Macrolactamization via Palladium π-Allyl Alkylation. Preparation of CGS25155: A 10-Membered Lactam Neutral Endopeptidase 24.11 Inhibitor

Erik P. Johnson,* Guang-Pei Chen, Kevin R. Fales, Barbara E. Lenk, Robert J. Szendroi, Xiao-Jun Wang, and John A. Carlson

Chemical Operations, Pharmaceutical Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

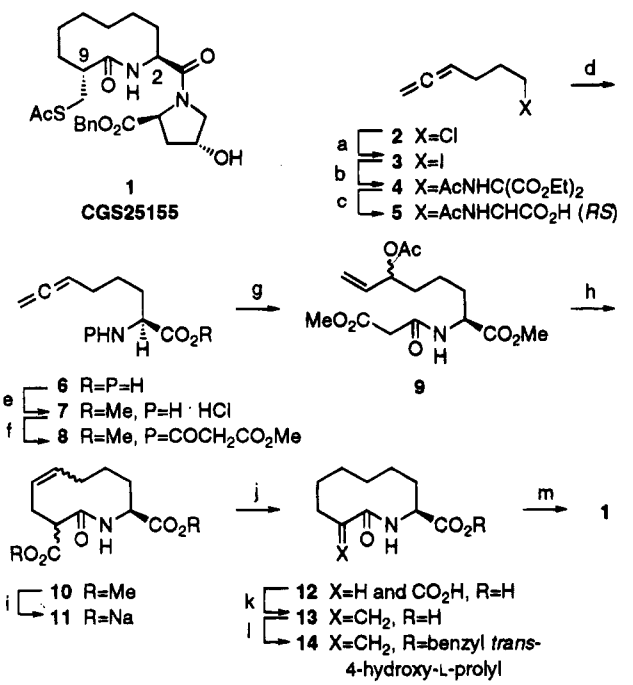
Received April 19, 1995

Due to current activities in the neutral endopeptidase (NEP) inhibitor program at Ciba, it recently became of interest to us to prepare multigram quantities of CGS25155 (**1**), a powerful inhibitor of this enzyme. Neutral endopeptidase 24.11 (EC 3.4.24.11) rapidly degrades the cardiac hormone ANF (atrial natriuretic factor) *in vivo*, increased levels of which lower blood pressure and increase diuresis. Potentiation of ANF through inhibition of NEP is thus a potentially new therapy for hypertension.[1] The original synthesis[1a] was unsuitable for preparing larger quantities of **1** due to its safety, wastestreams, and throughput. We have since prepared multigram quantities of **1** via a new, enantioselecive synthesis in which the pivotal intermediate is an enantiomerically pure 10-membered lactam.

Medium-ring lactams,[2-5] have occasionally been targets for synthesis, via either α,ω-ring closure[2,4] or ring expansion approaches.[3,5] Despite the variety and elegance of these methods, none was judged suitable. We then posited that a medium-ring lactone preparation[2,3,6,7] might prove adaptable, particularly intramolecular Pd π-allyl alkylation[8] technology, due to mild conditions and high regioselectivity.[9] Surprisingly, we found no example of lactam synthesis via this chemistry.

The reported synthesis of **2**[10] from allene was judged unacceptable for large-scale work (very low temperatures). Note, also, that allene anion isomerizes rapidly to propargyl dianion at −20 °C.[11] The answer was to generate lithioallene and consume it immediately through slow addition of butyllithium to a solution of allene and bromochloropropane at ≤−5 °C. In this way, good yields of **2** containing <5% isomeric acetylene (GC) were obtained.

Scheme 1[a]



[a](a) NaI, 83%; (b) di-Et acetamidomalonate, KO-*tert*-amylate, 86%; (c) i) KOH, aq EtOH; ii) 20% aq citric acid, 88%; (d) Acylase I (*Aspergillus*), 40%; (e) $SOCl_2$, MeOH, 88%; (f) MeO_2CCH_2COCl, Et_3N, 69%; (g) NaOAc, AgOTf, AcOH 94%; (h) $MeOCO_2^-$ $Me_3N^+CH_2Ph$, dppe (cat.), $Pd(Ph_3P)_4$ (cat.); (i) NaOH/EtOH; (j) i)10% Pd/C, H_2; ii) HCl, 51% from **9**; (k) i) $(CH_2O)_x$, piperidine (cat.); ii) HCl, 75%; (l) *trans*-4-hydroxy-L-proline benzyl ester HCl , HOBt, EDCI, N-methylmorpholine, 54%; (m) AcSH, 90%.

The sequence **2** to **3** to **4** runs acceptably (Scheme 1). In situ conversion of **2** into **4** was also explored. The former method gives somewhat higher overall yields, but is inferior for cost, time, and waste considerations. In both protocols, it was found that the potassium salt is needed for useful alkylation rates.

Saponification and decarboxylation of **4** provides high yields of **5**. However, during decarboxylation, it was found that some decomposition of the allene function occurs if the acidity is not controlled (pH 2–2.5). Although dosing with HCl is successful, using excess citric acid as the acidulant is more convenient.

With **5** in hand, we attempted its resolution. The studies of Whitesides and co-workers[12] give much valuable experimental data concerning the stability, reactivity, and substrate preferences of several acylases. Treat-

(1) (a) MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Bohacek, R. S.; Clarke, F. H.; Ghai, R. D.; Sakane, Y.; Berry, C. J.; Peppard, J. V.; Trapani, A. J. *J. Med. Chem.* **1993**, *36*, 3821–3828. (b) Stanton, J. L.; Sperbeck, D. M.; Trapani, A. J.; Cote, D.; Sakane, Y.; Berry, C. J.; Ghai, R. D. *J. Med. Chem.* **1993**, *36*, 3829–3833 and references contained therein.

(2) (a) Bartra, M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 5132–5138. (b) Stach, H.; Hesse, M. *Tetrahedron* **1988**, *44*, 1573–1590.

(3) Heimgartner, H. *Chimia* **1980**, *34*, 333–341.

(4) (a) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248–2260. (b) Quinkert, G.; Nestler, H. P.; Schumacher, B.; Del Grosso, M.; Durner, G.; Bats, J. W. *Tetrahedron Lett.* **1992**, *33*, 1977–1980. (c) Lamas, C.; Saa, C.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1992**, *33*, 5653–5654.

(5) (a) Koch, T.; Hesse, M. *Synthesis* **1992**, 931–932. (b) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 6857–6858. (c) Edstrom, E. D. *Tetrahedron Lett.* **1991**, *32*, 5709–5712. (d) Ognyanov, V.; Hesse, M. *Helv. Chim. Acta* **1989**, *72*, 1522–1526. (e) Mahajan, J. R.; Ferreira, G. A. L.; Araujo, H. C.; Nunes, B. J. *Synthesis* **1976**, 112–113. (f) Mahajan, J. R.; Ferreira, G. A. L.; Araujo, H. C.; Nunes, B. J. *Synthesis* **1973**, 313.

(6) (a) Pirrung, F. O. H.; Hiemstra, H.; Kapstein, B.; Martinez Sobrino, M. E.; Petra, D. G. I.; Schoemaker, H. E.; Speckamp, W. N. *Synlett* **1993**, 739–740. (b) Bestmann, H. J.; Kellermann, W.; Pecher, B. *Synthesis* **1993**, 149–152. (c) Mori, K.; Tomioka, H. *Liebigs Ann. Chem.* **1992**, 1011–1017. (d) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889–3890. (e) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: Orlando, 1985; pp 131–153.

(7) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *40*, 8667–8676.

(8) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595–1597.

(9) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 979–981.

(10) Arseniyadis, S.; Gore, J.; Roumestant, M. L. *Tetrahedron* **1978**, *33*, 353–363.

(11) (a) Hooz, J.; Calzada, J. G.; McMaster, D. *Tetrahedron Lett.* **1985**, *26*, 271–274. (b) Michelot, D.; Clinet, J. C.; Linstrumelle, G. *Synth. Commun.* **1982**, *12*, 739–747.

(12) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354–6364. (b) Baldwin, J. E.; Hulme, C.; Schofield, C. J. *J. Chem. Res. (S)* **1992**, 173. (c) Mori, K.; Sugai, T.; Maeda, Y.; Okazaki, T.; Noguchi, T.; Naito, H. *Tetrahedron* **1985**, *41*, 5307–5311.

0022-3263/95/1960-6595$09.00/0

ment of **5** with Acylase I (*Aspergillus*) gives a 40% yield of pure **6** of high ee ([α] = +22.4°, ^{1}H NMR analysis of a derivative of **7**). The major limitation of any enzymatic resolution is the maximum 50% yield of the desired enantiomer, which, on large scale, is unacceptable. To offset this disadvantage, a recycling loop was developed exploiting easy racemization of recovered (*R*)-enriched **5**.[13] Note that two passes through this cycle allow an aggregate 65% yield of **6** to be obtained with no loss of chemical or optical purity. Three recycles were successfully run (see Experimental Section).

Acid-catalyzed esterification of **6** afforded **7** of high chemical purity. To ascertain the chiral purity of **7**, we prepared its (*R*)-*O*-methylmandelamide[14] derivative. This material proved suitable for ^{1}H NMR analysis and was found to be of 97+% ee. Conversion of **7** into **8** was uneventful.

Unmasking the allylic acetate moiety of **8** followed. Carboxylic acids add to allenes under catalysis, giving allyl or vinyl derivatives.[15] Unfortunately, typical mediators (Hg^{2+}, Tl^+, Pb^{2+}) are environmentally hazardous. A more acceptable catalyst, Ag^+, has been shown to catalyze efficient, regioselective intramolecular alkoxylation of allenes.[15a] Gratifyingly, use of this catalyst formed **9** in high yield, along with its allylically transposed isomer (^{1}H NMR, see Experimental Section). For our purpose, this result was inconsequential, as both allylic acetates were expected to be convertible to **10**. Initial studies with only 25 mol % of Ag^+ have been mildly encouraging. Reaction times are very long, however.

We next began to explore Pd-mediated macrolactamization. Initially, **9** was subjected to reaction conditions from the literature.[8] Product analysis revealed <25% yields of **10** as a variable mixture of diastereo- and *E* and *Z* double bond isomers (^{1}H NMR, MS). Also, tedious chromatographic purification of **10** was needed to remove hydrogenation catalyst poisons and facilitate reaction optimization. By converting crude **10** to **11**, however, chromatography could be avoided.

We had observed much polymeric material to be formed during these studies and suspected catalyst and/or substrate instability as causative. An improved inert atmosphere (performing the reaction under Ar instead of N_2) increased yields 5%. Changing ligands from 1,2-bis(diphenylphosphino)ethane (dppe) to 1,3-bis(diphenylphosphino)propane, Ph_3P, dibenzylideneacetone, or PhCN gave no improvement (at best) under these conditions. Variations in either the rate of addition of preformed **9** anion, or catalyst or substrate concentration, also did not improve yield (if **9** is more concentrated than 3% w/v, yield decreases). Substrate stability, though, proved important. Subjection of **9** to reaction conditions without catalyst (NaH base) resulted in rapid, complete decomposition. Slow addition of base during a Pd π-allylation is attained via the approach of Tsuji, wherein allylic methyl carbonates slowly form methoxide in situ.[16] We believed that an alternative source of slowly generated methoxide was benzyltrimethylammonium methyl carbonate (BTMC). Use of BTMC raised crude yields to 55–60% (**9** to **12**, three steps overall)! No further optimization was attempted.

Multistep introduction of the methylene group at C-9 of **12**, as disclosed previously,[1a] was shortened in our approach. Decarboxylative methylenation of **12** afforded **13** in good yield. Synthesis of **1** was completed by introducing the thioacetate and 4-hydroxy-L-proline benzyl ester units (**13** to **14** to **1**) in the order opposite to that used by MacPherson and co-workers.[1a] This protocol improved the diastereomeric ratio obtained for the 1,4-addition of the thioacetate group from 5:1 to 9:1. All transformations proceed with low racemization (^{1}H NMR analysis of the TBDMS ether of crude **14** indicated ~97% de). Diastereomeric purity of **1** was determined to be 97.3% 2(*S*),9(*R*) by HPLC.

In summary, we have developed an extension of Pd π-allyl alkylations that gives access to a 10-membered lactam in good yield and applied the methodology to the preparation of CGS25155, an NEP 24.11 inhibitor. Several features of the present synthesis are advantageous in comparison with the initial synthesis.[1a] These include avoiding the need for chiral auxiliary-based resolution, more direct introduction of the methylene at C-9, and enhanced stereoselectivity in the thioacetate 1,4-addition.

General. Reactions were run under N_2, except as noted. All reagents were used as supplied by commercial sources; *trans*-4-hydroxy-L-proline benzyl ester hydrochloride salt was prepared via a procedure supplied by Dr. L. MacPherson of Ciba-Geigy Corp., Summit, NJ.[17] Standard workup consisted of drying over $MgSO_4$, filtering, and concentrating with a rotary evaporator (20–30 torr). Column chromatography was performed on silica gel (230–400 mesh ASTM). Analyses were obtained as follows: GC, on either a R_{tx}-5 30 m × 0.53 mm i.d. (1.5 mm df) column (FID) or a DB-1 10 m × 0.53 mm i.d. Megabore column (TCD); HPLC, on a Nucleosil 10 C18 250/8/4 column; MS, by chemical ionization (CH_4); ^{1}H NMR and ^{13}NMR spectra, at 270.13 and 67.79 MHz, respectively, in $CDCl_3$ with TMS as the reference, unless otherwise noted. Elemental analyses were performed by Robertson Microlit Labs, Madison, NJ.

6-Chloro-1,2-hexadiene (2). Allene (24.4 g, 0.609 mol) was passed into a dry THF (200 mL) solution of $ClCH_2CH_2CH_2Br$ (63.7 g, 0.404 mol) at −10 to −15 °C. BuLi (1.6 M in hexanes, 303 mL, 0.485 mol) was added, keeping the temperature below −10 °C. The mixture was stirred at 23 °C for 16 h and quenched with H_2O (200 mL). The organic phase was dryed ($MgSO_4$) and distilled (8 in. Vigreux column @ 760 torr). The forecut (≤68 °C) was discarded; the main cut gave 39.6 g (84.1%) of colorless **2**, bp 130–40 °C (@ 30–35 torr). Spectral data matched those reported by Arseniyadis, Gore, and Roumestant.[10]

6-Iodo-1,2-hexadiene (3). This material was prepared as previously in 82.8% yield.[10]

Diethyl (Acetylamino)(4,5-hexadien-1-yl)propanedioate (4). Method A. Diethyl acetamidomalonate (11.9 g, 0.055 mol) in absolute EtOH (60 mL) was treated with potassium *tert*-amylate (25 wt % in toluene, 30.3 mL, 0.055 mol) at reflux for 0.5 h. A solution of **3** (11.4 g, 0.055 mol) in absolute EtOH (20 mL) was added. After stirring in the dark at reflux for 16 h, the concentrated mixture was partitioned between methyl *tert*-butyl ether (250 mL) and H_2O (50 mL). Standard workup afforded

(13) Vigneaud, V.; Meyer, C. E. *J. Biol. Chem.* **1932**, *98*, 295–308.
(14) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929–4932.
(15) (a) Chilot, J.-J.; Doutheau, A.; Gore, J. *Bull. Soc. Chim. Fr.* **1984**, 307–316. (b) Smadja, W. *Chem. Rev.* **1983**, *83*, 263–320.
(16) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145.
(17) MacPherson, L. J. Ciba-Geigy Corporation, private communication, 1992.

14.1 g (86.4%) of syrupy **4**, which solidified. Typically, crude **4** was used directly.

Method B. A slurry of **2** (4.0 g, 26.0 mmol), KI (4.3 g, 26.0 mmol), diethyl acetamidomalonate (5.7 g, 26.0 mmol) K_2CO_3 (325 mesh, 5.4 g, 39.0 mmol), and dry DMF (50 mL) was stirred at 60 °C for 12 h. The concentrated residue was dissolved in methyl *tert*-butyl ether (100 mL) and H_2O (100 mL). Extraction with aqueous citric acid (10 wt %, 2 × 100 mL) and brine (100 mL) and then standard workup gave 4.5 g (58.1%) of **4**. Recrystallization (hexane, 73.1% recovery) gave white **4**: mp 67–68.5 °C; IR (KBr) ν 3250, 1850, 1744, 1640 cm^{-1}; ^1H NMR δ 6.78 (br s, 1 H), 5.07 (m, 1 H), 4.66 (m, 2 H), 4.24 (q, 2 H, J = 7.1 Hz), 2.36 (m, 2 H), 2.03 (s, 3 H), 2.00 (m, 3 H), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 208.2, 168.7, 167.9, 89.0, 74.8, 66.2, 62.1, 31.4, 27.4, 22.8, 22.7, 13.7; MS *m/z* (rel intensity) 299 (M + 1, 17), 298 (100), 256 (13), 252 (14). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.44; H, 7.77; N, 4.63.

(*RS*)-2-(Acetylamino)-6,7-octadienoic Acid (5). A solution of crude **4** (13.7 g, 46.0 mmol), KOH (85%, 12.2 g, 184 mmol), and aqueous EtOH (85%) was stirred for 16 h at 60 °C. The concentrated residue was dissolved in H_2O (40 mL) and methyl *tert*-butyl ether (60 mL). The acidified aqueous phase (20% citric acid, 100 mL) was heated for 6 h at 100 °C. Extraction with EtOAc (3 × 100 mL) and then standard workup gave 8.00 g (88.3%) of yellow **5**, which solidified: mp 82.5–84 °C; IR (KBr) ν 3360, 3250–2550 (br), 1949, 1715, 1625 cm^{-1}; ^1H NMR δ 10.38 (br s, 1 H), 6.34 (d, 1 H, J = 6.7 Hz), 5.07 (m 1 H), 4.67 (m, 2 H), 4.60 (m, 1 H), 2.07 (s, 3 H), 2.06 (m, 2 H), 1.96 (m, 1 H), 1.78 (m, 1 H), 1.51 (m, 2 H). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.00; H, 7.89; N, 6.93.

(2*S*)-2-Amino-6,7-octadienoic Acid (6). To a 37 °C, pH 7.4 (NaOH) solution of **5** (38.9 g, 0.197 mol) in H_2O (500 mL) was added Acylase I (*Aspergillus*). The temperature and pH (7.2–7.6, 1 N NaOH) were strictly controlled. More Acylase I (1.0 g) was added after 2 h. The mixture was acidified (pH 2.7, 6 N HCl) after 14 h, treated at 65–70 °C with norit (4 g), filtered hot, and concentrated to half volume. Extraction (~65 °C) with EtOAc (5 × 250 mL) removed (2*R*)-2-(acetylamino)-6,7-octadienoic acid ((*R*)-**5**, 21.8 g, 56%), which was racemized directly. The aqueous layer was basified (pH 4.9, 2 N NaOH) and concentrated nearly to dryness. Suspension of the residue in 85% MeOH (200 mL) at 50 °C for 2 h, filtration, and concentration afforded 12.2 g (39.9%) of off-white **6**: mp ~185 °C dec; $[\alpha]^{25}_D$ = +22.4°, (c = 7.4 mg/mL, 1 N HCl); IR (Nujol) ν 3300–2500 (br), 1949, 1578, 1420, 1385, 1378 cm^{-1}; ^1H NMR (D_2O, DSS) δ 4.99 (m, 1 H), 4.55 (m, 2 H), 3.54 (t, 1 H, J = 6.8 Hz), 1.88 (m, 2 H), 1.73 (m, 1 H), 1.35 (m, 2 H). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.70; H, 8.63; N, 9.02.

A solution of (*R*)-**5** (25.9 g, 0.131 mol) in aqueous NaOH (1 N, 150 mL) was heated to 60 °C and treated dropwise with Ac_2O (57.6 mL, 66.3 g, 0.65 mol) over 3 h. The mixture was kept at 60 °C for 16 h, concentrated, diluted with EtOAc (150 mL), and acidified (pH 4.9, 6 N HCl). Clarification and concentration of the organic layer gave 26.3 g (101.5%) of oily **5**, which was resubmitted directly to enzymatic resolution.

Methyl (2*S*)-2-Amino-6,7-octadienoate Hydrochloride (7). A slurry of **6** (22.1 g, 0.142 mol) in MeOH (500 mL) was treated dropwise at −5 °C with $SOCl_2$ (42.0 g, 352 mmol), keeping the temperature at 0–5 °C. After stirring at 23 °C for 12 h, the mixture was clarified and concentrated. The residue was triturated in methyl *tert*-butyl ether (230 mL) for 8–12 h to provide 25.6 g (87.7%) of tan **7**: mp 80.5–82 °C; $[\alpha]^{25}_D$ = +28.4° (c = 10.2 mg/mL, MeOH), (the *N*-(*R*)-α-methoxyphenylacetamide exhibited >97% de by ^1H NMR); IR (Nujol) ν 3190–2500 (br), 2075, 1953, 1741 cm^{-1}; ^1H NMR δ 8.85 (br s, 3 H), 5.11 (m, 1 H), 4.68 (m, 2 H), 4.13 (m, 1 H), 3.82 (s, 3 H), 2.12 (m, 4 H), 1.75 (m, 2 H), 1.64 (m, 2 H). Anal. Calcd for $C_9H_{15}NO_2$·HCl: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.73: H, 7.89; N, 6.62.

Methyl (2*S*)-2-[[2-(Methoxycarbonyl)acetyl]amino]-6,7-octadienoate (8). A solution of **7** (10.7 g, 51.8 mmol) and $CH_3O_2CCH_2COCl$ (7.1 g, 51.8 mmol) in CH_2Cl_2 (220 mL) was treated at −10 to −5 °C with Et_3N (5.4 g, 53.0 mmol) in CH_2Cl_2 (15 mL). After 12 h at 23 °C, the mixture was extracted with saturated $NaHCO_3$ (2 × 50 mL) and 20% citric acid (100 mL). Standard workup gave 10.3 g (69.1%) of oily red **8**. Analytically pure **8** was purified by chromatography (EtOAc–hexane, 1:2): IR (neat) ν 3363, 1950, 1742, 1625 cm^{-1}; ^1H NMR δ 7.53 (br s, 1 H), 5.06 (m, 1 H), 4.65 (m, 2 H), 4.61 (m, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.37 (s, 2 H), 2.02 (m, 2 H), 1.90 (m, 1 H), 1.75 (m, 1 H), 1.46 (m, 2 H); ^{13}C NMR δ 208.4, 172.4, 169.3, 164.7, 89.0, 74.9, 52.3, 52.2, 52.0, 40.9, 31.4, 27.4, 24.4; MS *m/z* (rel intensity) 271 (M + 1, 14.6), 270 (100), 238 (10), 210 (38). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.86; H, 7.42; N, 5.10.

Methyl (2*S*,6*RS*)-6-Acetoxy-2-[[2-(methoxycarbonyl)acetyl]amino]-7-octenoate (9). A slurry of **8** (10.3 g, 38.2 mmol), NaOAc (6.3 g, 77.0 mmol), AgOTf (20.7 g, 80.6 mmol), and glacial AcOH (100 mL) was stirred in the dark at 95 °C for 48 h. The mixture was filtered, concentrated, diluted with EtOAc (200 mL), refiltered, and extracted with saturated $NaHCO_3$ (2 × 100 mL). The aqueous layers were extracted with EtOAc (3 × 50 mL), and then the organic layers were extracted with acidified brine (50 mL containing 5 drops of 12 N HCl). Standard workup afforded 12.6 g (94.4%) of oily brown **9**, which was used directly. The major impurity is the 8-acetoxy isomer (^1H NMR): IR (neat) ν 3359, 3116, 1743, 1626, 884 cm^{-1}; ^1H NMR δ 7.55 (m, 1 H), 5.80–5.50 (m, 1.2 H), 5.19 (m, 1.8 H), 4.58 (m, 1.1 H), 4.47 (m, 0.5 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.34 (s, 2 H), 2.16–1.27 (m, 9.4 H); ^{13}C NMR δ 171.8, 170.3, 169.6, 168.4, 164.8, 135.7, 134.5, 124.0, 116.1, 73.6, 73.5, 64.3, 52.7, 51.7, 51.6, 51.5, 50.6, 40.8, 32.8, 31.1, 31.0, 23.8, 20.4, 20.3; MS *m/z* (rel intensity) major isomer 330 (9, M + 1), 288 (24), 270 (100), 238 (33), 209 (95), minor isomer 330 (21, M + 1), 270 (73), 238 (66), 209 (100).

(2*S*,9*RS*)-Decahydro-10-oxo-2,9-azecinedicarboxylic Acid (12). A solution of $Ph_2PCH_2CH_2PPh_2$ (1.6 g, 3.89 mmol), $(PPh_3)_4Pd$ (3.0 g, 2.60 mmol), BTMC (12.3 g, 54.7 mmol), and dry degassed THF (300 mL) heated at reflux under Ar was treated with **9** (12.0 g, 36.5 mmol) in dry, degassed THF (100 mL) over 6 h (syringe pump). After 6 h, the mixture was filtered and concentrated, and the residue dissolved in CH_2Cl_2 (150 mL) and H_2O (150 mL). The organic phase was stirred with norit (2 g) and silica gel (7 g). Standard workup gave dimethyl (6*E*+*Z*)-(2*S*,9*RS*)-1,2,3,4,5,8,9,10-octahydro-10-oxo-2,9-azecinedicarboxylate (**10**), which was used directly. Chromatography (EtOAc–hexane, 1:3) gave an analytical sample: IR (KBr) ν 3349, 2877, 1751, 1672, 1553 cm^{-1}; ^1H NMR δ 6.03 (m, 1 H), 5.64 (m, 1 H), 5.43 (m, 1 H), 4.82 (m, 0.4 H), 4.45 (m, 0.6 H), 3.76–3.67 (2 s, 6 H), 3.19 (m, 0.6 H), 2.95 (d, 0.4 H, J = 11.4 Hz), 2.58 (m, 1 H), 2.42–1.82 (m,

4.5 H), 1.81–1.33 (m, 2.5 H); MS *m/z* (rel intensity) major isomer 270 (100, M + 1), 238 (36), 210 (39), 170 (61), minor isomer 270 (97, M + 1), 252 (22), 238 (100), 210 (58), 170 (87). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.02; H, 7.06; N, 5.16.

Crude **10** was dissolved in 95% EtOH (500 mL) and NaOH (1 N, 100 mL), stirred for 1 h at 25 °C and then acidified to pH 7.5 (1 N HCl). After concentration, H_2O (200 mL) was added, and the mixture was basified (pH 10.0, 1 N NaOH) and extracted with CH_2Cl_2 (3 × 200 mL). The aqueous phase containing disodium (6*E*+*Z*)-(2*S*,9*RS*)-1,2,3,4,5,8,9,10-octahydro-10-oxo-2,9-azecinedicarboxylate (**11**) was used directly.

A solution of **11** was hydrogenated over Pd/C (10 wt %, 2.5 g) at 40–50 psi and 23 °C. Catalyst was removed and the filtrate was acidified (pH 1.5, 1 N HCl) and extracted with EtOAc (3 × 150 mL). Concentration afforded 4.5 g (50.7%) of white **12**. Recrystallization (AcOH, 45%) gave analytically pure material: mp 195 °C dec; IR (KBr) ν 3600–2500 (br), 3369, 1742, 1676, 1568 cm^{-1}; ^1H NMR (C_5D_5N) δ 13.10 (br s, 2 H), 9.21 (d, 0.55 H, J = 8.0 Hz), 8.67 (m, 0.45 H), 5.20 (m, 0.55 H), 5.07 (m, 0.45 H), 4.06 (m, 0.55 H), 3.75 (m, 0.45 H), 2.64 (m, 0.45 H), 2.37 (m, 2 H), 2.07 (m, 1.55 H), 1.87–1.25 (m, 8 H); ^{13}C NMR (C_5D_5N) δ 174.94, 174.80, 172.90, 169.24, 54.58, 53.98, 53.66, 53.36, 28.67, 27.95, 26.46, 26.12, 25.21, 24.71, 24.16, 23.62, 22.63, 21.41; MS *m/z* (rel intensity) 244 (54, M + 1), 200 (100), 172 (21), 154 (28). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.30; H, 7.07; N, 5.69.

(2*S*)-9-Methylenedecahydro-10-oxo-2-azecinecarboxylic Acid (13). A slurry of **12** (3.33 g, 13.68 mmol), piperidine (0.30 mL, 3.03 mmol), and $(CH_2O)_x$ (492 mg, 16.41 mmol) in pyridine (30 mL) was heated at 65 °C for 4 h. After concentration, HCl (1 N, 90 mL) was added, and the mixture was extracted with EtOAc (2 × 150 mL). Standard workup gave oily **13** (2.26 g, 75.0%), which crystallized from CH_2Cl_2 (30 mL): mp 123–125 °C; IR (KBr) ν 3314, 3091–2500 (br), 1706, 1643 cm^{-1}; ^1H NMR (CD_3OD) δ 5.64 (d, 1 H, J = 1.5 Hz), 5.32 (d, 1 H, J = 1.5 Hz), 4.48 (m, 1 H), 2.65–2.25 (m, 4 H), 1.75–1.20 (m, 8 H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.49; H, 8.15; N, 6.48.

***trans*-1-[(10′*S*)-(3′-Methylenedecahydro-2′-oxo-10′-azecinyl)carbonyl]-4-hydroxy-L-proline Phenylmethyl Ester (14).** To a stirred 0 °C slurry of **13** (2.20 g, 10.40 mmol) and *trans*-4-hydroxy-L-proline benzyl ester HCl (2.68 g, 10.40 mmol) in CH_2Cl_2 (50 mL) was added HOBT (1.40 g, 5.40 mmol), *N*-methylmorpholine (2.30 mL, 20.8 mmol), and EDCl (3.98 g, 20.8 mmol). After 48 h at 23 °C, HCl (0.5 N, 160 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). Standard workup afforded solid **14** (2.33 g, 54.0%) which was used directly: IR (neat) ν 3272, 1748, 1641, 1620 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H), 6.84 (d, 1 H, J = 6.6 Hz), 5.71 (s, 1 H), 5.25 (s, 1 H), 5.15 (m, 2 H, J = 11.6 Hz), 4.85 (m, 1 H), 4.75 (t, 1 H, J = 9.5 Hz), 4.49 (m, 1 H), 4.24 (br s, 1 H), 3.84, d, 1 H, J = 7.5 Hz), 3.64 (m, 1 H), 2.45–1.85 (m, 6 H), 1.70–1.20 (m, 8 H).

***trans*-1-[(3′*R*),(10′*S*)-[3′-[(Acetylthio)methyl]decahydro-2′-oxo-10′-azecinyl]carbonyl]-4-hydroxy-L-proline Phenylmethyl Ester (1, CGS25155).** Crude **14** (2.00 g, 4.83 mmol) was dissolved in AcSH (5 mL), and the solution was stirred at 23 °C for 48 h. Dilution with EtOAc (70 mL), extraction with NaOH (2 N, 140 mL) and H_2O (50 mL), and standard workup gave an oil which was chromatographed (EtOAc) to yield 2.12 g (89.5%) of odorless **1** of 97.3% de (HPLC, 60% aqueous CH_3CN, desired isomer elutes last): mp 149–151 °C; $[\alpha]^{25}_D$ = +3.4 (c = 0.88, CH_2Cl_2); IR (KBr) ν 3341, 1752, 1687, 1673, 1629 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H), 6.75 (d, 1H, J = 7.5 Hz), 5.16 (m, 2 H), 4.75 (m, 2 H), 4.60 (m, 1 H), 3.80 (d, 1 H, J = 7.5 Hz), 3.68 (m, 1 H), 3.56 (br s, 1 H), 2.92 (m, 2 H), 2.37 (m, 2 H), 2.28 (s, 3 H), 2.09–1.50 (m, 5 H), 1.50–1.15 (m, 8 H). Anal. Calcd for $C_{25}H_{34}N_2O_6S$: C, 61.20; H, 6.99; N, 5.71. Found: C, 60.94; H, 7.08; N, 5.55.

Acknowledgment. We wish to thank Dr. Arthur D. Perez for insightful discussions and Dr. Lawrence J. MacPherson for running some initial lactamizations.

JO950738C