$ MeOH-d_4) δ 174.8, 153.5, 139.5, 138.1, 137.9, 129.0, 128.6, 128.4, 128.3, 128.2, 127.5, 126.8, 126.5, 65.2, 56.4, 51.2, 41.2, 37.2, 34.5; $[\alpha]_D^{25}$ −73.0 (*c* = 1.1, CH_2Cl_2); Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.01; H, 5.94; N, 2.66%.

Acid 12b. Yield, 97%; mp 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (dt, J = 13.4, 8.6 Hz, 1H, allyl CH_2), 2.25 (m, 1H, allyl CH_2), 2.46 (dd, J = 17.7, 3.8 Hz, 1H, COCH), 2.76 (dd, J = 17.7, 11.3 Hz, 1H, COCH), 3.98 (m, 1H, NCOCH), 4.40 (m, 2H, OCH_2), 4.65 (d, J = 6.5 Hz, 1H, Ph_2CH), 5.07 (m, 2H, vinyl CH_2), 5.37 (ddd, J = 9.7, 6.2, 2.7 Hz, 1H, NCH), 5.60 (m, 1H, vinyl CH), 7.15–7.37 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 174.3, 153.3, 139.4, 138.1, 134.1, 129.1, 128.9, 128.5, 128.4, 127.8, 127.0, 118.1, 65.5, 56.5, 51.6, 38.5, 35.6, 34.2; $[\alpha]_D^{25}$ −83.09 (*c* 1.1, CH_2Cl_2); Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89. Found: C, 70.00; H, 5.47%.

Acid 12e. Yield, 55% after crystallization; mp 185–188 °C (from hot EtOAc with very slow cooling); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 7.0 Hz, 3H, CH_3), 2.34 (dd, J = 17.5, 4.3 Hz, 1H, COCH), 2.84 (dd, J = 17.5, 10.7 Hz, 1H, COCH), 3.92 (m, 1H, NCOCH), 4.42 (m, 2H, OCH_2), 4.65 (d, J = 6.7 Hz, 1H, Ph_2CH), 5.37 (m, 1H, NCH), 7.13–7.37 (m, 10H, Ar); ^{13}C NMR (100 MHz, Acetone-d_6) δ 176.0, 173.4, 153.8, 141.0, 139.9, 130.2, 129.6, 129.4, 129.2, 128.2, 127.5, 65.8, 56.8, 52.1, 37.1, 35.0, 17.6; $[\alpha]_D^{26}$ −92.2 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{21}H_{21}NO_5 \cdot H_2O$: C, 65.61; H, 5.84; N, 3.55. Found: C, 65.44; H, 6.01; N, 3.63%.

Curtius rearrangement of 12a, 12b and 12e

See procedure for **9a**.

Amino oxazolidinone 13a. Yield, 68%; mp 65–67 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.49 (m, 1H, benzyl CH), 2.98 (m, 1H, benzyl CH), 3.21 (m, 1H, NCH), 3.58 (m, 1H, NCH), 4.12 (m, 1H, NCOCH), 4.41 (m, 2H, OCH_2), 4.60 (d, J = 5.1 Hz, 1H, Ph_2CH), 4.76 (m, 1H, NH), 5.32 (m, 1H, NCH), 6.85–7.35 (m, 15H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 173.8, 155.7, 153.2, 139.5, 137.9, 129.6, 129.2, 129.1, 128.7, 128.6, 128.5, 128.3, 127.6, 126.9, 79.2, 64.8, 56.4, 50.8, 45.8, 41.1, 35.5, 28.2; $[\alpha]_D^{25}$ −102.72 (*c* 1.15, CH_2Cl_2); Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66. Found: C, 71.85; H, 6.69%.

Amino oxazolidinone 13b. Yield, 69%; mp 45 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 1.98 (m, 1H, allyl CH), 2.29 (m, 1H, allyl CH), 3.19 (m, 1H, NCH), 3.44 (m, 1H, NCH), 3.74 (m, 1H, NCOCH), 4.43 (m, 2H, OCH_2), 4.64 (d, J = 6.7 Hz, 1H, Ph_2CH), 4.75 (m, 1H, NH), 5.08 (m, 2H, vinyl CH), 5.31 (m, 1H, NCH), 5.65 (m, 1H, vinyl CH), 7.12–7.34 (m, 10H, Ar); ^{13}C NMR (65 MHz, $CDCl_3$) δ 173.9, 155.7, 153.2, 139.5, 138.1, 134.6, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 127.8, 127.1, 79.2, 65.3, 56.6, 51.5, 43.6, 40.5, 33.7, 28.3; $[\alpha]_D^{25}$ −107.17 (*c* 1.1, CH_2Cl_2); Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94. Found: C, 69.42; H, 6.68%.

Amino oxazolidinone 13e. Yield, 66%; mp 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 7.0 Hz, 3H, CH_3), 1.42 (s, 9H, $C(CH_3)_3$), 3.20 (m, 1H, NCH), 3.32 (m, 1H, NCH), 3.67 (m, 1H, NCOCH), 4.37 (dd, J = 9.1, 2.7 Hz, 1H, OCH), 4.43 (m, 1H, OCH), 4.63 (d, J = 6.4 Hz, 1H, Ph_2CH), 5.33 (m, 1H, NCH), 7.13–7.34 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 155.6, 152.8, 139.2, 137.9, 128.9, 128.7, 128.4, 128.2, 127.6, 126.9, 79.0, 65.2, 56.1, 51.3, 42.2, 39.0, 28.1, 14.9; $[\alpha]_D^{26}$ −100.8 (*c* 1.2, CH_2Cl_2); Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90. Found: C, 68.01; H, 6.81%.

Cleavage of the chiral auxiliary

For procedures see preparation of **8a**.

***N*-Boc-amino acid 14a.** Yield, 87%; mp 81–82 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.39 (s, 9H, $C(CH_3)_3$), 2.81–2.94 (m, 5H, $PhCH_2$, NH, COCH, NCH), 3.30 (apparent t, J = 5.4, 4.8 Hz, 1H, NCH), 7.19–7.30 (m, 5H, Ar); ^{13}C NMR (100 MHz, Acetone-d_6) δ 175.1, 156.7, 140.0, 129.6, 128.9, 126.9, 78.6, 48.0, 42.5, 36.1, 28.4; $[\alpha]_D^{25}$ +40.10 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58. Found: C, 64.07; H, 7.45%.

***N*-Boc-amino acid 14b.** Yield, 97%; oil; ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.39 (s, 9H, $C(CH_3)_3$), 2.34 (m, 2H, allyl CH_2), 2.67 (m, 1H, COCH), 3.27 (apparent t, J = 5.9, 5.4 Hz, 2H, NCH_2), 5.01 (br d, J = 10.2 Hz, 1H, vinyl CH), 5.10 (dq, J = 16.9, 1.5 Hz, 1H, vinyl CH), 5.85 (m, 1H, vinyl CH); ^{13}C NMR (100 MHz, Acetone-d_6) δ 175.3, 156.5, 136.1, 117.0, 78.6, 45.8, 42.1, 34.3, 28.4; $[\alpha]_D^{25}$ +17.0 (*c* 1.0, CH_2Cl_2); Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35. Found: C, 57.67; H, 8.59%.

***N*-Boc-amino acid 14e.** Yield, 83%; mp 72–73 °C (lit.[36] 69.5–70.5 °C); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.13 (d, J = 7.0 Hz, 3H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.65 (dd, J = 14.0, 7.0 Hz, 1H, NCH), 2.87 (br d, J = 12.9 Hz, 1H, NCH), 3.17 (m, 1H, COCH), 3.31 (m, 1H, NH); ^{13}C NMR (100 MHz, Acetone-d_6) δ 176.5, 156.6, 78.6, 43.8, 40.3, 28.5, 14.9; $[\alpha]_D^{26}$ −18.0 (*c* 1.9, CH_3OH), $[\alpha]_D^{26}$ −7.7 (*c* 1.0, CH_2Cl_2) (lit.[36] $[\alpha]_D^{26}$ −18.4 (*c* 2.0, CH_3OH)).

Phenyl methyl succinic acid

CF_3COOH (0.46 mL, 5.98 mmol) was added to the solution of *tert*-butyl hydrogen (2-phenyl methyl)succinate **8a** (0.158 g, 0.59 mmol) in CH_2Cl_2 (5 mL) and allowed to stir for 12 h. The solvent was evaporated and the residue was chromatographed on silica gel to afford the title compound (0.120 g) in quantitative yield.

^{1}H NMR (270 MHz, $CDCl_3$) δ 2.41 (dd, J = 17.2, 4.0 Hz, 1H, COCH), 2.65 (dd, J = 17.6, 8.06 Hz, 1H, COCH), 2.79 (m, 1H, PhCH), 3.14 (m, 2H, PhCH, COCH), 7.16–7.32 (m, 5H, Ar);

^{13}C NMR (65 MHz, $CDCl_3$ Acetone-d_6) δ 175.1, 172.8, 138.5, 128.8, 128.2, 126.2, 42.4, 36.9, 34.1; $[\alpha]_D^{25}$ +26.64 (*c* 1.7, EtOAc) (lit.[38] for the (*S*)-enantiomer $[\alpha]_D^{26}$ −27.0 (*c* 2, EtOAc)).

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Notes and references

1 For a discussion of the synthesis and biology of β-amino acids *see: Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi, Wiley-VCH, New York, 1997; For comprehensive reviews on β-amino acids see: D. C. Cole, *Tetrahedron* 1994, **50**, 9517; E. Juaristi, D. Quintana and J. Escalante, *Aldrichimica Acta*, 1994, **27**, 3.

2 For a recent review on β-peptides see: S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; (*a*) S. Shinagawa, T. Kanamaru, S. Harada, M. Asai and H. Okazaki, *J. Med. Chem.*, 1987, **30**, 1458; (*b*) A. Bongini, G. Cardillo, M. Orena, G. Porzi and S. Sandri, *Tetrahedron*, 1987, **43**, 4377; (*c*) N. Kabawata, T. Inamoto and S. Hashimoto, *J. Antibiot.*, 1992, **45**, 513; (*d*) H. Oki, M. Hirano, K. Tomatsu, K. I. Numata and H. Kamei, *J. Antibiot.*, 1989, **42**, 1756; (*e*) G. Casiraghi, L. Colombo, G. Rassu and P. Spanu, *J. Org. Chem.*, 1991, **56**, 6523; (*f*) F. Matsuura, Y. Hamada and T. Shioiri, *Tetrahedron*, 1994, **50**, 11303; (*g*) M. F. Beatty, C. J. White and M. A. Avery, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1637.

3 (*a*) F. Gueritte-Voegelein, V. Senilh, B. David, D. Guenard and P. Potier, *Tetrahedron*, 1986, **42**, 4451; (*b*) L. Mangatal, M. T. Adeline, D. Guenard and F. Gueritte-Voegelein, *Tetrahedron*, 1989, **45**, 4177.

4 K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, 1989, 1678.

5 For conversion of β-amino acids to β-lactams see: (*a*) N. Mayachi and M. Shibasaki, *J. Org. Chem.*, 1990, **55**, 1975; (*b*) D. Tanner and P. Somfai, *Tetrahedron*, 1988, **44**, 613.

6 (*a*) D. Guérnard, F. Guéritte-Voegelein and P. Potier, *Acc. Chem. Res.*, 1993, **26**, 160 and references cited therein; (*b*) P. Potier, *Chem. Soc. Rev.*, 1992, **21**, 113.

7 For general information see: P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon: Oxford, 1992. For a selected example see D. Enders, H. Wahl and W. Bettray, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 455.

8 (*a*) I. Brackenridge, S. G. Davies, D. T. Fenwick, O. Ichihara and M. E. C. Polywka, *Tetrahedron*, 1999, **55**, 533 and references therein; (*b*) M. E. Bunnage, A. N. Chernega, S. G. Davies and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2373. For related work see: (*c*) J. M. Hawkins and T. A. Lewis, *J. Org. Chem.*, 1994, **59**, 649; (*d*) E. Juaristi, J. Escalante, B. Lamatsch and D. Seebach, *J. Org. Chem.*, 1992, **57**, 2396.

9 F. Dumas, B. Mezrhab and J. d'Angelo, *J. Org. Chem.*, 1996, **61**, 2293.

10 (*a*) F. A. Davis, P. Zhou and B.-C. Chen, *Chem. Soc. Rev.*, 1998, **27**, 13 and references therein; also see: (*b*) T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1998, **64**, 12.

11 (*a*) D. Seebach, A. Boog and W. B. Schweizer, *Eur. J. Org. Chem.*, 1999, 335 and references therein; (*b*) T. Hintermann and D. Seebach, *Synlett*, 1997, 437; also see (*c*) D. Seebach and H. Estermann, *Tetrahedron Lett.*, 1987, **28**, 3103.

12 (*a*) E. Juaristi, D. Quintana, B. Lamatsch and D. Seebach, *J. Org. Chem.*, 1991, **56**, 2553; (*b*) E. Juaristi and D. Quintana, *Tetrahedron: Asymmetry*, 1992, **3**, 723; (*c*) E. Juaristi, M. Balderas and X. Ramirez-Quirós, *Tetrahedron: Asymmetry*, 1998, **9**, 3881.

13 (*a*) K. S. Chu, G. R. Negrete, J. P. Konopelski, F. J. Lakner, N.-T. Woo and M. M. Olmstead, *J. Am. Chem. Soc.*, 1992, **114**, 1800; (*b*) K. S. Chu, G. R. Negrete and J. P. Konopelski, *Tetrahedron*, 1993, **49**, 9183.

14 For an alternate synthesis of β-amino acids using oxazolidinones see: E. Arvanitis, H. Ernst, A. A. Ludwig, A. J. Robinson and P. B. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 521; also see: T. Hintermann and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 2093.

15 D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johnson, D. H. B. Ripin and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411.

16 L. Falborg and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2823.

17 (*a*) T. Ishikawa, K. Nagai, M. Senzaki, A. Tatsukawa and S. Saito, *Tetrahedron*, 1998, **54**, 2433; (*b*) T. Ishikawa, K. Nagai, T. Kudoh and S. Saito, *Synlett*, 1998, 1292.

18 M. P. Sibi, J. J. Shay, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 1998, **120**, 6615.

19 (*a*) P. O'Brien, *Angew. Chem., Int. Ed. Engl.*, 1998, **38**, 326; (*b*) L. J. Goossen, H. Liu, K. R. Dress and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 1999, **39**, 1080 and references therein.

20 E. J. Corey, C. P. Decicco and R. C. Newbold, *Tetrahedron Lett.*, 1991, **32**, 5287.

21 K. Ishihara, M. Miyata, K. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, 1994, **116**, 10520.

22 For uses of differentially functionalized succinates in synthesis see: (*a*) M. P. Sibi, P. K. Deshpande and A. J. La Loggia, *Synlett*, 1996, 343; (*b*) M. P. Sibi, J. Lu and C. L. Talbacka, *J. Org. Chem.*, 1996, **61**, 7848; (*c*) M. P. Sibi, J. Lu and J. Edwards, *J. Org. Chem.*, 1997, **62**, 5864.

23 For other selected methods for the synthesis of substituted succinates see: (*a*) C.-B. Xue, X. He, J. Roderick, W. F. DeGrado, R. J. Cherney, K. D. Hardman, D. J. Nelson, R. A. Copeland, B. D. Jaffee and C. P. Decicco, *J. Med. Chem.*, 1998, **41**, 1745; (*b*) R. P. Becket, M. J. Crimmins, M. H. Davis and Z. A. Spavold, *Synlett*, 1993, 137.

24 G. Buchi and E. C. Robert, *J. Org. Chem.*, 1968, **33**, 460.

25 G.-J. Ho and D. J. Mathre, *J. Org. Chem.*, 1995, **60**, 2271.

26 M. P. Sibi, P. K. Deshpande, A. J. La Loggia and J. W. Christensen, *Tetrahedron Lett.*, 1995, **36**, 8961.

27 For the use of this auxiliary see: (*a*) M. P. Sibi, C. P. Jasperse and J. Ji, *J. Am. Chem. Soc.*, 1995, **117**, 10779; (*b*) M. P. Sibi and J. Ji, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 190; (*c*) M. P. Sibi, P. K. Deshpande and J. Ji, *Tetrahedron Lett.*, 1995, **36**, 8965.

28 For selective aldol or alkylation of similar structural units see: (*a*) D. A. Evans and J. M. Takacs, *Tetrahedron Lett.*, 1980, **21**, 4233; (*b*) D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; (*c*) D. A. Evans, J. Bartroli and T. L. Shih, *J. Am Chem. Soc.*, 1981, **103**, 2127; (*d*) D. A. Evans, F. Urpi, T. C. Somer, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215; (*e*) D. A. Evans, M. T. Bilodeau, T. C. Somer, J. Clardy, D. Cherry and Y. Kato, *J. Org. Chem.*, 1991, **56**, 5750; (*f*) W. Oppolzer, P. Cintas-Moreno, O. Tamura and F. Cardinaux, *Helv. Chim. Acta*, 1993, **76**, 187.

29 (*a*) J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511; (*b*) C. Kaiser and J. Weinstock, *Org. Synth.* 1988, **coll. vol. 6**, 910; The use of diphenylphosphoryl azide for the Curtius rearrangement gave lower yields and product purification was also difficult.

30 The diastereomers were purified by silica gel column chromatography. The two diastereomers from compound **7e** were inseparable on column chromatography.

31 (*a*) J. M. Takacs, M. R. Jaber and A. S. Vellekoop, *J. Org. Chem.*, 1998, **63**, 2742; (*b*) K. Burgess, D. Lim, K.-K. Ho and C.-Y. Ye, *J. Org. Chem.*, 1994, **59**, 2179; (*c*) N. De Kimpe, M. Boeykens and K. A. Tehrani, *J. Org. Chem.*, 1994, **59**, 8215; (*d*) F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult and T. Norin, *Tetrahedron Lett.*, 1985, **26**, 4957; (*e*) M. Martín-Vità, C. Minguillón and R. M. Ortuño, *Tetrahedron: Asymmetry*, 1995, **9**, 4291.

32 The absolute stereochemistry of the alkylation product **7a** was established by removal of both carboxy protecting groups to yield benzyl succinic acid and comparison of its sign of rotation with that reported in the literature (see Experimental section).

33 J. M. Bland, *Synth. Commun.*, 1995, **25**, 467 and references cited therein.

34 **11**: mp 61 °C, $[\alpha]_D^{26}$ +5.3 (*c* 0.9, MeOH); lit.[33] $[\alpha]_D^{26}$ +5.33 (*c* 1.0, MeOH).

35 The acid **12e** was purified to a single diastereomer by crystallization.

36 R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore and M. A. Tius, *J. Am. Chem. Soc.*, 1995, **117**, 2479.

37 For recent work on cryptophycins and the synthesis of **14e** see: J. D. White, J. Hong and L. A. Lobarge, *J. Org. Chem.* 1999, **64**, 6206.

38 H. Kawano, Y. Ishii, T. Ikariya, M. Saburi, S. Yoshikawa, Y. Uchida and H. Kumobayashi, *Tetrahedron Lett.*, 1987, **28**, 1905.