Synthesis of the Angiotensin-Converting Enzyme Inhibitors (−)-A58365A and (−)-A58365B from a Common Intermediate

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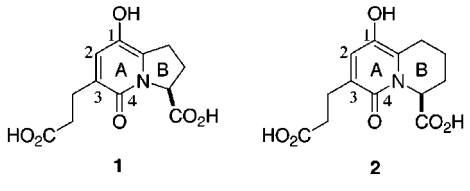
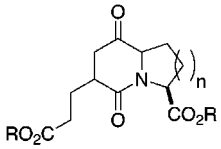
(−)-A58365A (**1**) and (−)-A58365B (**2**), which are inhibitors of angiotensin-converting enzyme, were synthesized from the subunits **9** and **10**. These were coupled, and the resulting individual amides **17a**,**b** were converted by ozonolysis into aldehydes **18a**,**b**, which underwent cyclodehydration to the enamides **19a**,**b**. Treatment with a stannane served to generate the vinyl stannanes **20a**,**b**, from which ketones **22a**,**b** were produced by protodestannylation and ozonolysis. Base treatment and hydrogenolysis then afforded (−)-A58365A (**1**). The intermediates **17a**,**b** were also converted into aldehydes **26a**,**b** by hydroboration and oxidation, and a similar sequence to that used for (−)-A58365A was then applied in order to complete the first enantiospecific synthesis of the congener, (−)-A58365B (**2**).

We report the synthesis[1] of (−)-A58365A (**1**) and (−)-A58365B (**2**), two natural products which were isolated[2a,b] in the Eli Lilly Laboratories at Indianapolis from the fermentation broth of a soil bacterium. The compounds are powerful inhibitors[2c] of angiotensin-converting enzyme, and this property should make their structures relevant to the design of blood-pressure-lowering drugs.[3]

When we began our studies, a route to (−)-A58365A had already been published,[5] and during the course of our work the synthesis of (±)-A58365B was also reported.[6]

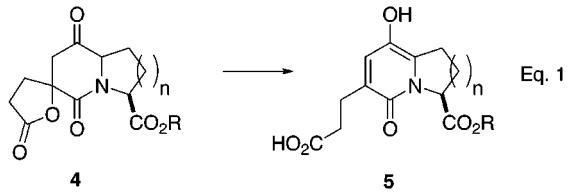


1 **2**



3

As the compounds are formally enols of α,β-unsaturated ketones, a potential synthetic approach is to aim for the corresponding saturated materials (cf. **3**), with the intention of then using one of the standard methods for introducing a double bond α to a ketone carbonyl. However, this approach is not straightforward and leads to poor yields.[6−8] Consequently, we decided to introduce the troublesome C(2)−C(3)[9] double bond in the disguised form of an additional ring, as shown in **4** (eq 1, R = protecting group). Such compounds (**4**) should be convertible by the action of base into **5**, which represent



4 **5** Eq. 1

protected versions of the target natural products. In the event, this approach was very successful, and we applied it first to (±)-A58365B.[1a] Extensive exploratory work was required, however, to devise an efficient synthesis of the intermediate spirolactone **4** (n = 2, R = Me), and we eventually developed a route based on the radical cyclization[10] summarized in Scheme 1. With **4** (n = 2, R = Me) in hand, conversion into **5** (n = 2, R = Me) was easy,

(1) Preliminary communications: (a) Clive, D. L. J.; Zhou, Y.; de Lima, D. P. *J. Chem. Soc., Chem. Commun.* **1996**, 1463−1464. (b) Clive, D. L. J.; Coltart, D. M. *Tetrahedron Lett.* **1998**, *39*, 2519−2522.

(2) (a) Isolation: Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Du Bus, R. H.; Baker, P. J. *J. Antibiot.* **1985**, *38*, 1003−1007. (b) Structure: Hunt, A. H.; Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Maciak, G. M.; Kirst, H. A.; Occolowitz, J. L.; Swartzendruber, J. K.; Jones, N. D. *J. Antibiot.* **1988**, *41*, 771−779. (c) Biological activity: O'Connor, S.; Somers, P. *J. Antibiot.* **1985**, *38*, 993−996.

(3) (a) Douglas, W. W. In *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; Macmillan: New York, 1985; pp 639−659. (b) For studies on analogues of **1**, see ref 4.

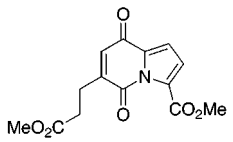
(4) (a) Mynderse, J. S.; Fukuda, D. S.; Hunt, A. H. *J. Antibiot.* **1995**, *48*, 425−427. (b) Mynderse, J. S.; Fukuda, D. S. EP 133038 (*Chem. Abstr.* **1985**, *103*, 160306).

(5) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621−3624.

(6) For a synthesis of (±)-A58365B and formal syntheses of (±)- and (−)-A58365A, see: Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434−11445.

(7) de Lima, D. P., Ph.D. Thesis, 1994, Universidade Federal Minas Gerais (Brazil). The studies on (±)-A58365B were done at the University of Alberta.

(8) For example, treatment of **3** (n = 1, R = Me) with DDQ leads to **i** (see ref 6). Desaturation of **3** (n = 1 or 2, R = Me) had to be done in an indirect way (see ref 6).



i

(9) Nonsystematic numbering.

(10) For intermolecular addition of radicals (carrying electron-withdrawing groups) to the distal terminus of an enamine double bond, see: Renaud, P.; Schubert, S. *Synlett* **1990**, 624−626. For intramolecular cyclization of a radical onto the proximal terminus of a enamide double bond, see: Yuasa, Y.; Kano, S.; Shibuya, S. *Heterocycles* **1991**, *32*, 2311−2314. Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A.

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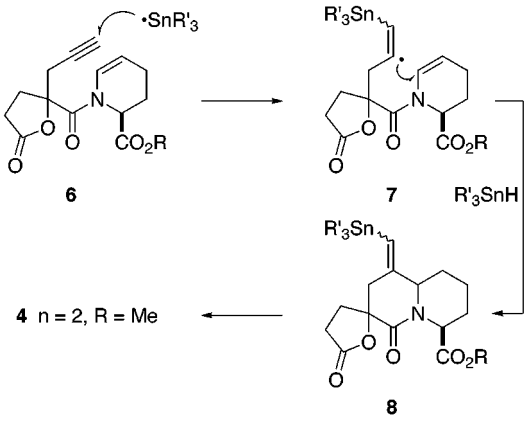
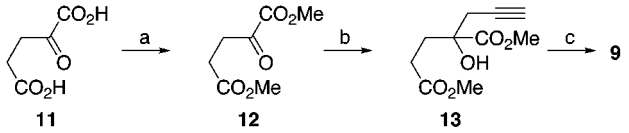
Scheme 1



Scheme 2[a]

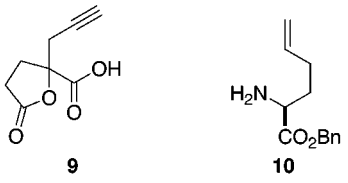


[a] (a) MeOH, $TsOH \cdot H_2O$, $CHCl_3$, azeotropic distillation; 94%; (b) propargyl bromide, Al, $HgCl_2$, THF, −78 °C; 95%; (c) LiOH, THF, H_2O; Amberlite IR-120; evaporate eluant at 60 °C; 95%.

and the last step—hydrolysis of the methyl ester—could be accomplished[1a] by using $Bu_3SnOSnBu_3$.[11]

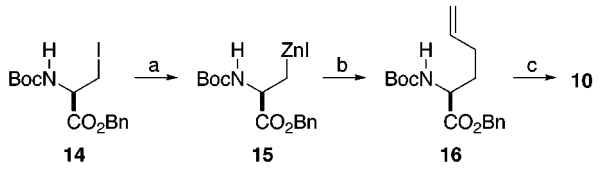
With these experiments as background, we were able to improve our approach by using a benzyl instead of a methyl ester, to facilitate the final deprotection. At the same time we introduced some modifications so that *both* **1** and **2** could be made optically pure from a common advanced intermediate.

The final version of our synthesis is based on the racemic acid **9** and the optically pure amino acid benzyl ester **10**.



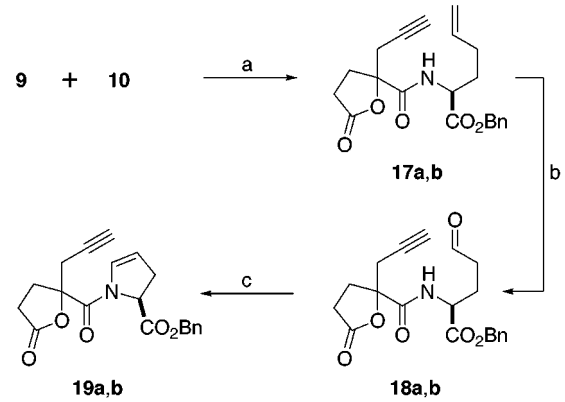
Synthesis of (−)-A58365A. Acid **9** was prepared from α-ketoglutaric acid (**11**) (Scheme 2) by methylation (**11** → **12**) and treatment with the reagent[12] generated from propargyl bromide and amalgamated aluminum. In this second step (**12** → **13**) no allene was detected,[13] and the required tertiary alcohol could be isolated in high (95%) yield. Conversion into acid **9** was achieved (95%) by base hydrolysis (LiOH), followed by ion-exchange chromatography (Amberlite IR-120), and evaporation of the eluant

Scheme 3[a]



[a] (a) Zn, $BrCH_2CH_2Br$, Me_3SiCl, THF; (b) CuCN, LiCl, THF, −15 °C to 0 °C; allyl chloride, −30 °C to 0 °C; 84% from **14**; (c) CF_3CO_2H, CH_2Cl_2; 97%.

Scheme 4[a]



[a] (a) 1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole, CH_2Cl_2, DMF; 95% of a 1:1 mixture of **17a** (chromatographically less polar diastereoisomer) and **17b**; (b) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to room temperature; 97% for **18a**, and 96% for **18b**; (c) BaO, CH_2Cl_2, sonication; P_2O_5, sonication; 71% or 93% (corrected for recovered **18a**) for **19a**; 87% for **19b**.

at 60 °C. We assume that the intermediate hydroxy diacid cyclizes during evaporation of the solvent.

The other component, optically active amino acid benzyl ester **10**, was a known compound,[14] which was made as shown in Scheme 3. We actually first prepared it in racemic form and found that considerable experimentation was needed in order to develop a reliable and efficient method for making the intermediate organozinc (cf. **15**). This was eventually accomplished by a judicious blend of two literature procedures.[15,16]

Compounds **9** and **10** were coupled under standard conditions [1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole; 95%] to obtain a mixture of diastereoisomers **17a**,**b**, which could be separated chromatographically (Scheme 4). Each of these was then ozonized to the corresponding aldehyde (**18a**,**b**) in very high yield (≥96%). The next step, cyclization to enamides **19a**,**b**, was first studied using racemic compounds. Application of the reagent system (CF_3CO_2H, 4 Å molecular sieves) used in our earlier synthesis[1a] of (±)-A58365B was unsuccessful,[17] but we eventually found

J. Org. Chem. **1993**, *58*, 4198−4199. Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269−5282. For cyclization onto the distal terminus of an enamide double bond, see: Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044−8050.

(11) Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, *29*, 6893−6896.

(12) Läuger, P.; Prost, M.; Charlier, R. *Helv. Chim. Acta* **1959**, *42*, 2379−2393. Schneider, D. F.; Weedon, B. C. L. *J. Chem. Soc. (C)* **1967**, 1686−1689. Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *J. Org. Chem.* **1993**, *58*, 7782−7788. Janardhanam, S.; Balakumar, A.; Rajagopalan, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 551−556.

(13) Cf. Klein, J. In *The Chemistry of the Carbon−Carbon Triple Bond*, Patai, S., Ed.; Wiley: Chichester, 1978; Part 1, pp 343−379.

(14) Dunn, M. J.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1992**, 319−320.

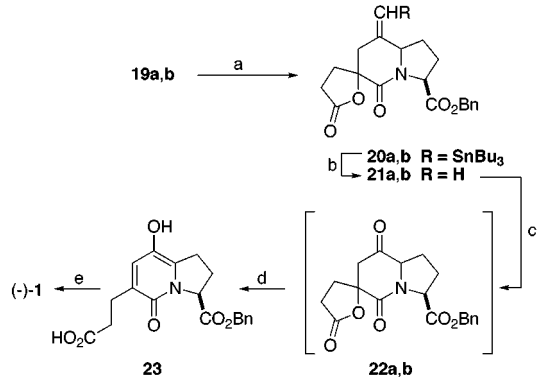
(15) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799−4802.

(16) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Wishart, N.; Ellis, D.; Wythes, M. J. *Synlett* **1993**, 499−500.

(17) Cyclization to six-membered enamides appears to be easier than for the five-membered series: Cf. Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393−396. Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078−7079.

(18) Cf. Paterson, I.; Cowden, C.; Watson, C. *Synlett* **1996**, 209−211.

Scheme 5[a]



[a] (a) Bu_3SnH, AIBN, PhMe, reflux; (b) CF_3CO_2H, THF; 93% overall for **21a**; 94% overall for **21b**; (c) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to room temperature; (d) Et_3N, THF, 60 °C; 95% overall from **21a**; 96% overall from **21b**; (e) H_2, Pd−C, MeOH; 93%.

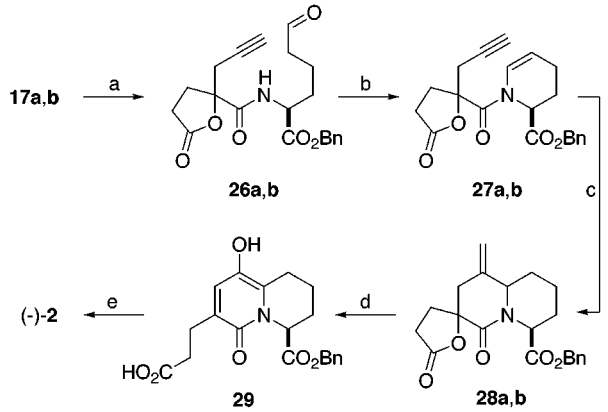
that sonication of the amido aldehydes with BaO, followed by addition of P_2O_5[18] (with continued sonication), led to smooth ring closure and dehydration, and the same conditions were used in the optically active series (Scheme 4, **18a** → **19a**, 71% or 93% based on recovered starting material; **18b** → **19b**, 87%). Both **19a** and **19b** exist as a mixture of rotamers, as judged by variable temperature ^1H NMR measurements.

Rapid addition (over a few seconds) of a PhMe solution (best added in two equal portions) of Bu_3SnH and AIBN to a refluxing solution of **19a** in the same solvent gave **20a** (77%) after a reflux period of ca. 5 h (Scheme 5). Similarly, **19b** gave **20b** (85%). However, as described below, the efficiency of the process is much greater than these yields would imply. Each vinyl stannane was a single compound of undetermined double bond geometry. Although the vinyl stannanes could be purified by flash chromatography and then subjected to protodestannylation with CF_3CO_2H, it was far more efficient to use the crude material directly for protodestannylation. In this manner, **19a** was converted into **21a** (93% from **19a**), and **19b** into **21b** (94%). Ozonolytic cleavage of the exocyclic double bond of each stereoisomer proceeded efficiently (**21a** → **22a**; **21b** → **22b**), but the ketones were difficult to separate from Ph_3PO, formed during reductive workup of the ozonolysis mixture. Therefore, the crude ketones were treated directly with Et_3N at 60 °C, and this operation served to open the lactone, introduce the C(2)−C(3) double bond, and release the propionate side chain (**21a** → **23**, 95%; **21b** → **23**, 96%). Finally, hydrogenolysis of the benzyl group gave (−)-A58365A (**1**) in 93% yield as a white foam.

The whole of the above sequence was also done using the racemic amino acid benzyl ester corresponding to **10**, so as to afford (±)-A58365A.

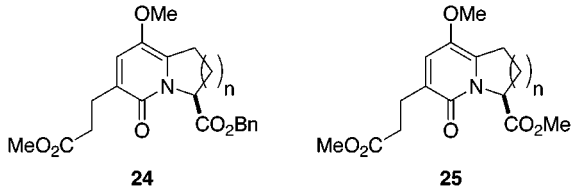
Our key amino acid **10** was made from serine of 97% ee (Aldrich), and the specific rotation of our synthetic

Scheme 6[a]



[a] (a) 9-BBN, THF, 0 °C to room temperature; PCC, CH_2Cl_2, 4 Å molecular sieves, reflux; 83% for **26a**; 74% for **26b**; (b) BaO, CH_2Cl_2, sonication; P_2O_5, sonication; 83% for **27a**, 80% for **27b**; (c) Bu_3SnH, AIBN, PhMe, reflux; CF_3CO_2H, THF; 74% overall from **27a**; 92% overall from **27b**; (d) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to room temperature; Et_3N, THF, 60 °C; 95% overall from **28a**; 96% overall from **28b**; (e) H_2, Pd−C, MeOH; 96%.

(−)-**1** corresponded to an optical purity of 98.5%.[19] This value was confirmed by the following experiments. Benzyl ester **23** was dimethylated (CH_2N_2) and the product (**24**, $n = 1$) examined by HPLC, using an optically active



stationary phase that gave baseline resolution with (±)-**24** ($n = 1$). Our optically active material was found to have an ee of 99.5%. Synthetic **1** was converted into its trimethyl derivative (**25**, $n = 1$), and this, as well as the corresponding racemic material, was examined by HPLC. An ee of 96.2% was determined, but in this case clear baseline resolution of the enantiomers was not obtained. We conclude that, within the limits of experimental error, the present route involves no loss of optical integrity.

Synthesis of (−)-A58365B. Intermediates **17a**,**b** served also for the synthesis of **2**. In the synthesis of **1**, described above, the olefinic carbon chain of **17a**,**b** was shortened by oxidative cleavage of the double bond. In the present case, to make **2**, oxidation of the double bond is again required, but with retention of the complete carbon chain, so that a six-membered ring can eventually be generated (see ring B in **2**). This oxidation was effected (Scheme 6) by taking advantage of the selectivity of 9-BBN for an alkene over an alkyne.[20] While the use of 9-BBN did indeed serve to functionalize the terminal double bond, we found it difficult to isolate the derived alcohols[21] because of hydrolysis of the benzyl ester during the borane oxidation step. We could, however, obtain the corresponding aldehydes directly, by oxidizing the intermediate boranes in situ with PCC[22] (**17a** → **26a**, 83%; **17b** → **26b**, 74%),[23] and so this temporary problem was actually an advantage, as we would otherwise have had to oxidize the alcohols in a separate step.

From **26a**,**b**, cyclization with the BaO/P_2O_5 combination again worked well and took the route as far as

(19) The reported $[\alpha]^{25}_D = -199.5°$ (*c* 1.0, H_2O) (see reference 2b); our material had $[\alpha]^{25}_D = -196.55°$ (*c* 0.87, H_2O).

(20) Brown, C. A.; Coleman, R. A. *J. Org. Chem.* **1979**, *44*, 2328−2329.

(21) These exploratory studies were done on the more polar (TLC, silica gel) diastereoisomer [(+)-**17b**].

(22) Cf. Brown, H. C.; Kulkarni, S. U.; Rao, C. G. *Synthesis*, **1980**, 151−153.

(23) Oxidation of the boranes to the aldehydes could also be done with TPAP, but in lower yield.

enamides **27a**,**b** (83% for **27a**; 80% for **27b**). In our earlier synthesis of (±)-A58365B[1a] cyclization of the corresponding methyl esters had been effected with CF_3CO_2H/4 Å molecular sieves, but in lower yield for one of the diastereoisomers.

With the individual diastereoisomers **27a** and **27b** in hand, treatment with Bu_3SnH/AIBN, this time added in one portion, followed directly by protodestannylation, gave **28a** and **28b**, respectively. One of the diastereoisomers of **27a**,**b** exists as a mixture of rotamers (cf. **19a**,**b**), each of which is observable by ^{1}H NMR measurements, and this isomer cyclizes less efficiently than the other (74% overall yield of the protodestannylated product versus 92%). The same phenomenon had been met[1a] in our earlier synthesis of (±)-A58365B, and in that case use of Ph_3SnH led to some improvement in the yield. In the present instance we did not vary the nature of the stannane, but did try the experiment in boiling xylene and found no improvement.

The exocyclic olefins **28a**,**b** were individually ozonized and treated with Et_3N, so as to generate benzyl ester **29** (95% for **28a**; 96% for **28b**), and final deprotection was again done by hydrogenolysis (**29** → **2**; 96%), thus completing the first synthesis of (−)-A58365B. The entire sequence was repeated in the racemic series. The optical purity of the synthetic natural product was established in the same manner as for its congener: 99% ee on the basis of optical rotation measurements,[24] 98.3% by HPLC analysis of the derived trimethyl derivative (**25**, $n = 2$), and 99.6% by HPLC analysis of the dimethyl benzyl derivative (**24**, $n = 2$). Again, we conclude that the route involves no loss of optical integrity.

In the above work the use of spirolactones constitutes an effective method for introduction of the C(2)−C(3) double bond, and it is likely that our route can be modified to make a variety of analogues, in particular, those differing in the length of the side chain or by the presence of substituents on the amino acid component, especially α to the carboxyl group.

Experimental Section

General Procedures. The same general procedures as used previously[25] were followed. The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively.

Dimethyl 2-Hydroxy-2-[2-(propynyl)]pentanedioate (13). A mixture of Al powder[12] (84.0 mg, 3.11 mmol) and $HgCl_2$ (5 mg, 0.02 mmol) in dry THF (3 mL) was stirred vigorously for 1 h (Ar atmosphere) in a three-necked flask fitted with a reflux condenser and closed by septa. Most of the solvent was then withdrawn by syringe from the resulting shiny Al, and fresh THF (3 mL) was injected. The mixture was warmed in an oil bath set at 40 °C, and propargyl bromide (363 mg, 3.05 mmol) in THF (1 mL) was then added slowly with vigorous stirring and at such a rate that the THF did not boil. The addition took ca. 10 min. After the addition, stirring at 40 °C was continued until a dark gray solution was obtained (ca. 1 h). This was cooled to room temperature and added by cannula at a fast dropwise rate to a stirred and cooled (−78 °C) solution of **12** (158 mg, 0.90 mmol) in THF (5 mL). Stirring at −78 °C was continued for 4 h, and the mixture was then poured into ice−water (100 mL) and extracted with Et_2O (4 × 30 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using 30:70 EtOAc−hexanes, gave pure (^{1}H NMR) **13** (185 mg, 95%) as a colorless oil: FTIR (KBr) 3502, 3286, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02−2.15 [m, 3 H including a t at δ 2.05 ($J = 2.7$ Hz)], 2.16−2.26 (m, 1 H), 2.41−2.52 (m, 1 H), 2.56 (A of an ABX system, apparent dd, $J = 16.9$, 2.7 Hz, 1 H), 2.66 (B of an ABX system, apparent dd, $J = 16.9$, 2.7 Hz, 1 H), 3.52 (s, 1 H), 3.65 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.65 (t′), 30.26 (t′), 32.89 (t′), 51.81 (q′), 53.26 (q′), 71.66 (s′), 75.83 (d′), 78.42 (s′), 173.36 (s′), 174.79 (s′); exact mass *m/z* calcd for $C_9H_{11}O_4$ (M − OCH_3) 183.0657, found 183.0657.

Tetrahydro-5-oxo-2-[2-(propynyl)]-2-furancarboxylic Acid (9). A solution of LiOH (509 mg, 10.4 mmol) in water (2 mL) was added to a solution of diester **13** (1.00 g, 4.67 mmol) in THF (20 mL), and the mixture was stirred overnight at room temperature. Evaporation of the solvent gave what we assume to be the dilithium salt, as a solid.

A column packed with Amberlite IR-120 ion-exchange resin (20−50 Å mesh, 2.5 × 16 cm) was washed with water until the eluant was colorless. The column was then washed successively with 2 M aqueous NaOH (4 bed volumes), water (until the eluant was neutral to pH paper), 2 M HCl (4 bed volumes), and finally with water (until the eluant was neutral to pH paper). The above dilithium salt was dissolved in water (2−3 mL), and the solution was passed down the column, using water. The eluant was monitored with pH paper or by TLC (silica gel, 10:90 MeOH−$CHCl_3$). Evaporation of the combined acidic fractions (water pump, rotary evaporator, bath temperature 65−70 °C) gave **9** (746 mg, 95%) as a pure (^{1}H NMR), light-yellow, powder: FTIR (KBr) 3500−2500 (br), 1770, 1720 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 2.45−2.70 (m, 3 H), 2.75−2.85 (m, 2 H), 2.92 (A of an ABX system, apparent dd, $J = 16.9$, 2.9 Hz, 1 H), 3.06 (B of an ABX system, apparent dd, $J = 16.9$, 2.9 Hz, 1 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 27.78 (t′), 29.03 (t′), 30.74 (t′), 73.35 (d′), 79.10 (s′), 86.90 (s′), 174.86 (s′), 180.54 (s′); exact mass *m/z* calcd for $C_5H_5O_4$ (M − $CH_2C{\equiv}CH$) 129.0188, found 129.0189; FABMS *m/z* calcd for $C_8H_8O_4$ 168.15, found 168.9.

Phenylmethyl (*S*)-2-[[(1,1-Dimethylethoxy)carbonyl]-amino]-5-hexenoate [(−)-16]. Zn dust (0.7452 g, 11.40 mmol) was added to a round-bottomed flask containing a magnetic stirring bar. The flask was sealed with a rubber septum, evacuated with an oil-pump, and refilled with Ar. The evacuation-filling process was repeated twice more, and then the system was placed under a static pressure of Ar. Dry THF (4 mL) and 1,2-dibromoethane (0.05 mL, 0.58 mmol) were added. The resulting mixture was heated to boiling with the aid of a heat gun and then allowed to cool for 1 min. The heating−cooling process was repeated three more times, and then the flask was allowed to cool for an additional 5 min. Freshly distilled, dry Me_3SiCl (0.07 mL, 0.55 mmol) was added, and the resulting mixture was stirred for 10 min and then placed in an oil bath set at 38 °C. Stirring was continued for 10 min. A solution of (−)-**14**[26] (1.1526 g, 2.84 mmol) in dry THF (5 mL) was added by cannula over ca. 1 min, and additional THF (3 × 1 mL) was used as a rinse. The resulting mixture was stirred at 38 °C (Ar atmosphere) until all the starting material had been consumed (ca. 6 h, TLC control, silica gel, 10:90 EtOAc−hexanes).

The above solution of alkylzinc iodide (**15**) was transferred by cannula over ca. 1 min to a stirred and precooled (bath temperature −15 °C) solution of CuCN (0.2811 g, 3.14 mmol) and LiCl (0.2661 g, 6.28 mmol) in dry THF (7 mL), and further portions of THF (2 × 1 mL) were used as a rinse to complete the transfer. The reaction flask was removed from the cold bath and placed in another at 0 °C. Stirring was continued for 15 min, and the reaction flask was then transferred to a cold bath at −30 °C. Stirring was continued for 10 min, allyl chloride (0.46 mL, 5.64 mmol) was added, and, finally, the

(24) The reported $[\alpha]^{25}_D = -141.2°$ (*c* 0.16, H_2O) (see reference 2b); our material had $[\alpha]^{25}_D = -139.82°$ (*c* 1.67, H_2O).

(25) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426−7437.

(26) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397−3404.

reaction flask was transferred to a cold bath at 0 °C. Stirring was continued for 14 h. The resulting solution was acidified with hydrochloric acid (2 M) and shaken with water (25 mL) and EtOAc (25 mL). The resulting white precipitate was filtered off, using a Whatman no. 2 filter paper, and the aqueous filtrate was extracted with EtOAc (2 × 15 mL), and filtered, as before, after each extraction to remove a small amount of precipitate. The combined organic extracts were washed with water (30 mL), filtered (as above), washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 30 cm), using 15:85 EtOAc−hexanes, gave (−)-**16** (0.7631 g, 84%) as a pure (^{1}H NMR), colorless oil: $[\alpha]^{25}_D = -18.90°$ (*c* 3.10, EtOH); FTIR ($CHCl_3$ cast) 3366, 1741, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9 H), 1.67−1.78 (m, 1 H), 1.86−1.98 (m, 1 H), 2.00−2.17 (m, 2 H), 4.32−4.42 (m, 1 H), 4.95−5.05 (m, 2 H), 5.09 (d, J = 7.7 Hz, 1 H), 5.14 and 5.20 (AB q, $\Delta\nu_{AB}$ = 26.0 Hz, J = 12.4 Hz, 2 H), 5.76 (ddt, J = 17.1, 10.3, 6.6 Hz, 1 H), 7.29−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.31 (q′), 29.43 (t′), 31.93 (t′), 53.12 (d′), 66.98 (t′), 79.85 (s′), 115.68 (t′), 128.26 (d′), 128.40 (d′), 128.58 (d′), 135.43 (s′), 136.94 (d′), 155.30 (s′), 172.61 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{18}H_{25}NNaO_4$ (M + Na) 342.1681, found 342.1681.

Phenylmethyl (*S*)-2-Amino-5-hexenoate [(+)-10]. CF_3CO_2H (5 mL) was added over ca. 5 min to a stirred and cooled (ice−water bath) solution of (−)-**16** (0.2871 g, 0.90 mmol) in freshly distilled CH_2Cl_2 (5 mL). The ice−water bath was removed and stirring was continued until all the starting material had been consumed (ca. 30 min, TLC control, silica gel, 15:85 EtOAc−hexanes), by which time the mixture had warmed to room temperature. The solution was evaporated, and the residue was dissolved in EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and evaporated (<0.1 mmHg). Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 90:10 EtOAc−hexanes, gave (+)-**10** (0.1912 g, 97%) as a pure (^{1}H NMR), colorless oil: $[\alpha]^{25}_D$ = 7.94° (*c* 5.19, EtOH); FTIR ($CHCl_3$ cast) 3383, 3318, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58−1.72 [m, 3 H, including a s (NH_2) at δ 1.68], 1.78−1.89 (m, 1 H), 2.05−2.20 (m, 2 H), 3.48 (dd, J = 7.7, 5.3 Hz, 1 H), 4.93−5.06 [m, 2 H, including a dd at δ 5.01 (J = 17.2, 1.6 Hz)], 5.12 and 5.14 (AB q, $\Delta\nu_{AB}$ = 7.9 Hz, J = 12.3 Hz, 2 H), 5.76 (ddt, J = 17.2, 10.3, 6.6 Hz, 1 H), 7.26−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.77 (t′), 34.03 (t′), 53.84 (d′), 66.58 (t′), 115.33 (t′), 128.23 (d′), 128.31 (d′), 128.55 (d′), 135.72 (s′), 137.47 (d′), 175.95 (s′); exact mass *m*/*z* calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1262.

Phenylmethyl (2*S*)-2-[[[Tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]amino]-5-hexenoate [(−)-17a, (+)-17b]. Lactone acid **9** (2.8235 g, 16.79 mmol), 1-hydroxybenzotriazole (2.2733 g, 16.82 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (3.2349 g, 16.87 mmol) were added in that order to a stirred solution of (+)-**10** (3.3419 g, 15.24 mmol) in a mixture of dry CH_2Cl_2 (112 mL) and freshly distilled, dry (stored over 4 Å molecular sieves) DMF (29 mL) (Ar atmosphere). Stirring at room temperature was continued for 12 h, and the mixture was washed with water (2 × 60 mL) and saturated aqueous NaCl (60 mL), dried ($MgSO_4$), and evaporated, to give a dark purple oil. Chromatography of the oil over silica gel (4.5 × 30 cm), repeated three times, using 3.5:3.5:4 CH_2Cl_2−Et_2O−hexanes, gave the faster-eluting diastereomer [(−)-**17a**] (2.7374 g, 49%) as a pure (^{1}H NMR), colorless oil, and the slower-eluting diastereomer [(+)-**17b**] (2.6112 g, 46%), also as a pure (^{1}H NMR), colorless oil.

Compound (−)-**17a** had: $[\alpha]^{25}_D = -21.01°$ (*c* 2.68, EtOH); FTIR ($CHCl_3$ cast) 3350, 3295, 1789, 1741, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78−1.88 (m, 1 H), 1.92−2.10 (m, 4 H), 2.43−2.59 (m, 3 H), 2.69−2.84 [m, 3 H, including an apparent dd at δ 2.76 (A of an ABX system, J = 17.3, 2.6 Hz), and an apparent dd at δ 2.80 (B of an ABX system, J = 17.3, 2.6 Hz)], 4.57 (dt, J = 8.1, 5.0 Hz, 1 H), 4.96−5.03 (m, 2 H), 5.12 and 5.19 (AB q, $\Delta\nu_{AB}$ = 24.8 Hz, J = 12.2 Hz, 2 H), 5.72 (ddt, J = 17.8, 9.7, 6.4 Hz, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 7.28−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.38 (t′, two signals overlap), 29.46 (t′), 29.59 (t′), 30.93 (t′), 52.05 (d′), 67.28 (t′), 72.43 (d′), 77.19 (s′), 85.31 (s′), 116.16 (t′), 128.37 (d′), 128.54 (d′), 128.61 (d′), 135.14 (s′), 136.50 (d′), 170.83 (s′), 171.02 (s′), 175.03 (s′); exact mass *m*/*z* calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1565.

Compound (+)-**17b** had: $[\alpha]^{25}_D = 0.63°$ (*c* 3.98, EtOH); FTIR ($CHCl_3$ cast) 3350, 3297, 1790, 1740, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76−1.87 (m, 1 H), 1.95−2.14 [m, 4 H, including a t at δ 2.08 (J = 2.6 Hz)], 2.30−2.52 (m, 3 H), 2.58−2.71 (m, 1 H), 2.76−2.89 (m, 2 H), 4.61 (dt, J = 8.4, 4.7 Hz, 1 H), 4.97−5.05 (m, 2 H), 5.10 and 5.19 (AB q, $\Delta\nu_{AB}$ = 35.9 Hz, J = 12.2 Hz, 2 H), 5.74 (ddt, J = 16.6, 9.7, 6.6 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 7.27−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.09 (t′), 28.43 (t′), 29.52 (t′), 29.96 (t′), 30.77 (t′), 51.96 (d′), 67.28 (t′), 72.24 (d′), 77.40 (s′), 85.40 (s′), 116.27 (t′), 128.35 (d′), 128.54 (d′), 128.63 (d′), 135.13 (s′), 136.44 (d′), 170.66 (s′), 171.13 (s′), 175.05 (s′); exact mass *m*/*z* calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1574.

5-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-L-norvaline phenylmethyl ester [(−)-18a]. Freshly distilled CH_2Cl_2 (15 mL) was added to (−)-**17a** (0.5333 g, 1.44 mmol) contained in a three-necked flask closed by a stopper and fitted with a condenser (not attached to a water supply) closed by a drying tube packed with Drierite, and an ozone-oxygen inlet. The resulting solution was stirred and cooled (−78 °C), and ozone was then bubbled through the solution until all of the starting material had been consumed (ca. 8 min, TLC control, silica gel, 50:50 EtOAc−hexanes). The solution was purged with oxygen for 10 min, and then Ph_3P (0.7672 g, 2.93 mmol) was added. The cooling bath was removed and stirring was continued for 4 h, by which time the mixture had warmed to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm), using 90:10 EtOAc−hexanes, gave (−)-**18a** (0.5199 g, 97%) as an oil, containing trace amounts of what we take to be the corresponding *E* and *Z* enol tautomers (^{1}H NMR): $[\alpha]^{25}_D = -12.32°$ (*c* 3.79, $CHCl_3$); FTIR ($CHCl_3$ cast) 3356, 3288, 2834, 2731, 1789, 1740, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96−2.16 [m, 2 H, including a t at δ 2.03 (J = 2.7 Hz)], 2.24 (ddt, J = 13.9, 6.8, 4.9 Hz, 1 H), 2.39−2.62 (m, 5 H), 2.67−2.91 [m, 3 H, including an apparent dd at δ 2.74 (A of an ABX system, J = 17.2, 2.7 Hz), and an apparent dd at δ 2.78 (B of an ABX system, J = 17.2, 2.7 Hz)], 4.55 (dt, J = 8.0, 5.2 Hz, 1 H), 5.13 and 5.18 (AB q, $\Delta\nu_{AB}$ = 18.4 Hz, J = 12.1 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 1 H), 7.28−7.40 (m, 5 H), 9.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.02 (t′), 28.29 (t′), 28.44 (t′), 29.43 (t′), 39.84 (t′), 51.91 (d′), 67.49 (t′), 72.42 (d′), 77.21 (s′), 85.23 (s′), 128.50 (d′), 128.56 (d′), 128.64 (d′), 134.99 (s′), 170.50 (s′), 171.09 (s′), 175.16 (s′), 200.49 (d′); exact mass *m*/*z* calcd for $C_{20}H_{21}NO_6$ 371.1369, found 371.1371.

Phenylmethyl (2*S*)-2,3-Dihydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-1*H*-pyrrole-2-carboxylate [(−)-19a]. BaO (0.3412 g, 2.23 mmol) was tipped into a solution of (−)-**18a** (0.3865 g, 1.04 mmol) in dry CH_2Cl_2 (10 mL), contained in a round-bottomed flask fused onto a condenser (Ar atmosphere), and the suspension was sonicated (Branson, model B-12, 80 W; Ar atmosphere). Sonication was stopped after 1 h, and P_2O_5 (0.3922 g, 2.76 mmol) was tipped into the flask. The system was resealed with a septum and flushed with Ar, and the mixture was sonicated until no more aldehyde was being consumed (ca. 2.5 h, TLC control, silica gel, 60:40 EtOAc−hexanes). The suspension was then centrifuged. Evaporation of the supernatant liquid and flash chromatography of the orange residue over silica gel (2 × 25 cm), using 60:40 EtOAc−hexanes gave (−)-**19a** (0.2612 g, 71%, 93% after correction for recovered starting material) as a pure (^{1}H NMR), colorless oil, which was a mixture of rotamers. The material should be used within 24 h. Further elution with 90:10 EtOAc−hexanes gave starting material (0.0878 g, 0.24 mmol) (^{1}H NMR) as a light-yellow oil.

Compound (−)-**19a** had: $[\alpha]^{25}_D = -83.09°$ (*c* 5.56, $CHCl_3$); FTIR ($CHCl_3$ cast) 3283, 1792, 1745, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07−2.12 [m, 1 H, including a t at δ 2.10 (J = 2.6 Hz)], 2.36−2.78 [m, 5 H, including a dd at δ 2.64 (J = 17.4, 2.7 Hz), and a ddd at δ 2.72 (J = 17.4, 10.2, 6.4 Hz)],

2.79−3.24 (m, 3 H, including an apparent dd at δ 2.87 (A of an ABX system, J = 12.6, 2.6 Hz), and an apparent dd at δ 2.94 (B of an ABX system, J = 12.6, 2.6 Hz), and a ddt at δ 3.19 (J = 17.1, 11.2, 2.5 Hz)], 4.86−5.42 [m, 4 H, including a dd at δ 4.89 (J = 11.5, 4.2 Hz), an AB q at δ 5.07 and 5.20 ($\Delta\nu_{AB}$ = 52.7 Hz, J = 12.0 Hz), overlapping an AB q at δ 5.11 and 5.23 ($\Delta\nu_{AB}$ = 47.4 Hz, J = 12.2 Hz), overlapping a dd at δ 5.25 (J = 7.0, 2.7 Hz), a dd at δ 5.28 (J = 4.6, 2.6 Hz), and a dd at δ 5.39 (J = 11.1, 2.7 Hz)], 7.05−7.23 [m, 1 H, including a ddd at δ 7.07 (J = 4.4, 2.8, 1.6 Hz), and a dt at δ 7.21 (J = 4.4, 2.2 Hz)], 7.31−7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.72 (t′), 28.07 (t′), 28.59 (t′), 29.34 (t′), 30.67 (t′), 31.21 (t′), 32.17 (t′), 36.39 (t′), 59.32 (d′), 59.71 (d′), 67.17 (t′), 67.86 (t′), 72.18 (d′), 72.79 (d′), 86.13 (s′), 86.28 (s′), 109.94 (d′), 111.33 (d′), 128.34 (d′), 128.50 (d′), 128.54 (d′), 128.63 (d′), 128.68 (d′), 129.44 (d′), 130.97 (d′), 135.16 (s′), 135.32 (s′), 165.94 (s′), 167.83 (s′), 170.22 (s′), 172.39 (s′), 175.14 (s′), 175.35 (s′), one pair of d′ in the aromatic region overlap; the internal acetylene carbon signals overlap the solvent signals; exact mass m/z calcd for $C_{20}H_{19}NO_5$ 353.1263, found 353.1261.

If the aldehyde solution is not pretreated with BaO for ca. 1 h before addition of P_2O_5, the overall yield is <50%. In the absence of BaO, the P_2O_5 turns into a reddish-brown gummy material after sonication in CH_2Cl_2 for 1 h or more; when BaO is present, the P_2O_5 stays as a fine powdered suspension. If additional P_2O_5 is added to the system during the course of the reaction in an attempt to improve the conversion, an unidentified byproduct is formed, and the yield of (−)-**19a** is reduced.

Phenylmethyl (3′*S*)-Octahydro-8′-methylene-5,5′-dioxospiro[furan-2(3*H*),6′(5′*H*)-indolizine]-3′-carboxylate [(+)-21a]. A solution of AIBN (0.0281 g, 0.17 mmol, 7.79 mM) and Bu_3SnH (0.63 mL, 2.34 mmol, 0.11 M) in dry PhMe (22 mL) was injected by syringe over ca. 2 min into a stirred and refluxing solution (0.05 M with respect to the acetylene) of (−)-**19a** (0.3911 g, 1.11 mmol) in PhMe (22 mL) (Ar atmosphere). Stirring at reflux was continued for 3 h. A solution of AIBN (0.0277 g, 0.17 mmol, 15.3 mM) and Bu_3SnH (0.63 mL, 2.34 mmol, 0.21 M) in dry PhMe (11 mL) was then injected by syringe over ca. 30 s. Stirring under reflux was continued until no more starting material remained (ca. 1.5 h, TLC control, silica gel, 40:60 EtOAc−hexanes), and the mixture was allowed to cool to room temperature. Evaporation (<0.1 mmHg) of the solvent gave the crude vinyl stannane, which was treated as follows.

Dry CF_3CO_2H (1.5 mL) was injected rapidly into a stirred solution of the above crude vinyl stannane in THF (15 mL) (Ar atmosphere). After ca. 45 min no more vinyl stannane could be detected (TLC control, silica gel, 40:60 EtOAc−hexanes). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 25 cm), using 60:40 EtOAc−hexanes, gave (+)-**21a** (0.3658 g, 93%) as a pure (^{1}H NMR) white solid: mp 135−138 °C; $[\alpha]^{25}_D$ = 21.02° (c 2.84, $CHCl_3$); FTIR ($CHCl_3$ cast) 1779, 1739, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−2.01 [m, 2 H, including a dt at δ 1.88 (J = 12.8, 9.9 Hz)], 2.03−2.12 (m, 1 H), 2.16−2.32 (m, 2 H), 2.48 (ddd, J = 17.4, 9.6, 2.9 Hz, 1 H), 2.62−2.74 (m, 2 H), 2.79 (dt, J = 17.4, 9.8 Hz, 1 H), 3.01 (dd, J = 14.8, 1.3 Hz, 1 H), 4.31−4.38 (m, 1 H), 4.53 (d, J = 8.8 Hz, 1 H), 5.00−5.04 (m, 1 H), 5.05−5.24 [m, 3 H, including an AB q at δ 5.07 and 5.21 ($\Delta\nu_{AB}$ = 55.1 Hz, J = 12.3 Hz)], 7.29−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.36 (t′), 28.54 (t′), 29.04 (t′), 31.03 (t′), 42.19 (t′), 58.14 (d′), 61.80 (d′), 67.11 (t′), 83.04 (s′), 112.03 (t′), 128.19 (d′), 128.42 (d′), 128.60 (d′), 135.42 (s′), 139.07 (s′), 167.30 (s′), 171.01 (s′), 176.39 (s′); exact mass m/z calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1417.

(*S*)-1,2,3,5-Tetrahydro-8-hydroxy-5-oxo-3-[(phenylmethoxy)carbonyl]-6-indolizinepropanoic Acid [(−)-23] from (+)-21a. Freshly distilled CH_2Cl_2 (10 mL) was added to (+)-**21a** (0.6011 g, 1.69 mmol) contained in a three-necked flask closed by a stopper and fitted with a condenser (not attached to a water supply) closed by a drying tube packed with Drierite, and an ozone-oxygen inlet. The resulting solution was stirred and cooled (−78 °C), and ozone was then bubbled through the solution until all of the starting material had been consumed (ca. 10 min, TLC control, silica gel, 60:40 EtOAc−hexanes). The solution was purged with oxygen for 10 min, and then Ph_3P (0.8892 g, 3.39 mmol) was added. The cooling bath was removed and stirring was continued for 1.5 h, by which time the mixture had warmed to room temperature. Evaporation (<0.1 mmHg) of the solvent gave a light-yellow solid; the ketonic product (**22a**) could not be separated chromatographically from Ph_3PO, and so the crude mixture was used directly.

Dry Et_3N (1.0 mL, 7.17 mmol) was added to a stirred solution of the above crude ozonolysis product in dry THF (10 mL) (Ar atmosphere). Stirring was continued at 60 °C (oil bath) for 1.5 h, and the mixture was then cooled and evaporated. Flash chromatography of the light-yellow oily residue over silica gel (2 × 20 cm), using 80:20:5 EtOAc−hexanes−AcOH, gave (−)-**23** (0.5746 g, 95%) as pure (^{1}H NMR), light-yellow crystals: mp 159−161 °C; $[\alpha]^{25}_D$ = −158.64° (c 2.28, MeOH); FTIR ($CHCl_3$ cast) 3450−2400, 1744, 1543 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 2.26 (ddt, J = 13.3, 8.7, 3.3 Hz, 1 H), 2.48−2.63 (m, 3 H), 2.68−2.83 (eight-line m, 2 H), 2.95−3.16 [m, 2 H, including a tt at δ 3.03 (J = 17.2, 8.7 Hz), overlapping a ddd at δ 3.11 (J = 17.2, 9.5, 3.4 Hz)], 5.13−5.24 [m, 3H, including a dd at δ 5.15 (J = 9.7, 3.1 Hz), overlapping an AB q at δ 5.17 and 5.21 ($\Delta\nu_{AB}$ = 13.6 Hz, J = 12.3 Hz)], 7.24 (s, 1 H), 7.27−7.38 (m, 5 H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 26.90 (t′), 27.48 (t′), 28.11 (t′), 33.75 (t′), 63.93 (d′), 68.34 (t′), 129.21 (d′), 129.40 (d′), 129.62 (d′), 129.80 (s′), 133.99 (s′), 134.92 (d′), 137.00 (s′), 137.12 (s′), 160.37 (s′), 171.47 (s′), 176.74 (s′); exact mass m/z calcd for $C_{19}H_{19}NO_6$ 357.1213, found 357.1208.

(*S*)-3-Carboxy-1,2,3,5-tetrahydro-8-hydroxy-5-oxo-6-indolizinepropanoic Acid [(−)-1]. 10% Pd−C (ca. 25 mg) was added to a stirred solution of (−)-**23** (0.1614 g, 0.45 mmol) in MeOH (20 mL). The reaction flask was flushed with hydrogen, and the mixture was stirred under hydrogen (balloon) until all of the starting material had been consumed (ca. 15 min, TLC control, silica gel, 95:5 EtOAc−AcOH). The mixture was filtered through a sintered glass frit (grade D) and evaporated. Flash chromatography of the residue over reverse phase C-18 silica gel (Toronto Research Chemicals Inc., 10% capped with TMS) (2 × 20 cm), using 90:10 water−MeCN, gave (−)-**1** (0.1128 g, 93%) as a pure (^{1}H NMR), white foam: $[\alpha]^{25}_D$ = −196.55° (c 0.87, H_2O), lit.[2b] $[\alpha]^{25}_D$ = −199.5° (c 1.0, H_2O); FTIR (microscope) 3650−2300, 1721 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ 2.30 (ddt, J = 13.5, 8.4, 3.8 Hz, 1 H), 2.48−2.73 (m, 5 H), 2.95−3.13 [m, 2 H, including a tt at δ 3.03 (J = 17.3, 8.8 Hz), overlapping a ddd at δ 3.08 (J = 17.3, 9.5, 3.9 Hz)], 5.06 (dd, J = 9.9, 3.0 Hz, 1 H), 7.25 (s, 1 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 25.56 (t′), 26.63 (t′), 27.52 (t′), 33.06 (t′), 63.72 (d′), 128.26 (s′), 134.73 (d′), 135.28 (s′), 135.88 (s′), 159.74 (s′), 174.63 (s′), 178.03 (s′); exact mass m/z calcd for $C_{12}H_{13}NO_6$ 267.0743, found 267.0735.

Methyl (*S*)-1,2,3,5-Tetrahydro-8-methoxy-5-oxo-3-[(phenylmethoxy)carbonyl]-6-indolizinepropanoate [(−)-24, *n* = 1]. An excess of ethereal CH_2N_2 was added to a stirred and cooled (ice−water bath) solution of (−)-**23** (0.0342 g, 0.096 mmol) in MeOH (10 mL). The cooling bath was removed, and the solution was stirred for 4 h, by which time all of the starting material had been consumed (TLC control, silica gel, 80:20:5 EtOAc−hexanes−AcOH). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm), using 80:20 EtOAc−hexanes, gave (−)-**24** (n = 1) (0.0277 g, 75%) as a pure (^{1}H NMR), light-yellow oil: $[\alpha]^{25}_D$ = −165.45° (c 1.32, $CHCl_3$); FTIR ($CDCl_3$ cast) 1739, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.20−2.31 (m, 1 H), 2.47 (ddd, J = 18.8, 13.4, 9.4 Hz, 1 H), 2.26−2.70 (m, 2 H), 2.75−2.93 (m, 2 H), 3.03−3.12 (m, 2 H), 3.64 (s, 3 H), 3.72 (s, 3 H), 5.11−5.30 [m, 3 H, including a dd at δ 5.15 (J = 9.5, 3.3 Hz), overlapping an AB q at δ 5.17 and 5.26 ($\Delta\nu_{AB}$ = 34.6 Hz, J = 12.4 Hz)], 7.26 (s, 1 H), 7.27−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.37 (t′), 26.54 (t′), 27.40 (t′), 32.47 (t′), 51.52 (q′), 58.96 (q′), 61.96 (d′), 67.38 (t′), 128.17 (d′), 128.41 (d′), 128.61 (d′), 129.31 (s′), 131.42 (d′), 135.30 (s′), 135.86 (s′), 137.51 (s′), 159.15 (s′), 170.00 (s′), 173.64 (s′); exact mass (HR electrospray) m/z calcd for $C_{21}H_{23}NNaO_6$ (M + Na) 408.1423, found 408.1432.

HPLC analysis [Chiralcel OD-H (0.46 × 25 cm), 15% EtOH in hexane] of the above material and comparison with the corresponding racemic compound indicated an ee of 99.5%.

Methyl (*S*)-1,2,3,5-Tetrahydro-8-methoxy-3-(methoxycarbonyl)-5-oxo-6-indolizinepropanoate [(−)-25 (*n* = 1)]. An excess of ethereal CH_2N_2 was added to a stirred and cooled (ice−water bath) solution of (−)-**1** (0.0835 g, 0.31 mmol) in MeOH (10 mL). The cooling bath was removed, and the solution was stirred for 4 h, by which time all of the starting material had been consumed (TLC control, silica gel, 95:5 EtOAc−MeOH). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 95:5 EtOAc−MeOH, gave (−)-**25** (*n* = 1) (0.0705 g, 74%) as a pure (^{1}H NMR), light-yellow oil: $[\alpha]^{25}_D = -158.37°$ (*c* 4.54, $CHCl_3$); FTIR ($CDCl_3$ cast) 1739, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21−2.31 (m, 1 H), 2.47 (ddd, *J* = 18.6, 13.4, 9.4 Hz, 1 H), 2.60−2.67 (m, 2 H), 2.71−2.90 (m, 2 H), 3.04−3.12 (m, 2 H), 3.61 (s, 3 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 5.07 (dd, *J* = 9.5, 3.4 Hz, 1 H), 7.24 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.30 (t′), 26.56 (t′), 27.39 (t′), 32.38 (t′), 51.46 (q′), 52.67 (q′), 58.88 (q′), 61.86 (d′), 129.19 (s′), 131.35 (d′), 135.87 (s′), 137.56 (s′), 158.99 (s′), 170.61 (s′), 173.55 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{15}H_{19}NNaO_6$ (M + Na) 332.1110, found 332.1112.

HPLC analysis [Chiralpak AS (0.46 × 25 cm), 10% EtOH in hexane] of the above material and comparison with the corresponding racemic compound (clear baseline resolution of the enantiomers was not obtained) indicated an ee of 96.2%.

6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]-carbonyl]-L-norleucine Phenylmethyl Ester [(−)-26a]. 9-BBN (0.5 M in THF, 1.79 mL, 0.90 mmol) was added by syringe pump over ca. 4 min to a stirred and cooled (ice−water bath) solution of (−)-**17a** (0.2968 g, 0.80 mmol) in dry THF (10 mL) (Ar atmosphere). The cooling bath was removed, and stirring was continued for 1 h. The mixture was then transferred by cannula to a stirred and cooled (ice−water bath) suspension of PCC (1.5620 g, 7.25 mmol) and crushed 4 Å molecular sieves (ca. 500 mg) in dry CH_2Cl_2 (10 mL). Additional dry CH_2Cl_2 (2 × 1 mL) was used as a rinse. The resulting mixture was transferred to an oil bath and stirred at reflux temperature for 1.5 h, allowed to cool to room temperature, and filtered through a pad (2.5 × 5 cm) of silica gel, using EtOAc as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 80:20 EtOAc−hexanes, gave (−)-**26a** (0.2539 g, 83%) as a pure (^{1}H NMR), colorless oil: $[\alpha]^{25}_D = -4.36°$ (*c* 1.56, $CHCl_3$); FTIR ($CDCl_3$ cast) 3360, 3288, 2850, 2750, 1788, 1739, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48−1.66 (m, 2 H), 1.67−1.78 (m, 1 H), 1.79−1.94 (m, 1 H), 2.03 (t, *J* = 2.0 Hz, 1 H), 2.34−2.63 (m, 5 H), 2.65−2.83 [m, 3 H, including an apparent dd at δ 2.74 (A of an ABX system, *J* = 17.3, 2.6 Hz), and an apparent dd at δ 2.79 (B of an ABX system, *J* = 17.3, 2.6 Hz)], 4.53 (dt, *J* = 8.1, 5.1 Hz, 1 H), 5.11 and 5.17 (AB q, $\Delta\nu_{AB}$ = 22.4 Hz, *J* = 12.1 Hz, 2 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 7.26−7.39 (m, 5 H), 9.66 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.66 (t′), 28.29 (t′, two signals overlap), 29.51 (t′), 30.99 (t′), 42.75 (t′), 52.04 (d′), 67.27 (t′), 72.37 (d′), 77.22 (s′), 85.26 (s′), 128.36 (d′), 128.57 (d′, two signals overlap), 135.03 (s′), 170.80 (s′), 170.94 (s′), 175.21 (s′), 201.35 (d′); exact mass (HR electrospray) *m*/*z* calcd for $C_{21}H_{23}NNaO_6$ (M + Na) 408.1423, found 408.1431.

Phenylmethyl (2*S*)-1,2,3,4-Tetrahydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-2-pyridinecarboxylate [(−)-27a]. BaO (0.1742 g, 1.14 mmol) was tipped into a solution of (−)-**26a** (0.0879 g, 0.23 mmol) in dry CH_2Cl_2 (5 mL), contained in a round-bottomed flask fused onto a condenser (Ar atmosphere), and the suspension was sonicated (Branson, model B-12, 80 W; Ar atmosphere). Sonication was stopped after 1 h, and P_2O_5 (0.1633 g, 1.15 mmol) was tipped into the flask. The system was resealed with a septum and flushed with Ar, and the mixture was sonicated until no more aldehyde remained (ca. 1 h, TLC control, silica gel, 50:50 EtOAc−hexanes). The suspension was then centrifuged. Evaporation of the supernatant liquid and flash chromatography of the orange residue over silica gel (1.5 × 20 cm), using 40:60 EtOAc−hexanes, gave (−)-**27a** (0.0704 g, 83%) as a pure (^{1}H NMR), colorless oil, which was a mixture of rotamers: $[\alpha]^{25}_D = -57.77°$ (*c* 1.21, $CHCl_3$); FTIR ($CDCl_3$ cast) 3278, 1792, 1742, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80−2.16 (m, 4 H, including a t at δ 2.09 (*J* = 2.4 Hz), and a t at δ 2.14 (*J* = 2.6 Hz)], 2.24−2.79 (m, 5 H), 2.88−3.10 (m, 2 H), 4.98−5.54 (m, 4 H, including a dd at δ 5.02 (*J* = 8.1, 5.5 Hz), and a br s at δ 5.52)], 7.11−7.22 [m, 1 H, including a d at δ 7.15 (*J* = 8.6 Hz), and a d at δ 7.20 (*J* = 8.6 Hz)], 7.27−7.42 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 19.06 (t′), 19.19 (t′), 23.70 (t′), 24.35 (t′), 27.76 (t′), 28.21 (t′), 28.73 (t′), 30.41 (t′), 30.70 (t′), 33.06 (t′), 54.20 (d′), 56.59 (d′), 67.43 (t′), 67.86 (t′), 72.47 (d′), 72.87 (d′), 77.12 (s′), 77.73 (s′), 86.64 (s′), 87.80 (s′), 108.64 (d′), 110.81 (d′), 124.58 (d′), 125.24 (d′), 128.46 (d′), 128.71 (d′), 128.89 (d′), 136.12 (s′), 167.93 (s′), 168.10 (s′), 170.23 (s′), 171.02 (s′), 174.95 (s′), 175.42 (s′), not all of the signals from the minor rotamer were observed; exact mass (HR electrospray) *m*/*z* calcd for $C_{21}H_{21}NNaO_5$ (M + Na) 390.1317, found 390.1325.

Phenylmethyl (6′*S*)-Octahydro-1′-methylene-4′,5-dioxospiro[furan-2(3*H*),3′(4′*H*)-[2*H*]quinolizine]-6′-carboxylate [(+)-28a]. A solution of AIBN (0.0083 g, 0.05 mmol, 7.49 mM) and Bu_3SnH (0.19 mL, 0.71 mmol, 0.10 M) in dry PhMe (6.75 mL) was injected by syringe over ca. 1 min into a stirred and refluxing solution (0.05 M with respect to the acetylene) of (−)-**27a** (0.1242 g, 0.34 mmol) in PhMe (6.75 mL) (Ar atmosphere). Stirring at reflux was continued for 2 h, by which time all of the starting material had been consumed (TLC control, silica gel, 30:70 EtOAc−hexanes), and the mixture was allowed to cool to room temperature. Evaporation (<0.1 mmHg) of the solvent gave the crude vinyl stannane, which was treated as follows.

Dry CF_3CO_2H (0.5 mL) was injected rapidly into a stirred solution of the above crude vinyl stannane in THF (5 mL) (Ar atmosphere). After ca. 50 min no more vinyl stannane could be detected (TLC control, silica gel, 30:70 EtOAc−hexanes). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 25 cm), using 50:50 EtOAc−hexanes, gave (+)-**28a** (0.0924 g, 74%) as a pure (^{1}H NMR), colorless oil: $[\alpha]^{25}_D = 0.32°$ (*c* 1.58, $CHCl_3$); FTIR ($CHCl_3$ cast) 1785, 1743, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.82 (m, 3 H), 1.85−2.14 (m, 4 H), 2.39−2.51 (m, 2 H), 2.69 (d, *J* = 13.4 Hz, 1 H), 2.80 (dt, *J* = 17.8, 10.6 Hz, 1 H), 2.94 (d, *J* = 13.4 Hz, 1 H), 4.09 (d, *J* = 11.8 Hz, 1 H), 4.37 (dd, *J* = 6.1, 5.0 Hz, 1 H), 5.05−5.25 [m, 4 H, including a d at δ 5.08 (*J* = 0.6 Hz), a d at δ 5.11 (*J* = 1.2 Hz), and an AB q at δ 5.09 and 5.22 ($\Delta\nu_{AB}$ = 54.6 Hz, *J* = 12.2 Hz)], 7.28−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.23 (t′), 24.17 (t′), 27.69 (t′), 28.52 (t′), 32.38 (t′), 41.74 (t′), 56.31 (d′), 57.16 (d′), 67.02 (t′), 81.85 (s′), 113.83 (t′), 128.35 (d′, two signals overlap), 128.58 (d′), 135.70 (s′), 138.57 (s′), 169.51 (s′), 170.92 (s′), 176.39 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{21}H_{23}NNaO_5$ (M + Na) 392.1474, found 392.1466.

(*S*)-1,3,4,6-Tetrahydro-9-hydroxy-6-oxo-4-[(phenylmethoxy)carbonyl]-2*H*-quinolizine-7-propanoic Acid [(−)-29] from (+)-28a. Freshly distilled CH_2Cl_2 (10 mL) was added to (+)-**28a** (0.0809 g, 0.22 mmol) contained in a three-necked flask closed by a stopper and fitted with a condenser (not attached to a water supply) closed by a drying tube packed with Drierite, and an ozone-oxygen inlet. The resulting solution was stirred and cooled (−78 °C), and ozone was then bubbled through the solution until all of the starting material had been consumed (ca. 7 min, TLC control, silica gel, 50:50 EtOAc−hexanes). The solution was purged with oxygen for 10 min, and then Ph_3P (0.1198 g, 0.46 mmol) was added. The cooling bath was removed, and stirring was continued for 1.5 h, by which time the mixture had warmed to room temperature. Evaporation (<0.1 mmHg) of the solvent gave a light-yellow solid; the ketonic product could not be separated chromatographically from Ph_3PO, and so the crude mixture was used directly.

Dry Et_3N (1.0 mL, 7.17 mmol) was added to a stirred solution of the above crude ozonolysis product in dry THF (10 mL) (Ar atmosphere). Stirring was continued at 60 °C (oil bath) for 1.5 h, and the mixture was then cooled and evaporated. Flash chromatography of the light-yellow oily residue over

silica gel (1.5 × 15 cm), using 80:20:5 EtOAc−hexanes-AcOH, gave (−)-**29** (0.0781 g, 95%) as a pure (^{1}H NMR), light-yellow oil: $[\alpha]^{25}_D = -131.61°$ (*c* 1.18, MeOH); FTIR ($CHCl_3$ cast) 3450−2400, 1743, 1538 cm^{-1}; ^{1}H NMR (CD_3OD, 360 MHz) δ 1.46−1.62 (m, 1 H), 1.69−1.81 (m, 1 H), 2.00−2.13 (m, 1 H), 2.21−2.33 (m, 1 H), 2.49−2.59 (m, 2 H), 2.60−2.82 (m, 3 H), 2.89 (dt, J = 18.3, 4.5 Hz, 1 H), 5.09−5.24 [m, 3 H, including an AB q at δ 5.13 and 5.20 ($\Delta\nu_{AB}$ = 26.4 Hz, J = 12.3 Hz)], 7.24 (s, 1 H), 7.25−7.37 (m, 5 H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 16.72 (t′), 23.81 (t′), 26.58 (t′), 27.29 (t′), 33.52 (t′), 57.12 (d′), 68.17 (t′), 127.72 (s′), 129.18 (d′), 129.31 (d′), 129.54 (d′), 130.74 (s′), 132.99 (d′), 137.11 (s′), 138.25 (s′), 161.86 (s′), 172.36 (s′, two signals overlap); exact mass (HR electrospray) *m*/*z* calcd for $C_{20}H_{21}KNO_6$ (M + K) 410.1006, found 410.1001.

(*S*)-4-Carboxy-1,3,4,6-tetrahydro-9-hydroxy-6-oxo-2*H*-quinolizine-7-propanoic Acid [(−)-2]. Pd−C (10%) (ca. 25 mg) was added to a stirred solution of (−)-**29** (0.0565 g, 0.152 mmol) in MeOH (5 mL). The reaction flask was flushed with hydrogen, and the mixture was stirred under hydrogen (balloon) until all of the starting material had been consumed (ca. 20 min, TLC control, silica gel, 80:20:5 EtOAc−hexanes−AcOH). The mixture was filtered through a sintered glass frit (grade D) and evaporated. Flash chromatography of the residue over reverse phase C-18 silica gel (Toronto Research Chemicals Inc., 10% capped with TMS) (1 × 20 cm), using 90:10 water−MeCN, gave (−)-**2** (0.0411 g, 96%) as a pure (^{1}H NMR), white foam: $[\alpha]^{25}_D = -139.82°$ (*c* 1.67, H_2O), lit.[2b] $[\alpha]^{25}_D = -141.2°$ (*c* 0.16, H_2O); FTIR ($CHCl_3$−MeOH cast) 3525−2375, 1723 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ 1.58−1.72 (m, 1 H), 1.78−1.90 (m, 1 H), 2.08−2.20 (m, 1 H), 2.27−2.38 (m, 1 H), 2.59−2.82 (m, 5 H), 2.91 (dt, J = 18.2, 4.9 Hz, 1 H), 5.11 (dd, J = 6.3, 4.0 Hz, 1 H), 7.35 (s, 1 H); ^{13}C NMR (D_2O, 50.3 MHz) δ 15.83 (t′), 23.43 (t′), 25.79 (t′), 26.17 (t′), 33.07 (t′), 57.30 (d′), 126.53 (s′), 132.35 (s′), 133.12 (d′), 137.43 (s′), 161.50 (s′), 175.85 (s′), 178.26 (s′); exact mass (HR electrospray) *m*/*z* calcd for $C_{13}H_{16}NO_6$ (M + H) 282.0978, found 282.0976.

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Supporting Information Available: NMR spectra for all compounds and experimental procedures for **12**, (−)-**18b**, (−)-**19b**, (−)-**21b**, (−)-**23** [from (−)-**21b**], (+)-**20a**, (−)-**20b**, (+)-**21a** (as part of two-step procedure), (−)-**21b** (as part of two-step procedure), (−)-**26b**, (−)-**27b**, (−)-**28b**, (−)-**29** [from (−)-**28b**], (−)-**24** (n = 2), (−)-**25** (n = 2), (+)-**28a** (two-step procedure), (−)-**28b** (two-step procedure), (±)-**14**, (±)-**16**, (±)-**10**, (±)-**17a**,**b**, (±)-**18a**, (±)-**18b**, (±)-**19a**, (±)-**19b**, (±)-**20a**, (±)-**20b**, (±)-**21a**, (±)-**21b**, (±)-**21a** (one-step procedure), (±)-**21b** (one-step procedure), (±)-**23** [from (±)-**21a**], (±)-**23** [from (±)-**21b**], (±)-**1**, (±)-**24** (n = 1), (±)-**25** (n = 1), (±)-**26a**, (±)-**26b**, (±)-**27a**, (±)-**27b**, (±)-**28a** (two-step procedure), (±)-**28b** (two-step procedure), (±)-**28a** (one-step procedure), (±)-**28b** (one-step procedure), (±)-**29** [from (±)-**28a**], (±)-**29** [from (±)-**28b**], (±)-**2**, (±)-**24** (n = 2), (±)-**25** (n = 2). This material is available free of charge via the Internet at http://pubs.acs.org.

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