Preparation of Chiral Bisoxazolines: Observations on the Effect of Substituents

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A series of enantiomerically pure 4-substituted bisoxazolines **1a–f**, **2c**, and **2e** was prepared from naturally derived or synthetic amino alcohols and malonyl dichloride derivatives. The formation of the bisoxazolines was accomplished in two stages: (1) preparation of the bis-amides of the malonyl derivatives with the amino alcohols and (2) cyclization of the hydroxy amides **4** by either of two general protocols; (1) heating with thionyl chloride in toluene or (2) formation of the bismesylate and then heating with aqueous or alcoholic base. The latter procedure was found to be more reliable especially for bisoxazolines with bulky substitutents at C(4). The C(4) trityl-substituted hydroxy amide **4f** produced the bis(acylaziridine) **10** by cyclization on the nitrogen atom using KOH/MeOH, but afforded the desired bisoxazoline **1f** by the action of $SOCl_2/Et_3N$. The synthesis of the non-naturally derived amino alcohols using the Evans asymmetric azidation procedure is also described.

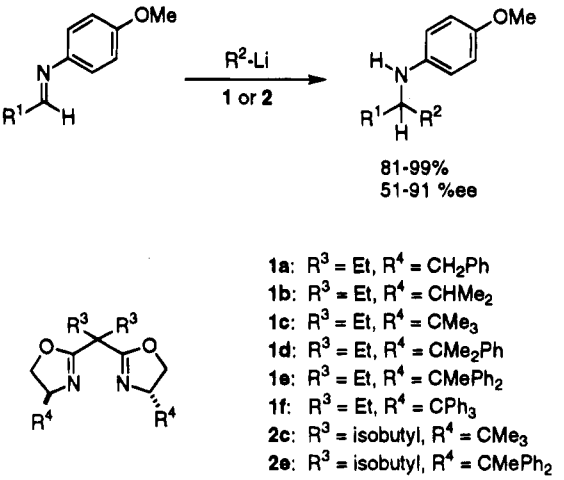
Introduction and Background

Chiral (2,2′-bisoxazolino)alkanes have recently been employed as ligands in a wide variety of metal-catalyzed asymmetric reactions.[1] The Lewis basic properties of the nitrogen donor atoms and the conformationally rigid framework of the chelate represent important structural features of this type of ligand. By virtue of ready substitution at the C(4) positions, the C_2-symmetric arrangement of the stereogenic centers in close proximity to the coordination site is expected to have a strong influence on the course of reactions mediated by bisoxazoline-ligated metal species. Although the majority of bisoxazoline metal complexes used in synthetic reactions employ transition metals (Cu, Pd, Fe), we have recently demonstrated the utility of these ligands as chelators for organolithium reagents as well, Scheme 1.[2]

The most expeditious preparation of bisoxazolines is the reaction of 1,2-amino alcohols with diacid derivatives.[3] Thus, a general approach to chiral bisoxazolines substituted at the C(4) position would employ readily available chiral amino alcohols derived from α-amino acids. The flexibility of the synthesis allows for high structural diversity of these derivatives. The (2,2′-bisoxazolino)alkanes used in the studies referred to above are generally obtained by a three-step process beginning with the condensation of malonic acid derivatives with amino alcohols to form the dihydroxy malondiamides. Activation of the free hydroxyl groups of the dihydroxy diamides followed by treatment with base effects cyclization on the oxygen atom to form the bisoxazolines.[4] The major variations within this general method for bisoxazoline construction involve the use of various activating agents to effect the closure such as dichlorodimethylstannane[1e,5] and $SOCl_2$.[1g,j] For certain dihydroxy diamides bearing tertiary hydroxyl groups, closure to the bisoxazoline could be effected by the action of methanesulfonic acid.[1m] Bisoxazolines can also be prepared by the zinc chloride-catalyzed condensation of amino alcohols with dinitriles.[6]

As part of our studies on the catalytic, asymmetric addition of organolithium reagents to imines and the

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

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(4) This is also a general preparation of oxazolines: (a) Gabirel, S.; Stelzner, R. *Chem. Ber.* **1895**, *28*, 2929. (b) Leffler, M. T.; Adams, R. *J. Am. Chem. Soc.* **1937**, *59*, 2252.

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(6) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

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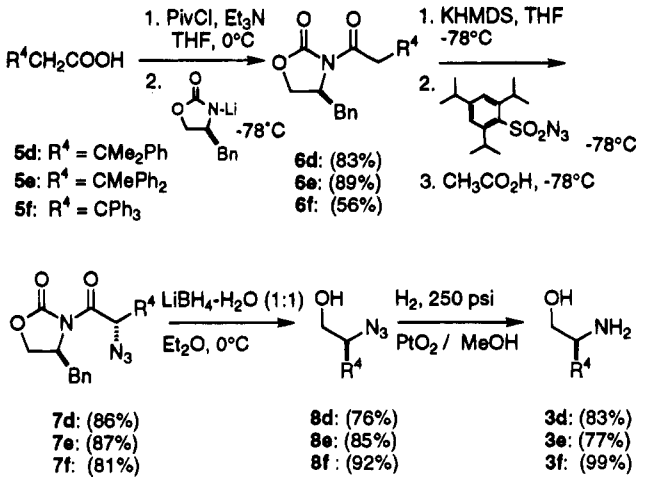
Scheme 2



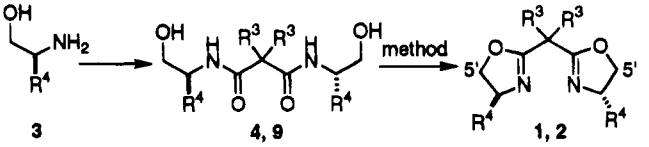
palladium-catalyzed cyclopropanation of olefins, we have prepared a series of chiral bisoxazolines. This paper reports in full our observations regarding the synthesis of this class of compounds.

Results and Discussion

The starting amino alcohols **3a**–**c** were easily obtained from reduction of the corresponding α-amino acids, L-phenylalanine, L-valine, and L-*tert*-leucine. The amino alcohols **3d**–**f** were obtained by asymmetric synthesis using Evans's *N*-acyl oxazolidinone method, Scheme 2.[7] Thus, the carboxylic acids **5d**,[8] **5e**,[9] and **5f** were converted to the corresponding *N*-acyl oxazolidinones by treatment of the mixed pivalic carboxylic anhydrides (generated *in situ*) with the lithiated oxazolidinone derived from L-phenylalanine. The oxazolidinones **6d**–**f** were deprotonated with potassium hexamethyldisilazide (KHMDS), and the resulting enolates were treated with 2,4,6-triisopropylphenylsulfonyl azide (trisyl azide)[10] followed by the addition of acetic acid to provide the α-azido acyl oxazolidinones **7d**–**f** as single diastereomers (determined by ^{1}H NMR and HPLC analysis). The azido alcohols were obtained by treatment of an ethereal solution of the oxazolidinones at 0 °C with lithium borohydride[11] in the presence of an equimolar amount of water to afford **8d**–**f** in high yield. The chiral oxazolidinone was also recovered in high yield in each case. High pressure hydrogenation in the presence of prereduced platinum oxide (Adams catalyst) afforded the desired amino alcohols **3d**–**f**, which were determined to be enantiomerically pure (>99% ee) within the detection limits of chiral HPLC analysis of the corresponding 3,5-dinitrobenzamides.[12]

The condensation of **3a**–**f** with diethylmalonyl dichloride was carried out in the presence of triethylamine (Et_3N) and the dihydroxy diamides **4a**–**f** were obtained as white solids in good yield, Table 1. Cyclization by treatment with thionyl chloride ($SOCl_2$) was generally successful for the preparation of **1a,b** but was nonreproducible and afforded low yields for **1c**–**f**. Thus, for the preparation of bisoxazolines bearing bulky C(4′) substituents (R^4), an alternative route which proceeded via the bismesylates was developed. The dihydroxy diamides **4a**–**c** were treated with methanesulfonyl chloride (MsCl) (2.2 equiv) and Et_3N (4.4 equiv) in CH_2Cl_2 at 0 °C to afford the corresponding bismesylates, which were then heated at reflux in an aqueous methanolic (1/1) solution of NaOH for 3 h to afford bisoxazolines **1a**–**c** in high yield. Potassium hydroxide in MeOH (5%) or potassium acetate in EtOH could also be used for the preparation of bisoxazolines bearing bulky R^4 substituents. Compounds **1d** and **1e** were isolated in 62% and 83% yields, respectively, using these bases without further purification of dihydroxy diamides **4d** and **4e**. This overall sequence proceeded cleanly on a large (10 g) scale and was reproducible.

Table 1. Preparation of Bisoxazolines 1



amino alcohol	R^3	R^4	hydroxy amide	yield, %	product	method[a]	yield, %
3a	Et	$PhCH_2$	**4a**	98	**1a**	A	78
3b	Et	Me_2CH	**4b**	97	**1b**	A	86
3c	Et	Me_3C	**4c**	86	**1c**	A	75
3d	Et	$PhMe_2C$	**4d**	ni[b]	**1d**	B	62
3e	Et	Ph_2MeC	**4e**	ni[b]	**1e**	C	83
3f	Et	Ph_3C	**4f**	ni[b]	**1f**	D	54
3f	Et	Ph_3C	**4f**	ni[b]	**10**	B	73
3c	*i*-Bu	Me_3C	**9c**	73	**2c**	A	81
3e	*i*-Bu	Ph_2MeC	**9e**	88	**2e**	A	40
3e	*i*-Bu	Ph_2MeC	**9e**	88	**12**	B	77

[a] Method A: (1) $MsCl/Et_3N/CH_2Cl_2$, (2) 0.5 M NaOH/MeOH/H_2O (1/1), 100 °C. Method B: (1) $MsCl/Et_3N/CH_2Cl_2$ (2) 5% KOH/MeOH, reflux. Method C: (1) $MsCl/Et_3N/CH_2Cl_2$ (2) KOAc/EtOH, reflux. Method D: $SOCl_2/Et_3N$/toluene, 100 °C. [b] Not isolated, the yield of **1** is for two step conversion from **3**.

The synthesis of the trityl substituted bisoxazoline **1f** was attempted following several of the procedures described above. The coupling of (*S*)-(triphenylmethyl)-glycinol with diethylmalonyl dichloride afforded dihydroxy diamide **4f**. Mesylation of **4f** ($MsCl/Et_3N$) followed by treatment of the bismesylate with a variety of bases (5% KOH/MeOH, 0.5 M NaOH/MeOH–H_2O (1:1), NaH/THF, and DBU/CH_2Cl_2) all gave the same product as a white solid, mp 69.0–71.0 °C. The spectroscopic properties of this compound were not consistent with the desired bisoxazoline **1f**, although the mass spectrum (FAB) and the combustion analytical data unambiguously established that it had the same elemental composition as **1f**. The spectroscopic data (Table 2) suggested the presence of a bis(acylaziridine) structure, **10**. Most notably, the ^{13}C chemical shifts of the imino carbons, C(2′), in the bisoxazolines **1a**–**e** were observed between 167–168 ppm, but **10** displayed a resonance at 184.88 ppm, consistent with the presence of a carbonyl carbon. Furthermore, the diagnostic IR band for the oxazoline C=N bond stretch which appeared at 1653–1657 cm^{-1} for **1a**–**e** was replaced by strong absorbances at 1703 and 1678 cm^{-1} indicative of a carbonyl group and within the

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(8) Leffler, J. E.; Barbas, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 7768.

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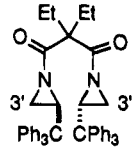
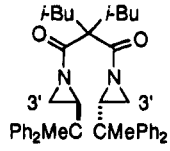
(12) (a) Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1988**, *441*, 311. (b) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. C.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991.

Table 2. Key Spectroscopic Data for 1, 2, 10, and 12



10

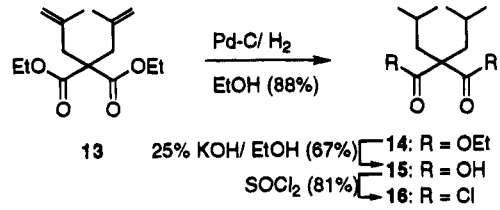


12

compound	δ C(2′) ^{13}C NMR, ppm	δ HC(5′) ^{1}H NMR, ppm	IR, cm^{-1}
1a	167.86	3.97	1653
1b	167.17	3.98–3.89	1657
1c	167.12	4.10	1657
1d	168.01	3.93	1655
1e	168.06	4.12	1657
1f	167.72	4.28	1647
10	184.88	2.25[a]	1703, 1678
2c	167.85	4.07	1653
2e	168.58	4.00	1653
12	185.93	2.61[a]	1659

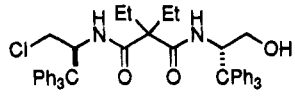
[a] HC(3′).

Scheme 3

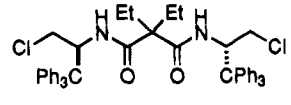


range for an acylaziridine (1665-1690 cm^{-1}).[13] Finally, the ^{1}H NMR chemical shifts of the methylene protons at C(5′) of **1a–e** (3.7–4.2 ppm) appeared significantly downfield of those in **10**, which were observed at 1.61 and 2.25 ppm, consistent with C(3′) of the three-membered ring structure shown for **10**.

Fortunately, the desired trityl-substituted bisoxazoline **1f** (mp 107.0–108.5 °C) could be synthesized in 54% yield from **4f** by the action of thionyl chloride and Et_3N in toluene at 100 °C. The use of Et_3N as the base was found to be essential to the success of this cyclization reaction. In the absence of Et_3N, the only product obtained was the monochloride **11a** (toluene, 80 °C) or dichloride **11b** (CH_2Cl_2, reflux). Moreover, the dichloride **11b** did not cyclize to a bisoxazoline ring system without the addition of Et_3N.



11a



11b

We also investigated the synthesis of another series of chiral bisoxazoline ligands represented by **2c** and **2e**, which contained isobutyl groups on the methano bridge. The corresponding dihydroxy diamides **9c** and **9e** were prepared by condensation of the amino alcohols **3c** and **3e** with diisobutylmalonyl dichloride **16**, which in turn was synthesized from diethyl 2,2-bis(2-methyl-2-propenyl)malonate **13**[14] following the three-step sequence shown in Scheme 3. Hydrogenation of **13** over Pd–C, followed by hydrolysis of the diester **14** afforded the diacid **15**.[15] Treatment of **15** with $SOCl_2$ provided the dichloride **16**.[16] The preparation of **9c** and **9e** proceeded uneventfully following the general method described above. Treatment of the bismesylate of **9c** with 0.5 M NaOH in 1/1 methanol/water at reflux afforded **2c** in 87% yield (mp 123.5–124.0 °C). Under the same conditions, the bismesylate of **9e** afforded **2e** (mp 213.5–214.5 °C) in a moderate yield (40%) in addition to monocyclized materials. Simply by changing to 5% methanolic NaOH (anhydrous), bis(acylaziridine) **12** (mp 143.5–144.5 °C) was obtained in 77% yield without a trace of the bisoxazoline **2e**. The spectral characteristics of **12**, now including the IR stretching frequency, clearly identified it as an acylaziridine.

Thus, the course of the cyclization of derivatives of dihydroxy diamides **4** and **9** bearing bulky R^3 and/or R^4 substituents was found to be highly dependent upon the selection of both the leaving group (mesylate vs chloride) and the experimental conditions (base, solvent). However, through the judicious choice of experimental parameters the desired bisoxazolines could be obtained. Treatment of β-halo and β-sulfonato amides with alcoholic base is a well established method for the preparation of 2-substituted oxazolines;[4] nevertheless, examples of aziridine formation are on record.[17] Moreover, the isomerization of *N*-acylaziridines to oxazolines has been demonstrated to occur thermally as well as under electrophilic and nucleophilic catalysis.[18] In the cases at hand, we feel it is unlikely that the bisoxazolines **1a–e** and **2c** are formed by isomerization of the corresponding acylaziridines, since both **10** and **12** could be isolated under the same conditions used for the bisoxazoline syntheses, e.g. method A. However, in the case of **1f**, it was not established if **10** was stable in refluxing toluene in the presence of Et_3NHCl.

The divergent cyclization pathways leading to oxazolines and aziridines from closure of acylamino alcohols has been addressed recently by Wipf and Miller.[19] The mechanistic scenario proposed by these authors identifies two key features: (1) conformational effects which influence the geometrical requirements for intramolecular displacement and (2) the presence of bases strong enough to generate the reactive amide anions. These authors suggest that aziridine formation occurs via the anions as intermediates, but note that the divergence is unique to closure with the Mitsunobu reagent and disappears with Burgess reagent or sulfonates.

Since both **1d** and **10** are formed under the same conditions, we believe that amide anions are the reactive intermediates leading to *both* products in the presence of hydroxide and that subtle conformational effects are responsible for the formation of bis(acylaziridines) from substrates bearing bulky substituents.[20] However, we

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(19) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267 and references cited therein.
(20) In this regard, the anomalously high frequency for the amide I band in **10** suggests that there is a significant steric inhibition of resonance in the ground state. Thus, the extreme bulk of the trityl and (diphenylmethyl)carbinyl groups may exert a type of Thorpe–Ingold effect which favors the aziridine formation. For a recent discussion, see: (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

agree that the neutral amide preferentially reacts at the oxygen. Thus, under more weakly basic conditions where amide anions are not generated (conditions D), even substrate **3f** reacts at oxygen to give the trityl bisoxazoline.[21] The behavior of **9e** is somewhat more mysterious as the only difference in reaction conditions for the formation of **2e** and **12** is the presence of water in the former. We conclude that the attenuated basicity of NaOH in H_2O versus KOH in MeOH is sufficient to change the nature of the reactive species from the neutral amide to its anion. Of course, solvation and other medium effects cannot be ruled out.

In summary, we have described general procedures for the synthesis of bisoxazoline derivatives **1** and **2** bearing R^4 substituents of various steric requirements, including triphenylmethyl. The desired bisoxazolines are generally obtained in high yield, except for those bearing bulky R^3 and R^4 substitutents, which are obtained in modest yields. The utility of these interesting chiral ligands in asymmetric metal-mediated reactions will be the subject of future reports.

Experimental Section

General. See supporting information.

Materials. Diethylmalonyl dichloride, phenylalanine, valine, 3,3,3-triphenylpropionic acid, and $LiBH_4$ were obtained from commercial sources and used without further purification. Mesyl chloride (MsCl), pivaloyl chloride, and triethylamine (Et_3N) were distilled from CaH_2. 3-Methyl-3-phenylbutyric acid,[8] 3,3-diphenylbutyric acid,[9] (4*S*)-4-(phenylmethyl)-2-oxazolidinone,[7] and trisyl azide[10] were prepared by literature methods. *n*-BuLi (hexane) and KHMDS (toluene) were titrated prior to use.

(4*S*)-3-(3-Methyl-3-phenyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (6d). General Procedure I. In a flame-dried, 250-mL, three-necked, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was added 3-methyl-3-phenylbutyric acid (10.0 g, 56.2 mmol) and THF (150 mL). This solution was cooled under nitrogen in a dry-ice bath (−72 °C internal), and Et_3N (10.2 mL, 73.0 mmol, 1.3 equiv) followed by pivaloyl chloride (7.3 mL, 59.0 mmol, 1.05 equiv) were added. After being stirred at this temperature for 15 min, the bath was changed to an ice−water bath and the mixture was maintained at this temperature for 1 h and then was cooled back down to −72 °C.

To a flame-dried, 500-mL, three-necked, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was added (4*S*)-4-(phenylmethyl)-2-oxazolidinone (11.93 g, 67.42 mmol, 1.2 equiv) and THF (100 mL). This solution was cooled down to −72 °C under nitrogen, and *n*-BuLi (1.61 M in hexane, 41.9 mL, 67.4 mmol, 1.2 equiv) was added slowly via syringe so that the reaction mixture never exceeded −60 °C. The resulting orange solution was stirred at −72 °C for 1 h and was transferred as quickly as possible to the above anhydride solution via cannula. No increase in temperature was observed during this process. After completion of the reaction (≥1 h), glacial acetic acid (6 mL) was added at −72 °C and the resulting solution was allowed to warm to rt over a 3 h period. The reaction mixture was then washed with pH 7 phosphate buffer solution (150 mL), and this aqueous phase was extracted twice with CH_2Cl_2 (300 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. Recrystallization of the residue (hexane/EtOAc, 1/1) afforded 15.65 g (83%) of **6d** as white needles: mp 105−106 °C (hexane/EtOAc, 1/1); $[\alpha]^{23}_D$ = +65.0° (*c* = 1.4, $CHCl_3$); ^{1}H NMR (300 MHz) 7.44−7.10 (m, 10 H), 4.44 (m, 1 H), 4.00 (dd, *J* = 2.7, 9.0, 1 H), 3.91 (t, *J* = 8.3, 1 H), 3.37 (d, *J* = 15.6, 2 H), 3.10 (dd, *J* = 3.2, 13.3, 1 H), 2.51 (dd, *J* = 9.9, 13.3, 1 H), 1.53 (s, 6 H); ^{13}C NMR (75.5 MHz) 171.0, 153.4, 147.7 and 135.3, 129.3, 128.8, 128.1 and 125.6, 127.2 and 125.9, 65.7, 55.1, 46.9, 37.8, 37.6, 29.5, 29.1; IR (CCl_4) 1777 (s); MS (CI, isobutane, 130 eV) 338 (MH^+, 100); TLC R_f 0.6 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{21}H_{23}NO_3$ (337.42): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.72; H, 6.85; N, 4.14.

(4*S*)-3-(3,3-Diphenyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (6e). Following general procedure I, from 3,3-diphenylbutyric acid (9.25 g, 38.5 mmol), Et_3N (7 mL, 50.1 mmol, 1.3 equiv), pivaloyl chloride (5.7 mL, 46.2 mmol, 1.2 equiv), (4*S*)-4-(phenylmethyl)-2-oxazolidinone (8.18 g, 46.2 mmol, 1.2 equiv), and *n*-BuLi (1.55 M in hexane, 29.8 mL, 46.2 mmol, 1.2 equiv) was obtained 13.74 g (83%) of **6e** as white needles after recrystallization (hexane/EtOAc, 1/1): mp 149.0−151.0 °C (hexane/EtOAc, 1/1); $[\alpha]^{23}_D$ = +84.3° (*c* =1.05, $CHCl_3$); ^{1}H NMR (300 MHz) 7.31−7.08 (m, 15 H), 4.36−4.28 (m, 1 H), 4.02 (d, *J* = 15.0, 1 H), 3.93 (dd, *J* = 2.5, 9.0, 1 H), 3.82 (d, *J* = 14.8, 1 H), 3.76 (d, *J* = 1.0, 8.5, 1 H), 3.02 (dd, *J* = 3.2, 13.4, 1 H), 2.43 (dd, *J* = 9.9, 13.4, 1 H), 1.94 (s, 3H); ^{13}C NMR (75.5 MHz) 171.01, 153.26, 148.35, 148.03, 135.30, 129.32, 128.04, 127.93, 127.27, 127.18, 126.07, 126.05, 65.66, 55.23, 46.19, 44.52, 37.48, 28.74; IR ($CHCl_3$) 1777 (s), 1701 (s); MS (CI, isobutane, 130 eV) 400 (MH^+, 30), 181 (100); TLC R_f 0.6 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{26}H_{25}NO_3$ (399.49): C, 78.17; H, 6.31; N, 3.51. Found: C, 78.17; H, 6.33; N, 3.51.

(4*S*)-3-(3,3,3-Triphenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (6f). Following general procedure I, from 3,3,3-triphenylpropanoic acid (3.0 g, 9.92 mmol), Et_3N (2.09 mL, 14.98 mmol, 1.52 equiv), pivaloyl chloride (1.63 mL, 13.2 mmol, 1.59 equiv), (4*S*)-4-(phenylmethyl)-2-oxazolidinone (2.11 g, 11.91 mmol, 1.2 equiv), and *n*-BuLi (1.55 M in hexane, 7.68 mL, 11.91 mmol, 1.2 equiv) was obtained 1.66 g of **6f** as a white solid after recrystallization (cyclohexane/EtOAc, 10/1). The mother liquors were purified by chromatography (silica gel, hexane/EtOAc, 4/1) to afford and additional 0.97 g of **6f** for a combined yield of 2.63 g (56%). An analytical sample was prepared by recrystallization from hexane/EtOAc: mp 159−160 °C; $[\alpha]^{23}_D$ = +56.5° (*c* = 0.96 $CHCl_3$); ^{1}H NMR (400 MHz) 7.34−7.04 (m, 20 H), 4.49 (s, 2 H), 4.34 (m, 1 H), 3.98 (dd, *J* = 2.7, 9.0, 1 H), 3.89 (t, *J* = 8.6, 1 H), 2.94 (dd, *J* = 3.3, 13.3, 1 H), 2.45 (dd, *J* = 9.9, 13.2, 1 H); ^{13}C NMR (100.6 MHz) 170.38, 153.30, 146.39, 135.18, 129.37, 129.16, 128.82, 127.80, 127.20, 126.18, 65.64, 56.33, 55.20, 44.31, 37.39; IR ($CHCl_3$), 1777(s), 1702 (w); MS (70 eV) 461 (16), 417 (12), 244 (100), 243 (100); TLC R_f 0.1 (hexane/EtOAc, 5/1). Anal. Calcd for $C_{31}H_{27}NO_3$ (461.57): C, 80.67; H, 5.90; N, 3.03. Found: C, 80.45; H, 5.84; N, 3.39.

(2*S*,4*S*)-3-(2-Azido-3-methyl-3-phenyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (7d). General Procedure II. The azide transfer was done according to Evans's procedure.[7] To 50 mL of dry THF at −72 °C (internal) in a flame-dried, 250-mL, three-necked, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was added KHMDS (0.71 M in toluene, 21.9 mL, 13.5 mmol, 1.15 equiv). To this solution was added via cannula a precooled (−72 °C) solution of (4*S*)-3-(3-methyl-3-phenyl-1-hydroxybutyl)-4-(phenylmethyl)-2-oxazolidinone (4.56 g, 13.5 mmol) in THF (50 mL). Stirring at −72 °C was maintained for 30 min. To the solution of the potassium enolate, held at −72 °C, was added via cannula a precooled (−72 °C) solution of trisyl azide (5.02 g, 16.2 mmol, 1.2 equiv) in THF (50 mL). After 2 min, the reaction was quenched with acetic acid (3.6 mL, 62.2 mmol, 4.6 equiv). The reaction mixture was allowed to warm to ~30 °C in a water bath over 45 min. The solution was then partitioned between CH_2Cl_2 (300 mL) and brine (300 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification of the crude residue twice by column chromatography (silica gel, hexane/EtOAc, 5/1 and then silica gel, $CHCl_3$) afforded 4.42 g (86%) of the **7d** as a colorless, nondistillable oil and as a single diastereomer as shown by ^{1}H NMR: $[\alpha]^{23}_D$ = +109.3° (*c* = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz) 7.42−7.15 (m, 10 H), 5.65 (s, 1 H), 4.10 (m, 1 H), 3.93 (dd, *J* = 1.6, 8.9, 1 H), 3.48 (t, *J* = 8.2, 1 H), 3.21 (dd, *J* = 3.2, 13.4, 1 H), 2.68 (dd, *J* = 10.0, 13.4, 1 H), 1.58 (s, 3 H), 1.56 (s,

(21) The effect of base on the direction of closure has been noted by Miller: Krook, M. A.; Miller, M. J. *J. Org. Chem.* **1985**, *50*, 1126.

3 H); ^{13}C NMR (100.6 MHz) 168.9, 152.6, 144.0 and 134.9, 129.4, 129.0, 128.3 and 126.5, 127.4 and 127.0, 66.6, 66.0, 55.8, 43.9, 37.6, 26.5, 22.0; IR (neat) 2097 (s), 1767 (s), 1696 (s); MS (CI, isobutane, 130 eV) 379 (MH^+, 3.8), 351 ($MH^+ - N_2$, 49), 336 ($M^+ - N_3$, 15), 119 ($C_6H_5(CH_3)_2C^+$, 100); TLC R_f 0.5 ($CHCl_3$). Anal. Calcd for $C_{21}H_{22}N_4O_3$ (378.43): C, 66.65; H, 5.86; N, 14.80. Found: C, 66.63; H, 5.86; N, 14.75.

(2*S*,4*S*)-3-(2-Azido-3,3-diphenyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (7e). Following general procedure II, from KHMDS (0.73 M in toluene, 3.77 mL, 2.75 mmol, 1.1 equiv), (4*S*)-3-(3,3-diphenyl-1-hydroxybutyl)-4-(phenylmethyl)-2-oxazolidinone (1.00 g, 2.50 mmol), trisyl azide (967 mg, 3.13 mmol, 1.25 equiv), and acetic acid (660 μL, 11.5 mmol, 4.6 equiv) was obtained 966 mg (88%) of **7e** (single diastereomer as shown by ^{1}H NMR) as a colorless, nondistillable oil after purification twice by column chromatography (silica gel, hexane/EtOAc, 5/1 then 3/1): $[\alpha]^{23}_D$ = +277.7° (c = 1.07, $CHCl_3$); ^{1}H NMR (300 MHz) 7.40–7.10 (m, 15 H), 6.37 (s, 1 H), 3.91–3.87 (m, 1 H), 3.83 (dd, J = 1.5, 8.7, 1 H), 3.28 (t, J = 8.0, 1 H), 3.18 (dd, J = 3.1, 13.4, 1 H), 2.67 (dd, J = 9.7, 13.4, 1 H), 2.05 (s, 3 H); ^{13}C NMR (75.5 MHz); 168.86, 152.36, 146.59, 144.23 and 134.80), 129.31, 128.89, 128.32, 128.17, 127.88, 127.35, 127.17, 126.91 and 126.52, 65.87, 61.89, 55.82, 52.32, 37.52, 22.16; IR (neat) 2004 (s), 1780 (s), 1693 (s); MS (CI, isobutane, 130 eV) 441 (MH^+, 0.9), 413 ($MH^+ - N_2$, 3.5), 398 ($MH^+ - N_3$,10.6), 181 (100%); TLC R_f 0.7 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{26}H_{24}N_4O_3$ (440.51): C, 70.89; H, 5.49; N, 12.72. Found: C, 70.74; H, 5.47; N, 12.58.

(2*S*,4*S*)-3-(2-Azido-3,3,3-triphenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (7f). Following general proedure II, from KHMDS (0.73 M in toluene, 3.26 mL, 2.38 mmol, 1.1 equiv), (4*S*)-3-(3,3,3-triphenyl-1-hydroxypropyl)-4-(phenylmethyl)-2-oxazolidinone (1.00 g, 2.17 mmol), trisyl azide (837 mg, 2.70 mmol, 1.25 equiv), and acetic acid (571 μL, 9.97 mmol, 4.6 equiv) was obtained 881 mg (81%) of **7f** (single diastereomer as shown by ^{1}H NMR) as a colorless, nondistillable oil after purification twice by column chromatography (silica gel, hexane/EtOAc, 5/1, and silical gel, $CHCl_3$) $[\alpha]^{23}_D$ = +38.6° (c = 1.0, $CHCl_3$); ^{1}H NMR: (300 MHz) 7.37–7.12 (m, 20 H), 6.90 (s, 1 H), 4.35 (m, 1 H), 4.05 (dd, J = 2.4, 9.1, 1 H), 3.90 (t, J = 8.4, 1 H), 3.16 (dd, J = 3.2, 13.5, 1 H), 2.75 (dd, J = 9.3, 13.5, 1 H); ^{13}C NMR (75.5 MHz) 167.35, 152.79, 143.32, 134.32, 130.09, 129.12, 128.63, 127.51, 127.13 and 126.73, 65.75, 64.49, 61.03, 55.24, 37.15; IR (neat) 2104 (s), 1771 (s), 1709 (s); MS (CI, isobutane, 130 eV) 503 (MH^+, 0.23), 413 ($MH^+ - N_2$, 1.5), 59 (100); TLC R_f 0.5 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{31}H_{26}N_4O_3$ (502.58): C, 74.09; H, 5.21; N, 11.15. Found: C, 73.91; H, 5.18; N, 11.23.

(2*S*)-2-Azido-3-methyl-3-phenyl-1-butanol (8d). General Procedure III. The reductive cleavage of the *N*-acyloxazolidinone was done according to a procedure described by Penning.[11] A solution of acyl oxazolidinone **7d** (4.02 g, 10.6 mmol) in 125 mL of Et_2O containing H_2O (401 μL, 22.3 mmol, 2.1 equiv) was cooled in an ice–water bath under nitrogen. Lithium borohydride ($LiBH_4$, 2.0 M in THF, 11.2 mL, 22.3 mmol, 2.1 equiv) was added, and the resulting opaque white reaction mixture was stirred at 0 °C until completion of the reaction (30 min). The reaction was then quenched at 0 °C with 2 N aqueous KOH (50 mL) and stirring was maintained until both layers became clear. The biphasic mixture was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (silica gel, hexane/EtOAc, 5/1 to 2/2 to $CHCl_3$/MeOH, 10/1) afforded 1.65 g (76%) of **8d** as a colorless oil along with the oxazolidinone auxiliary (1.43 g, 76%) as a white solid. Data for **8d**: $[\alpha]^{23}_D$ = −40.2° (c = 1.54, $CHCl_3$); ^{1}H NMR (400 MHz); 7.39–7.32 (m, 4 H), 7.27–7.23 (m, 1 H), 3.71 (dd, J = 2.9, 9.5, 1 H), 3.54 (ddd, J =2.9, 7.3, 11.2, 1 H), 3.40 (ddd, J = 4.6, 9.5, 11.2, 1 H), 1.59 (dd, J = 4.6, 7.3, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (100.6 MHz) 145.71, 128.47 and 126.01, 126.64, 74.88, 62.85, 41.26, 26.74, 23.31; IR (neat) 3345 (s, broad), 2097 (s); MS (CI, isobutane, 130 eV) 206 (MH^+, 3), 178 ($MH^+ - N_2$, 12), 163 ($MH^+ - N_3$, 13), 119 ($C_6H_5(CH_3)_2C$, 100); TLC R_f 0.5 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{15}N_3O$ (205.26): C, 64.32; H, 7.37; N, 20.47. Found: C, 64.29; H, 7.37; N, 20.26.

(2*S*)-2-Azido-3,3-diphenyl-1-butanol (8e). Following general procedure III, from **7e** (8.25 g, 18.7 mmol) H_2O (629 μL, 39.3 mmol, 2.1 equiv) and $LiBH_4$ (2.0 M in THF, 19.7 mL, 39.3 mmol, 2.1 equiv) was obtained 4.26 g (85%) of **8e** as a colorless, nondistillable oil along with the oxazolidinone auxiliary as a white solid after purification by column chromatography (silica gel, hexane/EtOAc, 4/1 to 3/1 to 0/1). Data for **8e**: $[\alpha]^{23}_D$ = +34.0° (c = 0.66, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$); 7.30–7.20 (m, 10 H), 4.32 (dd, J = 2.3, 9.2, 1 H), 3.80 (ddd, J = 2.3, 6.2, 11.3, 1 H), 3.46 (ddd, J = 4.6, 9.4, 11.4, 1 H), 1.86 (dd, J = 5.3, 6.1, 1 H), 1.72 (s, 3 H); ^{13}C NMR: (75.5 MHz) 145.6, 128.2 and 127.4, 126.5, 71.7, 63.7, 49.1, 24.0; IR (neat); 3400 (s broad), 2100 (s); MS (CI, isobutane, 130 eV); 268 (MH^+, 0.4), 267 (M^+, 0.2), 266 ($M^+ - 1$, 0.5), 188 (100); TLC R_f 0.50 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.82; H, 6.45; N, 15.68.

(2*S*)-2-Azido-3,3,3-triphenyl-1-propanol (8f). Following general procedure III, from **7f** (567 mg, 1.13 mmol), H_2O (40 μL, 2.37 mmol, 2.1 equiv), and $LiBH_4$ (2.0 M in THF, 1.2 mL, 2.37 mmol, 2.1 equiv) was obtained 344 mg (93%) of **8f** as a white solid along with the oxazolidinone auxiliary as a white solid after purification by column chromatography (silica gel, $CHCl_3$/acetone, 1/0 to 40/1 to 0/1). An analytical sample of **8f** was obtained by recrystallization (hexane/Et_2O). Data for **8f**: mp 124–125 °C (hexane/Et_2O); $[\alpha]^{23}_D$ = +3.41° (c = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz) 7.40–7.10 (m, 15 H), 5.16 (dd, J = 1.0, 8.6, 1 H), 3.98 (ddd, J = 1.0, 4.6, 11.4, 1 H), 2.94 (ddd, J = 4.7, 8.9, 11.5, 1 H), 2.35 (t, J = 5.0, 1 H); ^{13}C NMR: (75.5 MHz) 143.8, 129.2, 127.9 and 126.4, 68.9, 65.1, 59.0; IR (neat); 3620 (s broad), 2126 (s), 2093 (s); MS (CI, isobutane, 130 eV); 330 (MH^+, 0.5), 302 (7), 243 (($C_6H_5)_3C^+$, 100), 167 (($C_6H_5)_2CH^+$, 72); TLC R_f 0.44 ($CHCl_3$). Anal. Calcd for $C_{21}H_{19}N_3O$ (329.41): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.66; H, 5.80; N, 12.74.

(2*S*)-2-Amino-3-methyl-3-phenyl-1-butanol (3d). General Procedure IV. Platinum oxide (Adams catalyst) (226 mg, 1.00 mmol, 0.22 equiv) was prereduced at 100 psi of H_2 in MeOH (10 mL) for 15 min in an autoclave with stirring. Then a solution of the azido alcohol **8d** (932 mg, 4.55 mmol) in MeOH (5 mL) was added and the H_2 pressure was set at 250 psi and kept for 4 h. After venting the bomb, the reaction mixture was filtered through Celite and the filtrate was evaporated in vacuo. The resulting crude amino alcohol was purified by column chromatography (silica gel, $CHCl_3$/MeOH, 1/0 to 10/1) to afford 676 mg (83%) of **3d** as a white solid. An analytical sample was obtained by distillation: bp 200 °C (4 Torr); mp 45.0–46.0 °C; $[\alpha]^{23}_D$ = +17° (c = 1.55, $CHCl_3$); ^{1}H NMR (400 MHz) 7.33 (d, J = 4.2, 4 H,), 7.22 (dd, J = 4.4, 8.5, 1 H), 3.58 (dd, J = 3.5, 10.4, 1 H), 3.17 (t, J = 10.1, 1 H), 2.97–2.93 (dd, J = 9.6, 3.5, 1 H), 1.90 (br s, 3 H), 1.31 (s, 6 H); ^{13}C NMR (100.6 MHz) 147.12, 128.29 and 126.08, 62.57, 62.12, 40.76, 24.72, 23.79; IR ($CHCl_3$) 3407 (s), 3019 (s); MS (CI, isobutane, 130 eV); 180 (MH^+, 100); TLC R_f 0.25 ($CHCl_3$/MeOH, 10/1). Anal. Calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.69; H, 9.52; N, 7.78.

(2*S*)-2-Amino-3,3-diphenyl-1-butanol (3e). Following general procudure IV, from PtO_2 (200 mg, 0.88 mmol, 0.07 equiv) and **8e** (3.4 g, 12.72 mmol) was obtained 2.35 g (77%) of **3e** as a white solid after purification by column chromatography (silica gel, $CHCl_3$/MeOH, 1/0 to 10/1). An analytical sample was obtained by recrystallization (cyclohexane/Et_2O) to afford white needles: mp 88–89 °C (cyclohexane/Et_2O); $[\alpha]^{23}_D$ = +9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) 7.31–7.16 (m, 10 H), 3.74–3.68 (m, 2 H), 3.08 (t, J = 9.0, 1 H), 2.40–1.20 (br s, 3 H), 1.65 (s, 6 H); ^{13}C NMR: (100.6 MHz) 146.50, 146.24, 128.17, 127.65, 127.56, 126.10 and 126.07, 63.50, 58.77, 49.94, 23.48; IR ($CHCl_3$) 3019 (s); MS (CI, isobutane, 130 eV); 242 (MH^+, 100), 167 (($C_6H_5)_2CH$, 5.4); TLC R_f 0.25 ($CHCl_3$/MeOH, 10/1). Anal. Calcd for $C_{16}H_{19}NO$ (241.34): C, 79.63; H, 7.94; N, 5.80. Found: C, 79.55; H, 8.01; N, 5.62.

(2*S*)-2-Amino-3,3,3-triphenyl-1-propanol (3f). Following general procudure IV, from PtO_2 (189 mg, 0.83 mmol, 0.3 equiv) and **8f** (890 mg, 2.70 mmol) was obtained 822 mg (100%) of **3f** as a white foam after purification by column chromatog-

raphy (silica gel, $CHCl_3$/methanol, 1/0 to 10/1). An analytical sample was obtained by recrystallization (Et_2O/hexane) under inert atmosphere (**3f** is very hygroscopic): $[\alpha]^{23}_D = -27.3°$ (c = 1.47, $CHCl_3$); ^1H NMR (400 MHz) 7.35 (d, J = 7.6, 6 H), 7.28 (t, J = 7.6, 6 H), 7.19 (t, J = 7.2, 3 H), 4.56–4.53 (dd, J = 2.4, 9.3, 1 H), 3.87 (dd, J = 2.4, 11.0, 1 H), 2.58 (dd, J = 9.3, 11.0, 1 H), 1.85 (bs, 3 H); ^{13}C NMR (100.6 MHz) 129.34, 128.08 and 126.22, 64.6, 61.13, 56.15; IR ($CHCl_3$) 3375 (s), 3088 (s); MS (CI, isobutane, 130 eV); 304 (MH^+, 100), 243 ($(C_6H_5)_3C^+$, 8.4); TLC R_f 0.17 ($CHCl_3$/MeOH, 10/1). Anal. Calcd for $C_{21}H_{21}NO$ (303.41): C, 83.13; H, 6.98; N, 4.62. (Calcd for $[C_{21}H_{21}NO]$·0.25H_2O: C, 81.92; H, 7.04; N, 4.55.) Found: C, 82.30; H, 7.34; N, 4.37.

***N,N'*-Bis[(1*S*)-2-hydroxy-1-(phenylmethyl)ethyl]-2,2-diethyl-1,3-propanediamide (4a). General Procedure V.** To a cold (0 °C) solution of (*S*)-phenylalaninol (9.07 g, 60 mmol) and Et_3N (21 mL, 0.15 mol, 2.5 equiv) in CH_2Cl_2 (80 mL) was added a solution of diethylmalonyl dichloride (4.0 mL, 31 mmol, 0.52 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to rt and was stirred for 45 min. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and poured into saturated aqueous NH_4Cl solution (200 mL). The organic layer was removed and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were successively washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solid white residue was recrystallized from CH_2Cl_2/hexane (1/5) to afford **4a** (12.6 g, 98%) as colorless, fine white needles: mp 65–67 °C (CH_2Cl_2/hexane); $[\alpha]^{27}_D = -24.6°$ (c = 1.01, $CHCl_3$); ^1H NMR (300 MHz) 7.27–7.16 (m, 10 H), 6.85 (d, J = 7.9, 2 H), 4.50–4.25 (br m, 2 H), 3.75 (dd, J = 3.5, 11.1, 2 H), 3.50 (dd, J = 5.9, 11.3, 2 H), 3.31 (br s, 2 H), 2.84 (dd, J = 4.7, 13.9, 2 H), 2.69 (dd, J = 9.1, 13.9, 2 H), 1.72 (m, 4 H), 0.40 (t, J = 7.2, 6 H); ^{13}C NMR (75.5 MHz) 173.21, 137.62, 129.02, 128.45, 126.49, 64.48, 58.13, 52.90, 36.92, 26.09, 7.92; IR ($CHCl_3$) 3421 (m), 3019 (m), 1660 (s); MS (10 eV) 427 (M^+, 3); TLC R_f 0.11 ($CHCl_3$/acetone, 1/1). Anal. Calcd for $C_{25}H_{34}N_2O_4$ (426.56): C, 70.40; H, 8.03; N, 6.57. Found: C, 70.45; H, 8.06; N, 6.71.

***N,N'*-Bis[(1*S*)-1-(hydroxymethyl)-2-methylpropyl)]-2,2-diethyl-1,3-propanediamide (4b).** Following general procedure V, from (*S*)-valinol (4.20 g, 40 mmol), Et_3N (13.9 mL, 0.1 mol, 2.5 equiv), and diethylmalonyl dichloride (3.0 mL, 22 mmol, 0.55 equiv) was obtained 6.37 g (97%) of **4b** as fine white needles after recrystallization (CH_2Cl_2/hexane, 1/5): mp 95–96 °C (CH_2Cl_2/hexane); $[\alpha]^{28}_D = -21.3°$ (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz) 6.89 (d, J = 8.4, 2 H), 3.84–3.70 (m, 4 H), 3.56 (dd, J = 6.8, 11.2, 2 H), 3.30 (br s, 2 H), 2.05–1.79 (m, 6 H), 0.96 (d, J = 6.9, 6 H), 0.93 (d, J = 7.0, 6 H), 0.87 (t, J = 7.5, 6 H); ^{13}C NMR (75.5 MHz) 173.75, 63.65, 58.46, 57.13, 28.87, 27.26, 19.68, 19.93, 8.75; IR (KBr) 3324 (s), 3093 (s), 3058 (s), 2969 (s), 2880 (s), 1641 (s); MS (10 eV) 301 (5), 299 (M^+ − 31, 71), 228 (M^+ − $C_5H_{11}NO$, 100); TLC R_f 0.08 ($CHCl_3$/acetone, 1/1). Anal. Calcd for $C_{17}H_{34}N_2O_5$ (330.47): C, 61.77; H, 10.38; N, 8.48. Found: C, 61.92; H, 10.40; N, 8.48.

***N,N'*-Bis[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-diethyl-1,3-propanediamide (4c).** Following general procedure V, from (*S*)-*tert*-leucinol (0.99 g, 8.4 mmol), Et_3N (4.2 mL, 30 mmol, 3.5 equiv), and diethylmalonyl dichloride (0.82 g, 4.2 mmol, 0.50 equiv) was obtained 1.30 g (86%) of **4c** as white fine needles after recrystallization (CH_2Cl_2): mp 163.0–164.0 °C (CH_2Cl_2); $[\alpha]^{28}_D = +7.1°$ (c = 2.07, $CHCl_3$); ^1H NMR (300 MHz) 6.94 (d, J = 8.4, 2 H), 3.92–3.81 (m, 4 H), 3.54–3.47 (m, 2 H), 2.85 (br s, 2 H), 2.00 (dq, J_q = 7.5, J_d = 14.5, 2 H), 1.93 (dq, J_q = 7.5, J_d = 14.5, 2 H), 0.95 (s, 18 H), 0.90 (t, J = 7.5, 6 H); ^{13}C NMR (75.5 MHz) 175.83, 62.22, 60.96, 60.21, 34.61, 30.37, 27.54, 9.95; IR (KBr) 3326 (s), 2969 (s), 2907 (s), 2883 (s), 1641 (s); MS (10 eV) 343 (M^+ − 15, 2.3), 242 (100). Anal. Calcd for $C_{19}H_{38}N_2O_4$ (358.52): C, 63.65; H, 10.68; N, 7.81. Found: C, 63.63; H, 10.66; N, 7.79.

***N,N'*-Bis[(2*S*)-1-hydroxy-3,3,3-triphenylpropyl]-2,2-diethyl-1,3-propanediamide (4f).** From the reaction of (*S*)-(triphenylmethyl)glycinol **3f** (572 mg, 1.89 mmol), Et_3N (0.66 mL, 4.74 mmol, 2.51 equiv), CH_2Cl_2 (10 mL), and diethylmalonyl dichloride (198 mg, 1.0 mmol, 0.53 equiv) in CH_2Cl_2 (1 mL) at rt for 1 h was obtained the crude dihydroxy diamide **4f** (689 mg, 0.94 mmol) as a foamy, yellowish crystalline solid. This material was carried on directly to **1f** and **10** without further purification: ^1H NMR (300 MHz) 7.40–7.10 (m, 30 H), 6.71 (d, J = 8.7, 2 H), 5.72 (t, J = 7.7, 2 H), 3.95 (dd, J = 1.0, 11.6, 2 H), 3.0 (br m, 2 H), 2.87 (dd, J = 8.2, 11.6, 2 H), 1.65–1.42 (m, 4 H), 0.42 (t, J = 7.3, 6 H); TLC R_f 0.53 ($CHCl_3$/EtOAc, 1/1).

(4*S*)-2,2'-(1-Ethylpropylidene)bis[4-(1-phenylethyl)-4,5-dihydrooxazole] (1a). General Procedure VI. To a cold (0 °C) solution of dihydroxy diamide **4a** (9.4g, 22.0 mmol) and Et_3N (13.5 mL, 96.8 mmol, 4.4 equiv) in CH_2Cl_2 (180 mL) was added methanesulfonyl chloride (MsCl) (3.8 mL, 48.2 mmol, 2.2 equiv) via syringe. The reaction mixture was allowed to warm to rt and stirring was continued for 30 min. The reaction mixture was then poured into saturated aqueous NH_4Cl solution (200 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford the crude bismesylate quantitatively as a yellow oil.

The crude bismesylate was treated with 0.5 M NaOH/MeOH–H_2O (1/1) solution (60 mL) at reflux for 3 h. After the mixture was cooled to rt, it was concentrated to half the original volume. The residue was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a pale yellow oil. The oil was purified by column chromatography (silica gel, CH_2Cl_2/acetone, 10/1) followed by Kugelrohr distillation to afford 6.72 g (78%) of **1a** as a colorless oil: bp 200–205 °C (0.0022 mmHg); $[\alpha]^{24}_D = -21.8°$ ($CHCl_3$, c = 2.55); ^1H NMR (300 MHz) 7.32–7.19 (m, 10 H), 4.46–4.36 (m, 2 H), 4.14 (t, J = 8.9, 2 H), 3.97 (dd, J = 7.1, 8.5, 2 H), 3.16 (dd, J = 4.7, 13.7, 2 H), 2.60 (dd, J = 9.1, 13.7, 2 H), 2.00 (q, J = 7.5, 4 H,), 0.83 (t, J = 7.5, 6 H); ^{13}C NMR (75.5 MHz) 167.86, 137.88, 129.33, 128.51, 126.45, 71.62, 67.26, 46.59, 41.70, 25.42, 8.35; IR (CCl_4) 3087 (m), 3065 (m), 3029 (m), 2973 (s), 1653 (s), MS (70 eV) 391 (5), 390 (M^+, 13), 299 (100); TLC R_f 0.18 ($CHCl_3$/acetone, 20/1). Anal. Calcd for $C_{25}H_{30}N_2O_2$ (390.53): C, 76.89; H, 7.74; N, 7.17. Found: C, 76.80; H, 7.72; N, 7.18.

(4*S*)-2,2'-(1-Ethylpropylidene)bis[4-(1-methylethyl)-4,5-dihydrooxazole] (1b). Following general procedure VI, from **4b** (8.30 g, 25.1 mmol), Et_3N (15.4 mL, 0.11 mol, 4.4 equiv), and MsCl (4.28 mL, 55.3 mmol, 2.2 equiv) was obtained the crude bismesylate as a yellow solid.

This crude material was treated with a 0.5 M NaOH/MeOH-H_2O (1/1) solution (150 mL) as above to afford 6.38 g (86%) of **1b** as a clear, thick colorless oil after purification by column chromatography (silica gel, $CHCl_3$/acetone, 10/1) and Kugelrohr distillation: bp 120–125 °C (0.0012 mmHg); $[\alpha]^{25}_D = -108.3°$ ($CHCl_3$, c = 1.98); ^1H NMR (300 MHz) 4.19–4.11 (m, 2 H), 3.98–3.89 (m, 4 H), 2.05–1.89 (m, 4 H), 1.83-1.72 (m, 2 H), 0.91 (d, J = 6.8, 6 H), 0.86–0.79 (m, 12 H); ^{13}C NMR (75.5 MHz) 167.17, 71.72, 69.45, 46.57, 32.33, 25.17, 18.76, 17.68, 8.26; IR (CCl_4) 2965 (s), 2878 (s), 1657 (s), MS (CI, CH_4) 295 (MH^+, 100), 294 (6); TLC R_f 0.33 ($CHCl_3$/acetone, 10/1). Anal. Calcd for $C_{17}H_{30}N_2O_2$ (294.44): C, 69.35; H, 10.27; N, 9.51. Found: C, 69.27; H, 10.23; N, 9.49.

(4*S*)-2,2'-(1-Ethylpropylidene)bis[4-(1,1-dimethylethyl)-4,5-dihydrooxazole] (1c). Following general procedure VI, from **4c** (5.2 g, 14.5 mmol), Et_3N (8.9 mL, 63.8 mmol, 4.4 equiv), and MsCl (2.5 mL, 32.3 mmol, 2.2 equiv) was obtained the crude bismesylate quantitatively as a yellow oil: TLC R_f 0.30 (CH_2Cl_2/acetone, 10/1).

This crude bismesylate was treated with 0.5 M NaOH/MeOH-H_2O (1/1) solution (37 mL) for 11 h as above to afford 3.51 g (75%) of **1c** as a colorless oil (which solidified in the freezer) after purification by column chromatography (silica gel, CH_2Cl_2/acetone, 15/1) and Kugelrohr distillation: bp 150–160 °C (1.0 mmHg); mp 36.0–37.0 °C; $[\alpha]^{23}_D = -126.3°$ (c = 2.13, $CHCl_3$); ^1H NMR (300 MHz) 4.10 (dd, J = 8.6, 10.1, 2 H), 3.99 (dd, J = 7.4, 8.6, 2 H), 3.84 (dd, J = 7.4, 10.1, 2 H), 2.06 (dq, J_q = 7.3, J_d = 15.0, 2 H), 1.92 (dq, J_q = 7.3, J_d = 15.0, 2 H), 0.88 (s, 18 H), 0.84 (d, J = 7.3, 6 H); ^{13}C NMR (75.5 MHz) 167.12, 75.50, 68.36, 46.67, 33.81, 25.82, 25.28, 8.42; IR (KBr) 2957 (s), 2903 (s), 2870 (s), 1657 (s); MS (CI, CH_4) 323

(M^+, 100), 322 (8); TLC R_f 0.34 ($CHCl_3$/acetone, 40/1). Anal. Calcd for $C_{19}H_{34}N_2O_2$ (322.49): C, 70.76; H, 10.63; N, 8.69. Found: C, 70.62; H, 10.56; N, 8.65.

(4*S*)-2,2′-(1-Ethylpropylidene)bis[4-(1-methyl-1-phenylethyl)-4,5-dihydrooxazole] (1d). A solution of **3d** (409 mg, 2.28 mmol), Et_3N (0.84 mL, 6.03 mmol, 2.64 equiv), and diethylmalonyl dichloride (239 mg, 1.21 mmol, 0.53 equiv) in CH_2Cl_2 (7 mL) was stirred for 1 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was poured into saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were successively washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford *N,N*′-bis[(2*S*)-1-hydroxy-3-phenylbutyl]-2,2-diethyl-1,3-propanediamide (**4d**) quantitatively as a white solid which was used in the next reaction without further purification: ^1H NMR (300 MHz) 7.41−7.19 (m, 10 H), 6.88 (br d, J = 7.8, 2 H), 4.30 (ddd, J = 3.1, 7.8, 8.4, 2 H), 3.65 (dd, J = 3.1, 11.3, 2 H), 3.34 (dd, J = 8.3, 11.3, 2 H)), 2.27 (br s, 2 H*D*), 1.84−1.60 (m, 4 H), 1.362 (s, 6 H), 1.355 (s, 6 H), 0.67 (t, J = 7.4, 6 H); TLC R_f 0.19 ($CHCl_3$/EtOAc, 1/1).

A solution of dihydroxy diamide **4d** (551 mg, 1.14 mmol), Et_3N (0.48 mL, 3.44 mmol, 3.0 equiv), and MsCl (0.23 mL, 2.97 mmol, 2.6 equiv) in CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were successively washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the crude bismesylate quantitatively as a white crystalline solid which was used in the next reaction without further purification: ^1H NMR (300 MHz) 7.50−7.10 (m, 12 H), 4.75−4.60 (m, 2 H), 4.16 (dd, J = 3.1, 11.4, 2 H), 3.93 (dd, J = 8.3, 11.4, 2 H), 2.90 (s, 6 H), 1.95−1.70 (m, 4 H), 1.60 (s, 12 H), 0.80 (t, J = 7.1, 6 H); TLC R_f 0.43 ($CHCl_3$/EtOAc, 1/1).

The bismesylate (729 mg, 1.14 mmol) was treated with KOH (20 mL of a 5 wt % methanolic solution, 14.1 mmol, 12.4 equiv) for 14 h at rt. After removal of the solvent, the residue was purified by column chromatography (silica gel, $CHCl_3$/acetone, 40/1) followed by Kugelrohr distillation to afford 317 mg (62%) of **1d** as a colorless gum: bp 210−215 °C (0.00055 mmHg); $[\alpha]^{24}_D$ = −10.02° (c = 3.58, $CHCl_3$); ^1H NMR (300 MHz) 7.36−7.17 (m, 10 H), 4.43 (dd, J = 7.8, 10.1, 2 H), 3.93 (dd, J = 9.1, 9.9, 2 H), 3.72 (dd, J = 8.1, 8.6, 2 H), 2.08−1.89 (m, 4 H), 1.42 (s, 6 H), 1.22 (s, 6 H), 0.81 (t, J = 7.5, 6 H); ^{13}C NMR (75.5 MHz) 168.01, 146.74, 128.22, 126.55, 126.03, 75.29, 69.10, 46.86, 41.25, 28.00, 25.28, 21.39, 8.50; IR (CCl_4) 3090 (m), 3061 (m), 3029 (m), 2971 (s), 2880 (s), 1655 (s); MS (CI, CH_4) 448 (33), 447 (MH^+, 100), 446 (M^+, 5); TLC R_f 0.23 ($CHCl_3$/acetone, 40/1). Anal. Calcd for $C_{29}H_{38}N_2O_2$ (446.63): C, 77.99; H, 8.58; N, 6.27. Found: C, 77.71; H, 8.59; N, 6.25.

(4*S*)-2,2′-(1-Ethylpropylidene)bis[4-(1,1-diphenylethyl)-4,5-dihydrooxazole] (1e). A mixture of (*S*)-(diphenylmethyl)alaninol (**3e**) (1.011 g, 4.19 mmol) and Et_3N (1.40 mL, 10.05 mmol, 2.40 equiv) in CH_2Cl_2 (25 mL) was treated with diethylmalonyl dichloride (425 mg, 2.16 mmol, 0.51 equiv) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 h at rt. After the usual work up, *N,N*′-bis[(2S)-3,3-diphenyl-1-hydroxybutyl]-2,2-diethyl-1,3-propanediamide (**4e**) was obtained quantitatively as a white crystalline solid which was used in the next reaction without further purification: ^1H NMR (300 MHz) 7.33−7.19 (m, 20 H), 6.90 (d, J = 7.8, 2 H, 4.90 (dt, J = 7.9, 8.0, 2 H), 3.71 (dd, J = 2.1, 11.6, 2 H,), 3.27 (dd, J = 7.9, 11.5, 2 H), 1.80−1.42 (m, 6 H), 1.70 (s, 6 H), 0.55 (t, J = 7.4, 6 H); TLC R_f 0.30 ($CHCl_3$/EtOAc, 1/1).

A solution of dihydroxy diamide **4e** (1.27 g, 2.10 mmol), Et_3N (0.88 mL, 6.31 mmol, 3.01 equiv), and MsCl (0.41 mL, 5.30 mmol, 2.57 equiv) in CH_2Cl_2 (15 mL) was stirred for 50 min at 0 °C. After the usual workup, *N,N*′-bis[(2*S*)-3,3-diphenyl-1-[(methylsulfonyl)oxy]butyl]-2,2-diethyl-1,3-propanediamide was obtained quantitatively as a white crystalline solid which was used in the next reaction without further purification: ^1H NMR (300 MHz) 7.40−7.22 (m, 22 H), 5.40−5.25 (m, 2 H), 4.48 (dd, J = 3.2, 10.6, 2 H), 3.74 (dd, J = 7.9, 10.5, 2 H), 2.91 (s, 6 H), 1.75 (s, 6 H), 1.75−1.60 (m, 4 H), 0.65 (t, J = 7.3, 6 H); TLC R_f 0.38 ($CHCl_3$/acetone, 10/1).

To a suspension of the above bismesylate (1.60 g, 2.10 mmol) in absolute EtOH (30 mL) was added potassium acetate (841 mg, 8.62 mmol, 4.12 equiv), and the reaction mixture was then heated to reflux. After 1.75 h, the mixture was cooled to rt, diluted with H_2O (10 mL), poured into H_2O (20 mL), and extracted with CH_2Cl_2 (4 × 70 mL). The combined organic extracts were dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo to afford a white solid. The crude product was purified by column chromatography (silica gel, $CHCl_3$/acetone, 20/1) and was recrystallized (CH_2Cl_2/TBME) to afford 991 mg (83%) of **1e** as a white crystalline solid: mp 186−187 °C (CH_2Cl_2/TBME); $[\alpha]^{25}_D$ = −11.8° (c = 2.16, $CHCl_3$); ^1H NMR (300 MHz) 7.46−7.19 (m, 20 H), 5.14 (dd, J = 8.8, 9.8, 2 H), 4.12 (t, J = 9.6, 2 H), 3.90 (t, J = 8.8, 2 H), 2.01 (q, J = 7.4, 4 H), 1.64 (s, 6 H), 0.83 (t, J = 7.5, 6 H); ^{13}C NMR (75.5 MHz) 168.06, 148.74, 146.78, 128.53, 128.23, 128.13, 127.84, 126.18, 125.82, 73.20, 69.64, 50.25, 47.01, 25.63, 23.40, 8.62; IR (CCl_4) 3088 (w), 3061 (m), 3027 (w), 2973 (m), 1657 (s); MS (CI, CH_4) 572 (44), 571 (MH^+, 100), 570 (3); TLC R_f 0.62 ($CHCl_3$/acetone, 20/1). Anal. Calcd for $C_{39}H_{42}N_2O_2$ (570.77): C, 82.07; H, 7.42; N, 4.91. Found: C, 81.88; H, 7.45; N, 4.83.

(4*S*)-2,2′-(1-Ethylpropylidene)bis[4-(triphenylmethyl)-4,5-dihydrooxazole] (1f). To a cold (0 °C) solution of **4f** (106.3 mg, 0.145 mmol) and Et_3N (242 μL, 1.74 mmol, 12 equiv) in toluene (2 mL) was added thionyl chloride (64 μL, 0.89 mmol, 6.1 equiv) via syringe. The resulting mixture was heated at 100 °C for 2 h and then was cooled to rt, stirred for 60 min, and then diluted with 10 mL of EtOAc and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by column chromatography (silica gel, benzene/EtOAc, 150/1) afforded 54 mg (54%) of **1f** as a white solid. An analytical sample was obtained by recrystallization (EtOAc/hexane). mp 107.0−108.5 °C (EtOAc/hexane): $[\alpha]^{23}_D$ = −63.4° (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz) 7.33−7.14 (m, 30 H), 5.71 (dd, J = 8.4, 10.6, 2 H), 4.28 (dd, J = 9.4, 10.4, 2 H), 3.99 (t, J = 8.7, 2 H), 1.48 (q, J = 7.5, 4 H), 0.39 (t, J = 7.4, 6 H); ^{13}C NMR (75.5 MHz) 167.72, 130.00, 129.90, 127.63, 126.05, 72.80, 70.80, 61.00, 46.31, 25.36, 8.24; IR (CCl_4) 3054 (m), 2959 (s), 1647 (s), 1597 (m); MS (70 eV) 487 (1.2), 451 (M^+ − CPh_3, 96), (CPh_3^+, 100); TLC R_f 0.20 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{49}H_{46}N_2O_2$ (694.92): C, 84.69; H, 6.67; N, 4.03. Found: C, 84.45; H, 6.69; N, 3.97.

***N,N*′-Bis[(2*S*)-2-(triphenylmethyl)aziridinyl]-2,2-diethyl-1,3-propanediamide (10).** A solution of **4f** (689 mg, 0.94 mmol), Et_3N (0.39 mL, 2.80 mmol, 2.97 equiv), and MsCl (0.185 mL, 2.39 mmol, 2.54 equiv) in CH_2Cl_2 (5 mL), was stirred for 5.5 h at rt. After usual workup, the crude bismesylate was obtained quantitatively as a pale yellow solid which was used in the next reaction without further purification: ^1H NMR (300 MHz) 7.50−7.09 (m, 32 H), 6.18 (ddd, J = 8.7, 9.2, 10.7, 2 H), 4.69 (dd, J = 2.0, 10.7, 2 H), 3.35 (t, J = 9.9, 2 H), 2.87 (s, 6 H), 1.52−1.39 (m, 4 H), 0.31 (t, J = 7.3, 6 H). TLC R_f 0.53 ($CHCl_3$/acetone, 10/1).

The bismesylate (836 mg, 0.94 mmol) was treated with KOH (15 mL of a 5 wt % methanolic solution, 10.6 mmol, 11.2 equiv) for 14 h at rt. After evaporation of the solvent, the crude material was purified by column chromatography (silica gel, CH_2Cl_2) followed by drying overnight under high vacuum at 50 °C to afford 481 mg (73%) of **10** as a white crystalline solid: mp 69.0−71.0 °C; $[\alpha]^{25}_D$ = +56.3° (c = 2.07, $CHCl_3$); ^1H NMR (300 MHz) 7.28−7.11 (m, 30 H), 3.79 (dd, J = 3.6, 6.1, 2 H), 2.25 (d, J = 6.1, 2 H), 2.03−1.95 (m, 2 H) 1.84−1.74 (m, 2 H), 1.61 (d, J = 2.7, 2 H), 0.67 (t, J = 7.4, 6 H); ^{13}C NMR (75.5 MHz) 184.88, 144.35, 129.87, 127.62, 126.65, 63.77, 56.77, 41.83, 32.13, 23.89, 8.49; IR (CCl_4) 3061 (m), 3034 (w), 2971 (m), 1703 (s), 1678 (s); MS (CI, CH_4) 695 (MH^+, 3), 694 (1),

179 (100); TLC R_f 0.52 ($CHCl_3$). Anal. Calcd for $C_{49}H_{46}N_2O_2$ (694.92): C, 84.69; H, 6.67; N, 4.03. Found: C, 84.59; H, 6.65; N, 4.02.

Diethyl 2,2-Bis(2-methylpropyl)propanediolate (14). A suspension of 10% Pd-C (200 mg) and diethyl 2,2-bis(2-methyl-2-propenyl)malonate (**13**)[14] (3.18 g, 11.9 mmol) in EtOH (25 mL) was stirred at rt under 1 atm of H_2 for 16 h. The catalyst was filtered off through Celite pad, and the Celite was washed with 10 mL of EtOH. The filtrate was concentrated to afford an oil, which was purified by distillation to give 2.86 g (88%) of **14** as a colorless oil: bp 85–90 °C (0.1 mmHg); ^{1}H NMR (300 Hz) 4.13 (q, J = 7.1, 4 H), 1.89 (d, J = 6.3, 4 H), 1.64–1.55 (m, 2H), 1.23 (t, J = 7.1, 6 H), 0.85 (d, J = 6.6, 12 H); ^{13}C NMR (75.5 MHz) 172.35, 60.71, 55.93, 40.97, 23.93, 23.44, 13.78; IR (neat) 2957 (s), 2872 (m), 1732 (s), 1699 (m); MS (10 eV) 257 (M^+ − 15, 2), 229 (M^+ − OEt, 4.5), 173 (100). Anal. Calcd for $C_{15}H_{28}O_4$ (272.38): C, 66.14; H, 10.36. Found: C, 66.01; H, 10.38.

2,2-Bis(2-methylpropyl)propanedioic Acid (15). A solution of diethyl diisobutylmalonate **14** (19.92 g, 73.2 mmol) in 25% ethanolic KOH (78 mL) was heated to reflux for 20 h. The EtOH was removed under reduced pressure, and the residue was dissolved in H_2O (150 mL), cooled, and cautiously acidified with concd HCl to pH 7.0. The acidic solution was extracted with CH_2Cl_2 (150 mL) to remove unreacted ester. The acidification was continued to pH 3, and precipitated dicarboxylic acid was removed by extraction with CH_2Cl_2 (6 × 200 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to afford 13.5 g of crude diacid. The product was purified by recrystallization (acetone/hexane) to afford 10.7 g (67%) of **15** as white prisms: mp 153.5–155.0 °C (acetone/hexane); ^{1}H NMR (300 MHz) 1.96 (d, J = 6.8, 4 H), 1.69–1.55 (m, 2 H), 0.89 (d, J = 6.6, 12 H); IR (KBr) 3372 (m), 2969 (s), 1701 (s); MS (10 eV) 172 (6), 129 (100). Anal. Calcd for $C_{11}H_{20}O_4$ (216.28): C, 61.09; H, 9.32. Found: C, 61.06; H, 9.30.

2,2-Bis(2-methylpropyl)propanedioyl Dichloride (16). A mixture of dicarboxylic acid **15** (5.6 g, 25.8 mmol) and $SOCl_2$ (9.42 mL, 129 mmol, 5.0 equiv) was heated to reflux for 6 h. The excess $SOCl_2$ was evaporated and the residue was distilled to afford 5.31 g (81%) of **16** as colorless oil: bp 74–75 °C (0.2 mmHg); ^{1}H NMR (300 MHz, C_6D_6) 2.03 (d, J = 6.3, 2 H), 1.49–1.38 (m, 2 H), 0.73 (d, J = 6.3, 6 H), 0.73 (d, J = 6.5, 6 H); ^{13}C (75.5 MHz, C_6D_6) 171.85, 76.47, 41.53, 24.58, 23.22; IR (CCl_4) 3399 (w), 2961 (s), 2872 (s), 1786 (s), 1705 (s); MS (10 eV) 219 (2), 57 (100). Anal. Calcd for $C_{11}H_{18}Cl_2O_2$ (253.7): C, 52.19; H, 7.17; Cl, 28.01. Found: C, 52.28; H, 7.25; Cl, 27.83.

***N,N''*-Bis[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-bis(2-methylpropyl)-1,3-propanediamide (9c).** To a cold (0 °C) solution of (*S*)-*tert*-leucinol (4.85 g, 41 mmol) and Et_3N (11.4 mL, 82 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) was added a solution of diisobutylmalonyl dichloride (5.21 g, 20.6 mmol, 0.50 equiv) in 10 mL of CH_2Cl_2. The mixture was warmed to rt and stirring was continued for 60 min. After diluting with 50 mL of CH_2Cl_2, the organic layer was washed with saturated aqueous NH_4Cl solution (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and TBME (50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/acetone, 7/1) to afford 6.25 g (73%) of **9c** as fine white needles: mp 135.0–136.5 °C; $[\alpha]^{23}_D$ = −37.4° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz), 8.00 (d, J = 6.5, 2 H), 3.83 (dd, J = 2.2, 10.7, 2 H), 3.72 (dt, J = 2.2, 6.8, 2 H), 3.63 (dd, J = 6.8, 10.7, 2 H), 2.94 (br s, 2 H), 1.84 (d, J = 3.8, 4 H), 1.73–1.60 (m, 2 H), 1.01 (s, 18 H), 0.90 (d, J = 6.4, 6 H), 0.88 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (75.5 MHz) 175.85, 63.88, 61.09, 55.20, 49.26, 33.38, 27.14, 25.50, 23.56, 23.21; IR (KBr) 3546 (s), 3413 (s), 3262 (m), 2957 (s), 1651 (s); MS (70 eV) 399 (M^+ − 15, 3), 384 (18), 357 (M^+ − 57, 18), 298 (M^+ − $C_6H_{14}NO$, 95), 144 (100). Anal. Calcd for $C_{23}H_{46}N_2O_4$ (414.63): C, 66.63; H, 11.18; N, 6.76. Found: C, 66.56; H, 11.16; N, 6.78.

***N,N'*-Bis[(1*S*)-1-(hydroxymethyl)-2,2-diphenylpropyl]-2,2-bis(2-methylpropyl)-1,3-propanediamide (9e).** To a cold (0 °C) solution of (*S*)-(diphenylmethyl)alaninol (464.7 mg, 1.93 mmol) and Et_3N (0.68 mL, 4.87 mmol, 2.5 equiv) in CH_2Cl_2 (10 mL) was added a solution of diisobutylmalonyl dichloride (247 mg, 0.974 mmol, 0.50 equiv) in CH_2Cl_2 (2 mL). The mixture was warmed to rt and stirring was continued for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and poured into saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were successively washed with 0.5 N HCl and brine, dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5/1) to afford 564 mg (88%) of **9e** as a white foam: ^{1}H NMR (300 MHz) 7.64 (s, 2 H), 7.36–7.19 (m, 20 H), 4.57 (dd, J = 5.3, 6.1, 2 H), 4.00 (dd, J = 5.3, 11.8, 2 H), 3.48 (dd, J = 6.1, 11.8, 2 H), 3.40–3.00 (br s, 2 H), 1.71 (s, 6 H), 1.46–1.42 (m, 2 H), 1.46–1.22 (m, 4 H), 0.61 (d, J = 6.3, 6 H), 0.54 (d, J = 6.1, 6 H); IR (KBr) 3430 (m), 3056 (m), 2957 (s), 2869 (m), 1653 (s); MS (70 eV) 631 (M^+ − 31, 23), 481 (M^+ − $CMePh_2$, 92), 422 (M^+ − (diphenylmethyl)alaninol, 55), 268 ($C_{17}H_{18}NO_2$, 100); R_f 0.18 (hexane/EtOAc, 6/1). Anal. Calcd for $C_{43}H_{54}N_2O_4$ (662.91): C, 77.91; H, 8.21; N, 4.23. Found: C, 77.85, H, 8.30; N, 4.15.

(4*S*)-2,2'-(1-(2-Methylpropyl)-3-methylbutylidene)bis-[4-(1,1-dimethylethyl)-4,5-dihydrooxazole] (2c). Following general procedure VI, from **9c** (1.29 g, 3.1 mmol), Et_3N (2.16 mL, 15.5 mmol, 5.0 equiv), and MsCl (0.6 mL, 7.75 mmol, 2.5 equiv) was obtained the crude bismesylate quantitatively as a yellow foam.

The bismesylate was treated with a 0.5 M NaOH/MeOH–H_2O (1/1) solution (20 mL) for 3 h as described above to afford 0.95 g (81%) of **2c** as fine prisms after purification by column chromatography (silica gel, hexane/EtOAc, 25/1) followed by recrystallizaton (EtOAc): mp 123.5–124.0 °C (EtOAc); $[\alpha]^{23}_D$ = −144.3° (c = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz) 4.07 (dd, J = 10.1, 8.6, 1 H), 3.99 (dd, J = 8.6, 7.1, 2 H), 3.81 (dd, J = 7.1, 10.1, 2 H), 2.03 (dd, J = 7.5, 14.6, 2 H), 1.97 (dd, J = 4.4, 14.6, 2 H), 1.73–1.62 (m, 2 H), 0.93 (d, J = 6.7, 6 H), 0.88 (s, 18 H), 0.86 (d, J = 6.6, 6 H); ^{13}C NMR (75.5 MHz) 167.85, 75.48, 67.95, 45.00, 40.80, 34.00, 25.72, 25.00, 23.49, 22.81; IR (KBr) 2955 (s), 2869 (s), 1657 (s); MS (70 eV) 377 (M^+ − 1, 0.8), 363 (M^+ − 15, 16), 335 (M^+ − 43, 16), 321 (M^+ − C_4H_9, 47), 265 (100). Anal. Calcd for $C_{23}H_{42}N_2O_2$ (378.60): C, 72.97; H, 11.18; N, 7.40. Found: C, 72.98; H, 11.21; N, 7.39.

(4*S*)-2,2'-(1-(2-Methylpropyl)-3-methylbutylidene)bis-[4-(1,1-diphenylethyl)-4,5-dihydrooxazole] (2e). Following general procedure VI, from **9e** (90 mg, 0.136 mmol, 2.5 equiv), Et_3N (95 μL, 0.682 mmol), and MsCl (26 μL, 0.34 mmol) was obtained the crude bismesylate quantitatively as a white foam.

The bismesylate was treated with 0.5 M NaOH/MeOH–H_2O (2/1) solution (3 mL) for 13.5 h as described above for to afford 39.7 mg (40%) of **2e** as a white solid after purification by column chromatography (silica gel, CH_2Cl_2/acetone, 10/1). An analytical sample was obtained after recrystallization (CH_2Cl_2): mp 213.5–214.5 °C (CH_2Cl_2); $[\alpha]^{23}_D$ = −30.1° (c = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz) 7.38–7.13 (m, 20 H), 4.99 (dd, J = 8.8, 9.6, 2 H), 4.00 (t, J = 9.6, 2 H), 3.76 (t, J = 8.8, 2 H), 1.94 (dd, J = 4.8, 14.4, 2 H), 1.88 (dd, J = 6.5, 14.4, 2 H), 1.83–1.62 (m, 2 H), 1.53 (s, 6 H), 0.90 (d, 6 H), 0.85 (d, 6 H); ^{13}C NMR (75.5 MHz) 168.58, 148.67, 146.78, 128.44, 128.09, 128.01, 127.70, 125.68, 73.25, 69.26, 50.19, 45.73, 41.86, 24.97, 24.13, 23.36; IR (KBr) 2957 (s), 2899 (m), 2870 (m), 1653 (s); MS (FAB) 627 (M^+, 100); R_f 0.62 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{43}H_{50}N_2O_2$ (626.88): C, 82.40; H, 8.05; N, 4.47. Found: C, 82.39; H, 8.04; N, 4.47.

***N,N'*-Bis[(2*S*)-2-(1,1-diphenylethyl)aziridinyl]-2,2-bis-(2-methylpropyl)-1,3-propanediamide (12).** Following general procedure VI, from **9e** (146 mg, 0.22 mmol), Et_3N (153 μL, 1.10 mmol, 5.0 equiv), and MsCl (48 μL, 0.62 mmol, 2.5 equiv) was obtained the crude bismesylate quantitatively as a white foam.

The bismesylate was treated with a methanolic, 0.5 M NaOH solution (1.5 mL) for 2.5 h as described above to afford 106 mg (77%) of **12** as a white solid after purification by column chromatography (silica gel, CH_2Cl_2/hexane, 1/1). An analytical sample was obtained by recrystallization (hexane/

EtOAc, 10/1) to afford **12** as fine white needles: mp 143.5–144.5 °C (hexane/EtOAc, 10/1), $[\alpha]^{23}_D = -30.1°$ (c = 1.03, $CHCl_3$); ^1H NMR (300 MHz) 7.30–7.17 (m, 20 H), 3.22 (dd, J = 3.8, 5.9, 2 H), 2.61 (d, J = 6.0, 2 H), 2.04–2.00 (m, 6 H), 1.62–1.56 (m, 2 H), 0.86 (d, J = 6.4, 6 H), 0.85 (d, J = 6.5, 6 H); ^{13}C NMR (75.5 MHz) 185.93, 146.79, 146.44, 127.82, 126.20, 61.81, 46.88, 43.42, 40.23, 30.99, 25.01, 24.61, 24.56, 22.75; IR (KBr) 2959 (s), 2869 (m) 1659 (s); MS (FAB) 627 (M^+, 50), 119 (100); R_f 0.62 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{43}H_{50}N_2O_2$ (626.88): C, 82.40; H, 8.05; N, 4.47. Found: C, 82.40; H, 8.04; N, 4.45.

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Supporting Information Available: General experimental procedures along with complete ^1H and ^{13}C NMR assignments, IR and MS data for all characterized compounds (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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