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Stereoselective Synthesis of the Nonproteinogenic Amino Acid (2*S*,3*R*)-3-Amino-2-hydroxydecanoic Acid from (4*S*,5*S*)-4-Formyl-5-vinyl-2-oxazolidinone

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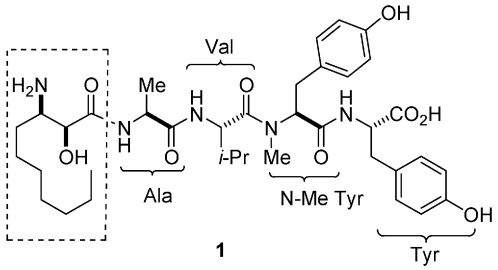
(4*S*,5*S*)-4-Formyl-5-vinyl-2-oxazolidinone (**4b**), which is readily obtained via a zinc−silver-mediated reductive elimination of α-D-*lyxo*furanosyl phenyl sulfone (**3b**), is successfully converted to the naturally occurring, nonproteinogenic amino acid (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (**2**). Also in this study, a facile "oxazolidinone rearrangement" reaction is uncovered during the attempted formation of the (methylthio)thiocarbonate derivative of the oxazolidinone alcohol **7**.

The secondary metabolites isolated from the cyanobacterium *Microcystis aeruginosa* are linear peptides that consist of either four, five, or six amino acids.[1] These peptides are biologically active and exhibit inhibitory activities against protease enzymes. Microginin (**1**) was the first of these linear peptides,[1] which was isolated from cultures of the cyanobacterium, and its structure was assigned on the basis of degradation studies, spectroscopic data, and total synthesis.[1,2] It is a linear pentapeptide wherein the N-terminal unit is a nonproteinogenic amino acid, (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (**2**, AHDA). Subsequently, it was found that (2*S*,3*R*)-AHDA is common to many other linear peptides isolated from the same species.[1b,c] Microginin possesses inhibitory activities against angiotensin-converting enzyme (ACE),[1] an enzyme that is involved in the vasoconstriction of blood vessels. Compounds that are structurally related to microginin are, therefore, of immense medicinal interest because of their potential use in the treatment of hypertension.[3]

The synthesis of (2*S*,3*R*)-AHDA (**2**) has been reported by several groups, and three key strategies[4] have emerged. The first strategy entailed the use of a "chiral pool" starting material.[4a,b] The second strategy employed chiral,

CHART 1. Microginin (1) and (2*S*,3*R*)-AHDA (2)



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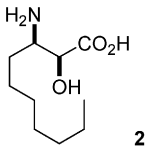
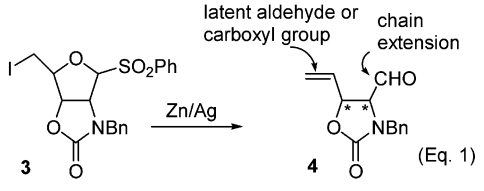


2

nonracemic vic-amino alcohols or their 2-oxazolidinone derivatives, which were prepared via the asymmetric functionalization of appropriately constituted alkenes.[2,4c−e] The third strategy involved the Lewis acid-mediated nucleophilic addition of ketene acetals to chiral, nonracemic imines.[4f]

Chemodifferentiated, bifunctionalized oxazolidinones are useful synthetic intermediates, and their use in the synthesis of amino alcohols and amino acids has not been fully investigated. In this vein, we have developed the use of chiral, nonracemic 4-formyl-5-vinyl-2-oxazolidinones (**4**, eq 1) as advanced building blocks for the synthesis of natural products.[5]



3 **4**

a; α-D-*ribo*furanosyl or **b**; α-D-*lyxo*furanosyl phenylsulfone

a; 4*R*,5*R* or **b**; 4*S*,5*S*

(1) (a) Ekino, T.; Matsuda, H.; Murakami, Y.; Yamaguchi, K. *Tetrahedron Lett*. **1993**, *34*, 501. (b) Ishida, K.; Kato, T., Murakami, M.; Watanabe, M.; Watanabe, M. F. *Tetrahedron* **2000**, *56*, 8643. (c) Ishida, K.; Matsuda, H.; Murakami, M. *Tetrahedron* **1998**, *54*, 13475. (d) Reshef, V.; Carmeli, S. *Tetrahedron* **2001**, *57*, 2885. Linear peptides from other algae species: (e) Sano, T.; Kaya, K. *Phytochemistry* **1997**, *44*, 1503. (f) Neumann, U.; Forchert, A.; Flury, T.; Weckesser, J. *FEMS Microbiol. Lett*. **1997**, *153*, 475.

(2) (a) Matsumura, F.; Hamada, Y.; Shiori, T. *Tetrahedron* **1994**, *50*, 11303. (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165.

(3) Wyvratt, M. J.; Patchett, A. A. *Med. Res. Rev*. **1985**, *5*, 483.

(4) Chiral pool: (a) Jefford, C. W.; McNulty, J.; Lu, Z.-H.; Wang, J.-B. *Helv. Chim. Acta* **1996**, *79*, 1203. (b) Tuch, A.; Saniere, M.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901. Asymmetric functionalization of alkenes: (c) Sugimura, H.; Miura, M.; Yamada, N. *Tetrahedron: Asymmetry* **1997**, *8*, 4089. (d) Righi, C.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903. (e) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem*. **1999**, *64*, 2852. Nucleophilic addition to chiral imines: (f) Ha, H. J.; Ahn, Y.-G.; Woo, J.-S.; Lee, G. S.; Lee, W. K. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 1667.

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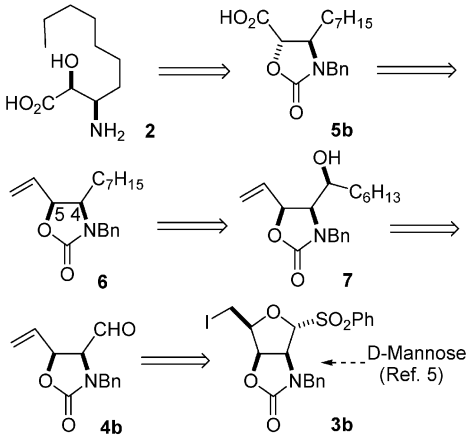
SCHEME 1. Retrosynthetic Analysis of (2*S*,3*R*)-AHDA



In previous reports, we showed[5] that (a) these versatile enantiomeric aldehydes **4** were readily generated via the Zn−Ag couple-mediated reductive elimination of the appropriate iodo phenyl sulfones **3** and (b) the in situ reaction of the aldehydes **4** with organocerium reagents proceeded efficiently and with high diastereoselectivity to give the corresponding secondary alcohols. We have employed aldehydes **4** as advanced chiral, nonracemic intermediates in the total synthesis of C-18-D-*ribo*-phytosphingosine[5b] and (2*R*,3*S*)-3-hydroxy-2-(hydroxymethyl)pyrrolidine.[5c] We now demonstrate the use of chiral, nonracemic aldehyde **4b** in the synthesis of (2*S*,3*R*)-AHDA (**2**) and report, herein, the details of our work.

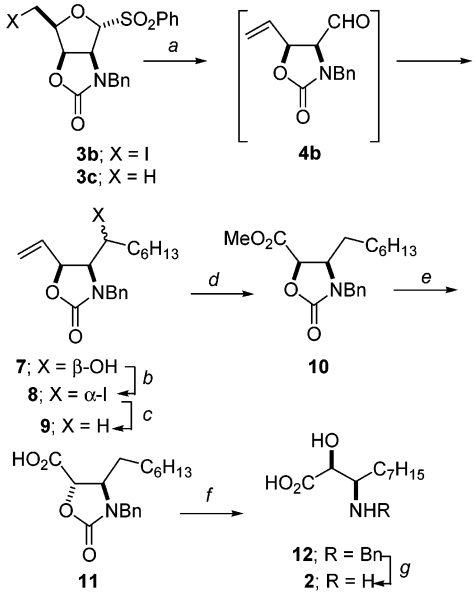
Results and Discussion

The retrosynthetic analysis of (2*S*,3*R*)-AHDA (**2**) is summarized in Scheme 1. Amino acid **2** could be envisioned to be derived from **5**, which in turn, should be accessible from the olefin **6**. Olefin **6** should be obtainable from the secondary alcohol **7**, which is prepared via the nucleophilic addition reaction of the organocerium reagent "$C_6H_{13}CeCl_2$" and the known 2-oxazolidinonecarbaldehyde **4b**,[5c] readily accessible from the iodo phenyl sulfone **3b**.

Thus, the readily prepared iodo phenyl sulfone **3b**[5c] was subjected to the previously described[5] reductive elimination to obtain the aldehyde **4b** which, without isolation, was reacted with preformed $C_6H_{13}CeCl_2$ at −78 °C. This provided an inseparable mixture of the *syn*-alcohol **7**[5a,b] and the known[5c] deiodinated compound **3c** in a 6.3:1 ratio (Scheme 2). To facilitate in the further characterization of **7**, a small amount of the mixture was treated with acetic anhydride to obtain the acetate derivative **7** (X = OAc), which was readily separated from **3c**. The next step in our synthesis of AHDA (**2**) required the removal of the hydroxyl group in **7** in order to complete the installation of the heptyl substituent. The mixture of alcohol **7** and **3c** was employed in the subsequent studies because compound **3c** was deemed to be chemically insert under the reaction conditions that would be used.

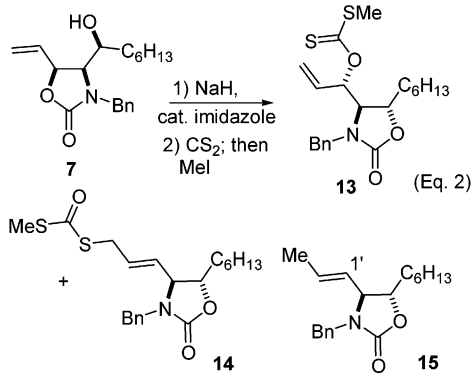
(5) (a) Wee, A. G. H.; Tang, F. *Tetrahedron Lett.* **1996**, *37*, 6677. (b) Wee, A. G. H.; Tang, F. *Can. J. Chem.* **1998**, *76*, 1070. (c) Wee, A. G. H.; McLeod, D. D.; Rankin, T. R. *Heterocycles* **1998**, *48*, 2263.

SCHEME 2 [a]



[a] Reagents: (a) (i) Zn/Ag, glacial AcOH; (ii) **4b**, THF, $C_6H_{13}CeCl_2$, −78 °C, 78%. (b) Ph_3P, I_2, imidazole, PhMe, 120 °C, 64%. (c) Bu_3SnH, cat. AIBN, PhMe, 110 °C, 85%. (d) Route a: (i) O_3, CH_2Cl_2, − 78 °C, Me_2S; (ii) Jones' reagent; CH_2N_2, 47% (over three steps). Route b: O_3, 2.5 M aq NaOH, MeOH, − 78 °C, 69%. (e) NaOMe (4 mol equiv), MeOH; then 1 M aq HCl, 99%. (f) 2 M aq KOH, 95% EtOH, reflux, quant. (g) 20% $Pd(OH)_2$, H_2, MeOH, 94%.

We chose to employ free-radical technology for the removal of the hydroxyl group in **7**. The Robins' method[6b,c] was first explored, which required the preparation of the secondary phenyl thionocarbonate derivative. Thus, the alcohol **7** was treated with phenyl chlorothioformate in the presence of DMAP according to the literature procedure.[6b,c] However, no phenyl thionocarbonate product was formed in this case, even after a prolonged reaction time (22 h, rt), and starting alcohol **7** (and **3c**) was recovered in 90% yield. The difficulty encountered in the acylation of the secondary hydroxyl group was somewhat unexpected. We reasoned that the hydroxyl moiety may be in a sterically encumbered environment and that approach of the bulky 4-(*N*,*N*-dimethyl)-1-(phenoxythiocarbonyl)pyridinium chloride to the hydroxyl group may be sterically hindered. Furthermore, if acylation had occurred, the corresponding tetrahedral intermediate would be energetically disfavored for steric reasons.



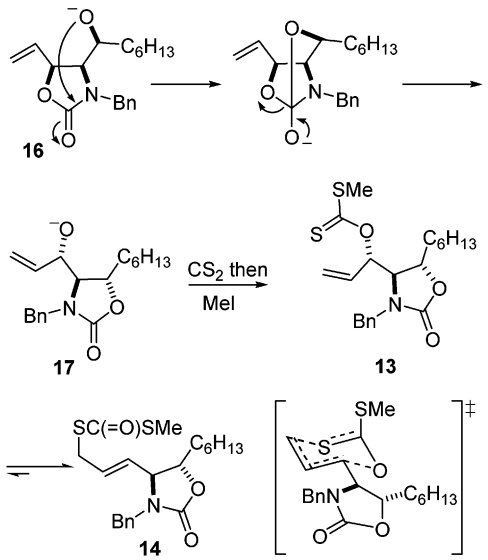
Therefore, we investigated the preparation of the (methylthio)thiocarbonate[6a,7] from the alcohol **7** (eq 2). It was hypothesized that (a) the alkoxide oxyanion would be more nucleophilic and (b) acylation by carbon disulfide (CS_2) would occur more efficiently compared to the use of the bulkier 4-(*N*,*N*-dimethyl)-1-(phenoxythiocarbonyl)-pyridinium chloride. Thus, the alcohol **7** was treated with NaH (0 °C, THF) in the presence of a catalytic amount of imidazole, according to the literature procedure,[7] and followed subsequently by the addition of CS_2 and iodomethane to afford two new compounds as revealed by TLC analysis of the reaction mixture. The two components were readily separated from **3c** and purified by flash chromatography: the less polar (R_f = 0.54, 3:1 petroleum ether/EtOAc) component was assigned structure **13**, and the more polar compound (R_f = 0.31, 3:1 petroleum ether/EtOAc) was assigned structure **14** on the basis of spectroscopic data. The ratio of **13**:**14** was 6:1; however, upon standing, compound **13** was found to slowly convert to **14** (72 h, rt).

The IR spectra of compounds **13** and **14** exhibited the characteristic absorptions for the thiocarbonyl group at ν_{max} 1058 cm^{-1} and the carbonyl moiety at ν_{max} 1647 cm^{-1}, respectively. For compound **13**, the salient features in its ^{1}H NMR spectrum were the set of multiplets at δ 5.32−5.49 and 5.58−5.79, which were ascribed to the terminal olefinic hydrogens, and a low-field multiplet at δ 6.25−6.33, which was due to the allylic hydrogen adjacent to the xanthate moiety. The characteristic resonances in the ^{1}H NMR spectrum of **14** were the set of double doublets, due to the allylic methylene hydrogens, one centered at δ 3.50 and the other at δ 3.58 and the multiplet at δ 5.32−5.55, which were attributed to the internal olefinic hydrogens. A comparison of the ^{1}H NMR spectra of **13** and **14** also revealed significant chemical shift differences in the resonances of the H-5 multiplet and the benzylic methylene hydrogens. In **13**, H-5 was deshielded and resonated at δ 4.32−4.45, whereas in **14**, H-5 appeared at δ 3.92−4.08. The benzylic methylene hydrogens in **13** resonated at δ 4.91 and 4.95, but in **14**, these hydrogens were shielded and occurred at δ 3.85 and 4.67.

For further structural confirmation, compound **14** was reduced with tributylstannane (catalytic AIBN) to provide the olefin **15** (eq 2). The ^{1}H NMR spectrum showed the absence of the characteristic set of double doublets of the allylic methylene hydrogens and the presence of a new signal (double doublet, J = 6.6, 1.3 Hz) centered at δ 1.74 due to the allylic methyl group. Furthermore, the H-1′ resonance centered at δ 5.62 revealed a vicinal coupling constant of $J_{1',2'}$ = 15.1 Hz, which indicated a trans geometry for the double bond in **15** and hence also in compound **14**.

A plausible mechanism to explain the formation of **13** and **14** from **7** under the reaction conditions used for (methylthio)thiocarbonate formation is shown in Scheme 3. The initially formed alkoxide **16** (from **7**) is envisaged

SCHEME 3. Reaction Pathway for the Formation of 13 and 14



to participate in a facile intramolecular nucleophilic substitution reaction with the 2-oxazolidinone moiety, which would result in the formation of the isomeric *trans*-2-oxazolidinone **17**. The driving force for this rearrangement is the relief of steric strain. The rearranged alkoxide **17** is intercepted by CS_2 followed by methyl iodide to form the corresponding (methylthio)thiocarbonate (**13**).

Compound **14** is formed from **13** via a thermally and orbital-symmetry-allowed thio-Claisen rearrangement reaction.[8a] The tendency for **13** to rearrange to **14** suggests that the former compound is thermodynamically less stable than **14**.[8b] The formation of the trans double bond in **14** indicates that the rearrangement had proceeded via a highly ordered chairlike transition state in which the bulky 2-oxazolidinonyl unit occupied a pseudoequatorial position.

Since the Robins and Barton−McCombie methods for deoxygenation were not suitable for use in the conversion of **7** to **9**, alternative methods based on the free-radical-mediated reduction of halides[9] were investigated. Therefore, the secondary iodide **8** was prepared from **7** (and **3c**) (Scheme 2), and we chose to use an iodination procedure based on the Mitsunobu reaction.[5,10] Initially, we were concerned that the sterically hindered hydroxyl group in **7** may prove to be resistant to conversion to the iodide. We were pleased that reaction of **7** with a mixture of Ph_3P, I_2, and imidazole in toluene at reflux afforded a 64% yield of the desired iodide **8**, which was easily separated from the deiodinated compound **3c**. Subsequent reduction of the secondary iodide **8** with tributylstannane under free-radical reaction conditions afforded the olefin **9** in 85% yield.

(2*S*,3*R*)-AHDA. With the olefin **9** successfully prepared, the next step in the synthesis entailed the conver-

(6) (a) Hartwig, W. *Tetrahedron* **1983**, *29*, 2609−2645. (b) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. (c) Martin, S. F.; Dapper, M. S.; Dupre, S.; Murphy, C. J. *J. Org. Chem.* **1987**, *52*, 3708.

(7) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(8) (a) Compared with: Martin, S. F.; Daniel, D.; Cherney, R. T.; Liras, S. *J. Org. Chem.* **1992**, *57*, 2523. (b) Semiempirical AM1 calculations (PC Spartan, version 6) of compounds **13** and **14** gave ΔH_f (**13**) = − 71.242 kcal/mol and ΔH_f (**14**) = − 99.755 kcal/mol.

(9) Review: Neumann, W. P. *Synthesis* **1987**, 665.

(10) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. (b) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813.

sion of the C5-ethenyl unit to an ester group. Two pathways were investigated. The first was a three-step procedure (route a, Scheme 2) that consisted of the ozonolysis of the ethenyl group to generate the aldehyde, Jones' oxidation of the aldehyde, and methylation of the corresponding carboxylic acid with ethereal diazomethane. Although this route afforded the methyl ester **10** in an overall (three steps) yield of 47%, a more concise route for the preparation of **10** was desired.

In 1993, Marshall and Garofalo reported[11] the direct conversion of alkenes to methyl esters via ozonolysis of the double bond in 2.5 M methanolic sodium hydroxide. Therefore, we decided to prepare **10** using this method (route b, Scheme 2). We were also aware that potential complications, resulting from base-mediated hydrolysis of the 2-oxazolidinone moiety, could arise. However, it was reasoned that since the oxidation was conducted at −78 °C, the 2-oxazolidinone moiety may be tolerated under the basic reaction conditions. Our line of reasoning was confirmed: the ozonolysis of olefin **9**, employing the prescribed conditions,[11] yielded the cis methyl ester **10** in a respectable yield of 69%. It is useful to note that *trans*-**10**, which could have arisen from an epimerization at the C-5 stereocenter under the basic reaction conditions, was not detected. The ^{1}H NMR spectrum of the crude product only showed the signals corresponding to *cis*-**10**.

With the *cis*-ester **10** in hand, we investigated a "one-pot" procedure,[12] for the preparation of the trans acid **11**, via the epimerization of the C-5 stereocenter and hydrolysis of the carbomethoxy group (Scheme 2). It was expected that epimerization would be facile because of the relief of steric strain in the conversion of *cis*-**10** to *trans*-**11**. When *cis*-**10** was treated with KOH in refluxing ethanol,[12] a 1:1 cis and trans mixture of the acid **11** was obtained. These results suggested that hydrolysis of the carbomethoxy group in *cis*-**10** was competitive with epimerization of the C-5 stereocenter; the hydrolysis of the ester group in *cis*-**10** would yield the corresponding carboxylate anion, which, in turn, would suppress further epimerization at C-5 by attenuating the acidity of the C-5 α-hydrogen.

It is clear from the above studies that epimerization at C-5 must precede the hydrolysis of the ester moiety, and we therefore examined the reaction using NaOMe in MeOH under anhydrous conditions. Initial studies quickly revealed that the use of neither catalytic amounts (30 mol %) nor 1 mol equiv of NaOMe was effective for causing epimerization; in fact, starting material was consumed and an unidentified product was obtained. It was found that the desired epimerization was best achieved using 4 equiv of NaOMe in methanol at room temperature (24 h) and that subsequent processing of the reaction mixture with 1 M aqueous HCl led directly to the desired trans acid **11** in quantitative yield.

To complete the synthesis of (2*S*,3*R*)-AHDA, acid **11** was treated with 2 M aqueous KOH in refluxing ethanol[5c] to give the crystalline *N*-benzyl amino acid **12** (Scheme 2) in quantitative yield. The *N*-benzyl protecting group in **12** was removed by hydrogenolysis [20% $Pd(OH)_2$, H_2 (balloon)] to yield synthetic **2** in 94% yield after purification via ion-exhange chromatography. The melting point of our synthetic **2** matched the reported literature melting point for (2*S*,3*R*)-AHDA.[2] The ^{1}H NMR data for synthetic **2** are also in accord with the data reported[2] in the literature.

(11) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem*. **1993**, *58*, 3675.
(12) Sunazuka, T.; Nagamitsu, T.; Tanaks, H.; Omura, S. *Tetrahedron Lett*. **1993**, *34*, 4447.

Conclusions

The readily accessible 2-oxazolidinone-4-carbaldehyde (**4b**) has proven to be an excellent and practical building block for the synthesis of (2*S*,3*R*)-AHDA (**2**, overall yield 27%). Besides 2-oxazolidinone's role as a masked vic-amino alcohol, its chemical stability to a variety of reagents is noteworthy, which permitted further synthetic manipulations to be applied to the C-4 and C-5 substituents culminating in the synthesis of **2**. Moreover, the "oxazolidinone rearrangement" reaction (**7** → **14**), which occurred during the attempted formation of the (methylthio)thiocarbonate derivative of alcohol **7**, provides a potential new route for the preparation of β-hydroxy-α-amino acids from oxazolidinone derivatives of type **7**. Studies directed at developing the "oxazolidinone rearrangement" reaction are ongoing.

Experimental Section

(4*R*,5*S*)-3-Benzyl-4-(1-hydroxyheptyl)-5-vinyl-2-oxazolidinone (7). The organocerium reagent, $C_6H_{13}CeCl_2$, was prepared by treating a suspension of anhydrous $CeCl_3$ (3.00 g, 12.2 mmol)[5a,c] in THF (27 mL) with 0.5 M $C_6H_{13}MgBr$ (24 mL) [prepared from 1-bromohexane (3.50 mL, 4.13 g, 25.0 mmol) and Mg turnings (0.945 g, 39.6 mmol) in THF (25 mL)] at 0 °C. The mixture was stirred at 0 °C for 1 h and then cooled to −78 °C.

The iodo phenyl sulfone **3b** (1.0 g, 2.0 mmol) was dissolved in THF (20 mL), and the solution was added, via cannula, to a suspension of Zn/Ag couple in dry THF.[8] The mixture was refluxed for 1 h, and the reaction mixture was cooled to room temperature. The filtered solution of aldehyde **4b** was transferred, via cannula, to the preformed $C_6H_{13}CeCl_2$ at −78 °C. The reaction mixture was stirred at −78 °C for 5 h and then slowly warmed to room temperature and stirred at room temperature for 1 h. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl (5 mL), and the organic phase was extracted, dried, filtered, and evaporated. Purification of the crude oily residue by flash chromatography (5:1 petroleum ether/EtOAc) gave 577 mg of an inseparable mixture of the secondary alcohol **7** and the known[5c] bicyclic oxazolidinone **3c**. The ratio of **7**:**3c** was 6.3:1 on the basis of the relative ratio of the integration of the multiplet due to the internal olefinic proton (δ 6.10) of **7** to the integration of the multiplets due to the protons of the phenyl sulfone moiety (δ 7.52−7.95) in **3c**. ν_{max}: 3426(br), 1744, 1496 cm^{-1}. ^{1}H NMR (discernible signals for **3c** in square brackets): δ 0.89 (t, 3H, J = 7.3 Hz), 1.02−1.69 (m, 10H), [1.38, d, J = 6.7 Hz], 2.00−2.19 (br. s, 1H), 3.57 (dd, 1H, J = 4.6, 8.6 Hz), 3.62−3.78 (m, 1H), 4.36 (d, 1H, J = 15.9 Hz), [4.38, d, J = 13.9 Hz], [4.63, s], [4.65, d, J = 13.9 Hz], 4.80−4.98 (m, 1H), 4.98 (d, 1H, J = 15.9 Hz), 5.40−5.52 (m, 2H), 6.10 (ddd, 1H, J = 18, 12, 6.7 Hz), 7.15−7.49 (m, 5H), [7.52−7.95, m].

A small amount of **7** (23.5 mg, 0.074 mmol, based on **7**) was reacted with Ac_2O (12.0 μL, 0.128 mmol) in dry pyridine (1 mL) containing a catalytic amount of DMAP (8.00 mg, 0.066 mmol). After 2 h at room temperature, the reaction mixture was concentrated and ethyl acetate was added. The mixture was washed several times with saturated $CuSO_4$, water, and then brine. The organic layer was dried, filtered, and evaporated. The residual oil was purified by flash chromatography

(6:1 petroleum ether/EtOAc and then 2:1 petroleum ether/EtOAc) to afford the acetate **7** (X = OAc, 91%, 20.9 mg) and the known[5c] bicyclic oxazolidinone **3c** (3 mg). **Compound 7 (X = OAc).** ν_{max}: 1744 cm^{-1}. ^1H NMR: δ 0.82 (t, 3H, J = 6.6 Hz), 0.87−1.72 (m, 10H), 1.97 (s, 3H), 3.65 (dd, 1H, J = 3.1, 7.9 Hz), 4.14 (d, 1H, J = 15.6 Hz), 4.76−4.99 (m, 3H), 5.37 (dd, 2H, J = 11.4, 16.9 Hz), 5.74−5.96 (m, 1H), 7.12−7.40 (m, 5H). ^{13}C NMR: δ 13.9, 22.4, 25.6, 28.9, 31.2, 31.5, 47.9, 58.3, 71.6, 78.1, 120.4, 127.9, 128.0, 128.9, 130.4, 135.9, 158.1, 170.0. HRMS: calcd for $C_{21}H_{30}NO_4$ (M + 1), 360.2175; found, 360.2175.

Compound 3c.[5c] ν_{max}: 1754, 1672 cm^{-1}. ^1H NMR: δ 1.37 (d, 3H, J = 6.7 Hz), 4.38 (d, 1H, J = 13.3 Hz), 4.59−4.63 (m, 1H), 4.64 (d, 1H, J = 13.3 Hz), 4.80−5.00 (m, 3H), 7.30−7.50 (m, 5H), 7.52−7.88 (m, 5H).

Formation of (4*R*,5*S*)-3-Benzyl-5-hexyl-4-[(1*S*)-1-(*S*-methyldithiocarbonyloxy)-2-propenyl]-2-oxazolidinone (13) and (4*S*,5*S*)-3-Benzyl-5-hexyl-4-[3-(methylthio)thiocarbonyloxy]-(1-propenyl)-2-oxazolidinone (14). The alcohol **7** (218 mg, 0.688 mmol) and imidazole (2.74 mg, 0.0403 mmol) were dissolved in THF (8 mL). Then, the solution was added to a suspension of NaH (50% in mineral oil, 38.3 mg, 0.799 mmol) in THF (2 mL) at 0 °C and stirred for 3 h. Carbon disulfide (0.42 mL, 6.98 mmol) was added to the reaction mixture, causing a bright yellow color to appear. After 1 h, methyl iodide (0.45 mL, 7.23 mmol) was added and the mixture was stirred for an additional 1 h and then slowly warmed to room temperature. Brine was added to the reaction mixture; the organic layer was separated and washed, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic phases were dried, filtered, and evaporated. The residue was subjected to flash chromatography (8:1 petpetroleum ether/EtOAc and then 1:1 petroleum ether/EtOAc) to give a 6:1 ratio of products **13** (55%, 168 mg) and **14** (9.5%, 38.7 mg). Compound **3c**[5c] (28 mg) was also isolated. **Compound 13.** ν_{max}: 1756, 1650, 1058, 912 cm^{-1}. ^1H NMR: δ 0.88 (t, 3H, J = 8.4 Hz), 1.04−1.68 (m, 10H), 2.61 (s, 3H), 3.40 (dd, 1H, J = 2.4, 4.1 Hz,), 4.07 (d, 1H, J = 15.3 Hz), 4.32−4.44 (m, 1H), 4.96 (d, 1H, J = 15.3 Hz), 5.32−5.49 (m, 2H), 5.58−5.79 (m, 1H), 6.24−6.35 (m, 1H), 7.23−7.50 (m, 5H). ^{13}C NMR: δ 14.6, 19.8, 22.5, 24.6, 29.4, 32.1, 36.0, 47.1, 61.6, 75.1, 80.8, 121.7, 126.1, 128.7, 128.9, 129.5, 130.0, 135.4, 157.8, 215.1. **Compound 14.** ν_{max}: 1751, 1647 cm^{-1}. ^1H NMR: δ 0.89 (t, 3H, J = 8.4 Hz), 1.00−1.40 (m, 8H), 1.40−1.60 (m, 2H), 2.37 (s, 3H), 3.47 (dd, 1H, J = 7.5, 7.5 Hz), 3.50 (dd, 1H, J = 12.3, 6.2 Hz), 3.58 (dd, 1H, J = 12.3, 5.5 Hz), 3.85 (d, 1H, J = 14.5 Hz), 3.94−4.08 (m, 1H), 4.67 (d, 1H, J = 14.5 Hz), 5.32−5.55 (m, 2H), 7.10−7.34 (m, 5H). ^{13}C NMR: δ 13.2, 14.1, 22.5, 24.7, 28.9, 31.6, 31.7, 33.7, 45.9, 62.8, 79.2, 127.8, 128.6, 128.7, 130.4, 131.9, 135.8, 157.6, 188.9. HRMS: calcd for $C_{19}H_{26}NO_2$ (M − MeSC(=O)S), 300.1963; found, 300.1958.

(4*S*,5*S*)-3-Benzyl-5-hexyl-4-(1-propenyl)-2-oxazolidinone (15). A solution of *n*-Bu_3SnH (176 mg, 0.603 mmol) in toluene (8 mL) was heated to 80 °C. A mixture of compound **14** (98.2 mg, 0.241 mmol) and AIBN (8 mg, 0.0487 mmol) in toluene (2 mL) was added to the hot *n*-Bu_3SnH solution via cannula. The mixture was heated at 80 °C for 16 h, and then the solvent was removed in vacuo. The product **15** was isolated by column chromatography, initially eluting with 20:1 petroleum ether/EtOAc to remove the tin residue and then with a gradient elution starting with 6:1 petroleum ether/EtOAc to 3:1 petroleum ether/EtOAc to give **15** (85%, 111 mg). ν_{max}: 1753, 1603 cm^{-1}. ^1H NMR: δ 0.88 (t, 3H, J = 8.3 Hz), 1.03−1.66 (m, 10H), 1.73 (dd, 3H, J = 7.1, 9.1 Hz), 3.54 (dd, 1H, J = 9.1, 7.1 Hz), 3.97 (d, 1H, J = 14.7 Hz), 3.97−4.14 (m, 1H), 4.72 (d, 1H, J = 14.7 Hz), 5.17−5.36 (m, 1H), 5.62 (dq, 1H, J = 15.1, 6.9 Hz), 7.12−7.44 (m, 5H). ^{13}C NMR: δ 14.0, 17.8, 22.5, 22.8, 28.9, 31.6, 33.6, 45.7, 63.5, 79.6, 127.6, 127.7, 127.8, 128.4, 128.6, 133.1, 136.1, 157.7. HRMS: calcd for $C_{19}H_{27}NO_2$, 301.2042; found, 301.2047.

(4*S*,5*S*)-3-Benzyl-4-(1-iodoheptyl)-5-vinyl-2-oxazolidinone (8). Imidazole (164 mg, 2.40 mmol) was dissolved in toluene (5 mL) at 80 °C, and to this was added Ph_3P (724 mg, 2.76 mmol) in toluene (3 mL) via cannula. Then, the alcohol **7** (283 mg, 0.892 mmol) in toluene (3 mL) was added, followed by I_2 (454 mg, 1.79 mmol) in toluene (14 mL). After all the additions were complete, the temperature was raised to 120 °C and the reaction was stirred overnight. The reaction was cooled to room temperature, and then EtOAc (15 mL) and Florisil were added. The mixture was stirred for 30 min. The organic layer was washed with sodium thiosulfate (to remove excess I_2) and brine, dried, filtered, and concentrated. This compound required a number of filtrations to remove the Ph_3PO. The residue was subject to column chromatography (8:1 petroleum ether/EtOAc and then 4:1 petroleum ether/EtOAc) to give the oily iodide **8** (64%, 267 mg) and **3c**[5c] (21 mg). ν_{max}: 1756 cm^{-1}. ^1H NMR: δ 0.88 (t, 3H, J = 8.1 Hz), 1.03−2.15 (m, 10H) 3.85−4.04 (m, 1H), 4.12 (dt, 1H, J = 4.6, 11.3 Hz), 4.47 (d, 1H, J = 16.3 Hz), 4.82 (dd, 1H, J = 7.3, 9.0 Hz), 5.03 (d, 1H, J = 16.3 Hz), 5.38−5.63 (m, 2H), 5.86−6.17 (m, 1H), 7.12−7.48 (m, 5H). ^{13}C NMR: δ 14.0, 22.6, 28.2, 29.7, 31.1, 31.6, 34.3, 46.6, 62.5, 79.6, 121.6, 128.1, 128.2, 128.9, 129.3, 135.8, 157.8.

(4*R*,5*S*)-3-Benzyl-4-heptyl-5-vinyl-2-oxazolidinone (9). The iodide **8** (145 mg, 0.339 mmol) and AIBN (11.4 mg, 0.0694 mmol) were dissolved in toluene (3 mL), and then added to a solution of *n*-Bu_3SnH (247 mg, 0.849 mmol) in toluene (6 mL) at 80 °C. The reaction temperature was raised to 110 °C after the addition was complete. After 6 h, the cooled reaction mixture was quenched with the addition of Et_2O (15 mL) and 10% aqueous KF[25] (10 mL); the mixture was stirred for 1 h. The layers were separated, and the aqueous layer was washed with Et_2O. The organic layers were combined, dried, and concentrated, and the crude product was subjected to column chromatography (8:1 petroleum ether/EtOAc and then 4:1 petroleum ether/EtOAc) to give the product **9** (85%, 86.7 mg). ν_{max}: 1754, cm^{-1}. ^1H NMR: δ 0.77−1.70 (m, 15H), 3.58 (dt, 1H, J = 7.6, 3.1 Hz), 4.04 (d, 1H, J = 15.1 Hz), 4.83 (d, 1H, J = 15.1 Hz), 4.87 (t, 1H, J = 6.9 Hz), 5.38 (d, 1H, J = 10.5 Hz), 5.46 (d, 1H, J = 16.8 Hz), 5.80−6.00 (m, 1H). ^{13}C NMR: δ 14.1, 22.6, 24.7, 27.0, 28.9, 29.5, 29.7, 31.7, 46.2, 57.5, 78.3, 120.5, 127.9, 128.0, 128.4, 128.8, 130.9, 136.1, 152.1.

(4*R*,5*R*)-3-Benzyl-4-heptyl-5-methoxycarbonyl-2-oxazolidinone (10): Route A. Compound **9** (24.0 mg, 0.0797 mmol) was dissolved in CH_2Cl_2 and cooled to −78 °C. Ozone was bubbled through the solution until it turned blue and TLC indicated that the reaction was complete. Ph_3P (23.7 mg, 0.120 mmol) was added to the solution at −78 °C, and the mixture was slowly warmed to room temperature. After 1 h of stirring, the solvent was evaporated and the aldehyde was dissolved in redistilled acetone (2 mL) and cooled to 0 °C. Jones' reagent (0.15 mL) was added to the solution, and the mixture was stirred at 0 °C until the orange color persisted for 20 min. After 20 min, 2-propanol was added to destroy excess Jones' reagent. Then, Celite was added and the mixture was stirred for an additional 15 min and then filtered through a Celite pad. The filtrate was evaporated to give an oil, which was taken into EtOAc; this solution was extracted with $NaHCO_3$. The extract was acidified with 10% HCl at 0 °C and extracted thoroughly with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residual oil was taken into Et_2O, and ethereal CH_2N_2 (2 M in Et_2O, 2 mL) was added at 0 °C. This mixture was stirred overnight, and then the excess CH_2N_2 was destroyed by careful addition of glacial acetic acid. The solution was evaporated, and the residue was subjected to column chromatography (5:1 petroleum ether/EtOAc) to give the ester **10** (47%, 12.5 mg). The IR and ^1H NMR spectra were identical to the ester obtained using route B. **Route B.** Compound **9** (61.0 mg, 0.203 mmol) was dissolved in a mixture of CH_2Cl_2 (2 mL) and 2.5 M methanolic NaOH (0.45 mL). The mixture was cooled to −78 °C, and ozone was bubbled into the solution. The mixture initially turned a bright yellow and then went clear and finally blue. Et_2O (20 mL) and H_2O (10 mL) were added at −78 °C to prevent hydrolysis of the ester, and the

mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was washed several times with Et_2O. The combined organic layers were dried, filtered, concentrated, and subjected to column chromatography (6:1 petroleum ether/EtOAc and then 1:1 petroleum ether/EtOAc) to give the ester **10** (69%, 46.8 mg). $[\alpha]^{23}_D$: −27.9° (*c* 1.70, $CHCl_3$). ν_{max}: 1769, 1496 cm^{-1}. ^1H NMR: δ 0.87 (t, 3H, J = 6.8 Hz), 1.03−1.78 (m, 12H), 3.81 (s, 3H), 3.74−3.87 (m, 1H), 4.09 (d, 1H, J = 15.3 Hz), 4.81 (d, 1H, J = 15.4 Hz), 4.92 (d, 1H, J = 8.3 Hz), 7.22−7.44 (m, 5H). ^{13}C NMR: δ 14.1, 22.6, 24.5, 28.3, 28.9, 29.5, 31.6, 46.3, 52.5, 56.7, 74.8, 128.0, 128.1, 128.9, 135.5, 157.3, 168.0. HRMS: calcd for $C_{19}H_{27}NO_4$, 333.1940; found, 333.1940.

(4*R*,5*S*)-3-Benzyl-4-heptyl-5-carboxylate-2-oxazolidinone (11). A solution of the ester **10** (41.3 mg, 0.124 mmol) in dry MeOH (2.4 mL, 100 mL distilled from 1.0 g Na) was treated with 1 M NaOMe (0.248 mL, 0.248 mmol) in MeOH. The mixture was stirred at room temperature, and after 6 h, another portion of 1 M NaOMe (0.248 mL, 0.248 mmol) was added. The reaction was stirred overnight and then quenched with 1 M HCl (1 mL); the resulting mixture was evaporated and subjected to column chromatography (4:1 CH_2Cl_2/MeOH) to give the acid **11** (99%, 39.6 mg). $[\alpha]^{23}_D$: +28.8° (*c* 1.0, $CHCl_3$). ν_{max}: 3530−2400, 1762, 1497 cm^{-1}. ^1H NMR: δ 0.86 (t, 3H, J = 6.6 Hz), 1.05−1.85 (m, 12H)., 3.60−3.75 (m, 1H), 4.11 (d, 1H, J = 15.2 Hz), 4.60 (d, 1H, J = 4.5 Hz), 4.79 (d, 1H, J = 15.1 Hz), 7.18−7.43 (m, 5H), 8.37−8.74 (br. s, 1H). ^{13}C NMR: δ 14.0, 22.5, 23.2, 29.0, 29.1, 31.5, 31.6, 46.2, 58.1, 74.3, 127.8, 128.1, 128.9, 135.1, 156.9, 172.4. HRMS calcd for $C_{18}H_{25}NO_4$ 319.1783, found 319.1778.

(2*S*,3*R*)-*N*-Benzyl-3-amino-2-hydroxydecanoic Acid (12). The acid **11** (11.5 mg, 0.0359 mmol) was dissolved in 96% EtOH (1.5 mL), and 2 M KOH (1 mL) was added. The mixture was refluxed for 40 h and cooled to room temperature, and the solvent was removed in vacuo. The residue was taken into 10% HCl and stirred for 1 h, and the acidic solution was evaporated to dryness. The residue was subjected to ion-exchange chromatography (Dowex 50w × 8, 200−400 mesh, H^+ form), using 5% NH_4OH as the eluent. The *N*-benzyl amino acid **12** was obtained with a small amount of impurity present (quantitative, 10.5 mg). Mp (MeOH/H_2O): 206.8−209.2 °C. $[\alpha]^{23}_D$: +5.1° (*c* 4.9, MeOH). ν_{max} (KBr): 3418−2300, 3313, 1734, 1636 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.84 (t, 3H, J = 6.5 Hz), 1.00−1.49 (m, 12H), 2.55−2.69 (m, 1H), 3.67 (d, 1H, J = 4.1 Hz), 3.74 (d, 1H, J = 13.4 Hz), 3.94 (d, 1H, J = 13.4 Hz). ^{13}C NMR (DMSO-d_6): δ 14.0, 22.1, 25.9, 29.2, 29.9, 31.3, 50.1, 58.8, 69.4, 126.8, 128.1, 128.4, 140.0, 175.1. FAB-HRMS: calcd for $C_{17}H_{28}NO_3$ (M + 1), 294.2069; found, 294.2063.

(2*S*,3*R*)-3-Amino-2-hydroxydecanoic Acid (2). The amino acid **12** (10.5 mg, 0.0358 mmol) was dissolved in MeOH (4 mL) at room temperature, and Pearlman's catalyst (20% $Pd(OH)_2$/C, 6.49 mg) was then added. The reaction mixture was stirred under H_2 gas (balloon, 1 atm). After 16 h, the mixture was filtered through a Celite pad moistened with MeOH. The solvent was evaporated under reduced pressure, and the residue was subjected to ion-exchange chromatography (Dowex 50w × 8, 200−400 mesh) using 5% NH_4OH as the eluent. The amino acid **2**, was obtained as the free base (94%, 6.84 mg). $[\alpha]^{22}_D$: +7.3 (*c* 0.34,1 M HCl). Lit.[2b] $[\alpha]^{25}_D$: +5.4 (*c* 0.59, 1 M HCl). Mp: 218.4−219.7 (dec). Lit.[2b] mp: 219−220 (dec). ^1H NMR (D_2O): δ 0.80 (t, 3H, J = 6.8 Hz), 1.20−1.70 (m, 12H), 3.30−3.39 (m, 1H), 4.03 (d, 1H, J = 3.7 Hz). FAB-HRMS: calcd for $C_{10}H_{22}NO_3$ (M + 1), 204.1600; found, 204.1549.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **3c** and **7**−**15** and ^1H NMR spectra of the rearrangement of **13** to **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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