Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1587–1592

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

AN EFFICIENT STEREOSELECTIVE SYNTHESIS OF [3*S*(1*S*,9*S*)]-3-[[[9-(BENZOYLAMINO)OCTAHYDRO-6,10-DIOXO-6H-PYRIDAZINO-(1,2-a)(1,2)-DIAZEPIN-1-YL]-CARBONYL]AMINO]-4-OXOBUTANOIC ACID, AN INTERLEUKIN CONVERTING ENZYME (ICE) INHIBITOR

M. H. Chen,* O. P. Goel, J.-W. Hyun, J. Magano, and J. R. Rubin

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105, U.S.A.

Received 22 February 1999; accepted 28 April 1999

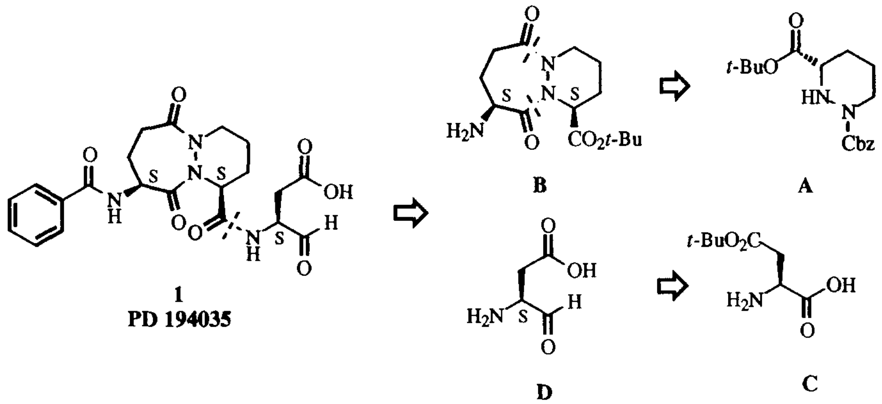
Abstract: The title compound **1** is a potent interleukin-1ß-converting enzyme (ICE) inhibitor. Recently, an efficient chiral synthesis of compound **1** has been accomplished in our labs. The overall yield of this 18-step stereoselective synthesis was 9.8%.

Interleukin-1ß-converting enzyme (ICE) is the obligate enzyme for processing biologically inactive pro IL-1ß to the biologically active cytokine, IL-1ß.[1] Since this original discovery, the biological role of the enzyme has broadened to include the regulation of certain apoptotic processes, and a large family of homologs has been identified.[2] One of the most potent inhibitors has been found to be the pyridazinodiazepine peptidomimetic class of ICE inhibitors which has displayed exceptionally high affinity for the enzyme. Some of the biological and bioavailability results of the inhibitor were described by Dolle and coworkers.[3] A few years ago, the syntheses of this type of compounds were disclosed by Batchelor, Dolle, and coworkers.[4] Recently, we have developed in our labs an improved chiral synthesis of [3*S*(1*S*,9*S*)]-3-[[[9-(benzoylamino)-octahydro-6,10-dioxo-6H-pyridazino-(1,2-a)(1,2)diazepin-1-yl]carbonyl]amino]-4-oxobutanoic acid (**1**), an important analog in the pyridazinodiazepine series. The key chiral intermediate (3*S*)-piperazic acid **A** was prepared, in 6 steps, using Evans oxazolidinone chiral auxiliary. Diazepine **B** was obtained by the reaction of **A** with protected glutamic acid **8**, in 5 steps. Final coupling of **B** with modified aspartic acid **C** gave the expected PD 194035 (**1**). The overall yield of this 18-step synthesis was 9.8%.

The retro-synthesis of compound **1** is described in Scheme 1. The disconnection of the C-N bond of the side chain leads to diazepine **B** and aldehyde **D**. Precursor **B** can be synthesized from the corresponding chiral piperazic acid **A**, while **D** from *L*-aspartic acid β-*t*-butyl ester **C**.

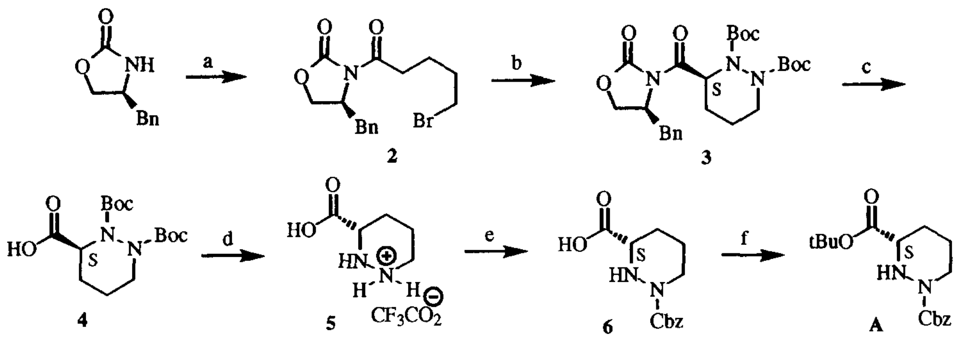
0960-894X/99/$ - see front matter
PII: S0960-894X(99)00236-X

Scheme 1
Retro-Synthesis of PD 194035



Instead of the racemic synthesis described in the published literature,[4] a chiral synthesis of (3*S*)-piperazic acid **A** was carried out in our labs using the modified method described by Hale[5] and Decicco.[6] The synthesis is shown in Scheme 2. The *N*-acylation of lithiated (4*S*)-benzyl-2-oxazolidinone with bromovaleryl chloride gave **2** in 85% yield. Deprotonation of **2** with LDA in THF, at -78 °C, followed by treatment with di-*tert*-butyl azodicarboxylate (DBAD) in DCM in the presence of catalytic amount of Bu_4NI and excess amount of DMPU (16.5 equiv)

Scheme 2
Chiral Synthesis of (3*S*)-Piperazic Acid (A)

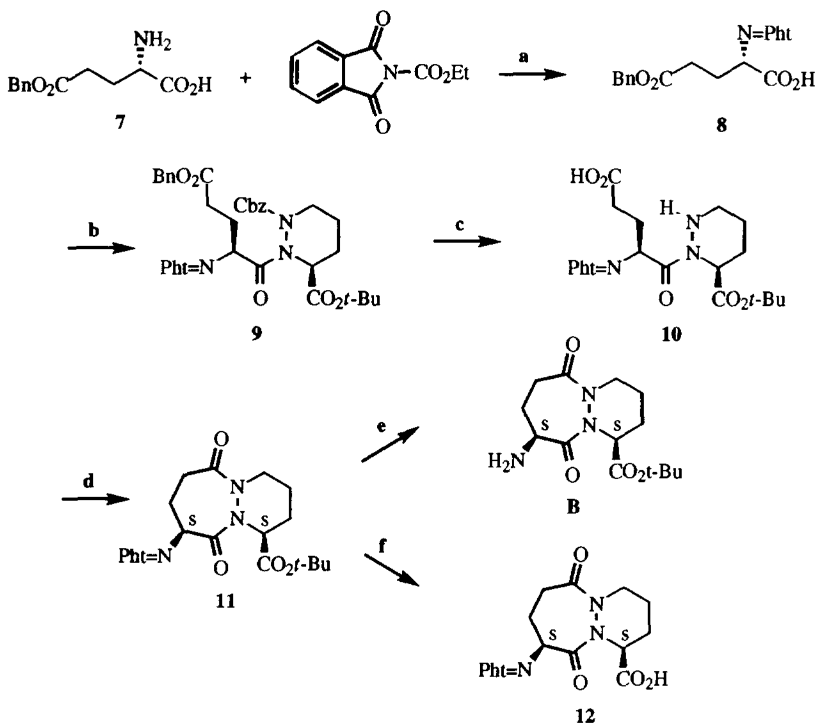


(a) 1. *n*BuLi, THF, -78 °C; 2. $Br(CH_2)_4COCl$, 85%; (b) 1. LDA, THF, -78 °C; 2. BocN=NBoc, Bu_4NI, DMPU, CH_2Cl_2, 92%; (c) LiOH, THF-H_2O/4:1, 98%; (d) 50% TFA in CH_2Cl_2, quantitative; (e) $ClCO_2Bn$, toluene, 1 N NaOH (aqueous), 98%; (f) Isobutylene, H_2SO_4, dioxane, 85%.

yielded hexahydropyridazine **3** (92%). The combination of the methods described by Hale and Decicco gave excellent yield of the cyclic product **3**. LiOH hydrolysis in THF-H_2O (4:1) to remove the chiral auxiliary of **3**, followed by removal of the Boc groups using 50% TFA in CH_2Cl_2 gave an almost quantitative yield of mono TFA salt of the (3*S*)-piperazic acid **5**. Selective Cbz protection of 1-nitrogen of **5** using benzyl chloroformate in toluene and aqueous 1N NaOH yielded compound **6** (98%).[7] The acid **6** was further converted to its *tert*-butyl ester **A** using isobutylene and catalytic amount of concentrated sulfuric acid (85%).

Attempts of preparing the diazepine intermediate **B** using the method described by Lawton, et al.[8] failed to give the expected product after many experiments. A modified synthesis was applied using the method previously reported.[4a] The free amino group of *L*-Glu-(OBn)-OH (**7**) (Scheme 3) was protected as a phthaloylamine using *N*-(ethoxylcarbonyl)phthalimide at reflux THF with TEA as base (98%).[9] The resulting *N*-phthaloyl-*L*-Glu(OBn)-OH (**8**) was converted to

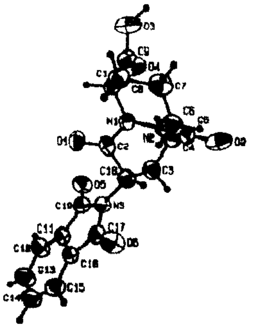
Scheme 3
Synthesis of Diazepine Intermediate B

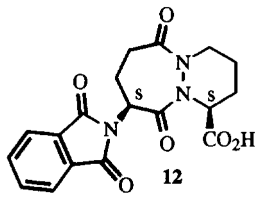


(a) TEA, THF, reflux, 98%; (b) 1. PCl_5, CH_2Cl_2; 2. **A**, $NaHCO_3$ (aq), 92%; (c) H_2, Pd/C, MeOH, 97%
(d) PCl_5, *N*-ethylmorpholine, THF, 76%; (e) NH_2NH_2•xH_2O, EtOH, 98%; (f) 50% TFA in CH_2Cl_2, 95%

the corresponding acid chloride with PCl_5 in CH_2Cl_2, then coupled with **A** in aqueous $NaHCO_3$ to give **9** in 92% yield. No racemization was observed by HPLC. Use of $SOCl_2$ or peptide coupling reagents, such as BOP, PyBOP, TBTU, DCC, etc., failed to give the expected product **9**. Removal of *N*-Cbz group and benzyl ester of **9** using standard catalytic hydrogenation in MeOH (97%), followed by another coupling via the acid chloride in THF and *N*-ethylmorpholine as base yielded the diazepine **11**, mp 182-183 °C, $[\alpha]_D$ -82.7° (*c* 0.51, MeOH), (76%).[10] Again, use of $SOCl_2$ and other coupling reagents produced no cyclization. Deprotection of the *N*-phthaloylamine using hydrazine hydrate yielded diazepine intermediate **B**, 98% yield, as a glassy solid. To obtain crystals, *tert*-butyl ester of compound **11** was converted to the corresponding acid **12** by TFA-CH_2Cl_2 hydrolysis, [α] -161.2° (*c* 0.50, DMF). The absolute configuration of chiral (1*S*,9*S*)-**12** was confirmed by single crystal X-ray crystallography (Figure 1), which showed the (*S*,*S*) configuration at the 1-C and 18-C of the bicyclic rings.

Figure 1
X-Ray Crystal Structure of Intermediate 12



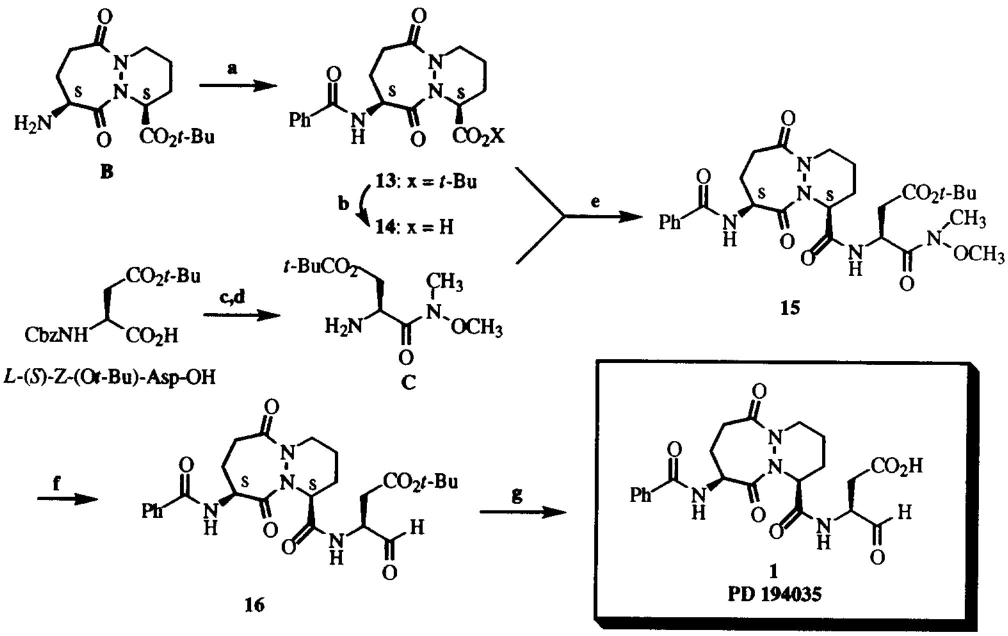


12

The amino group in diazepine **B** was benzoylated in aqueous $NaHCO_3$ to give amide **13**, $[\alpha]_D$ -94.5° (*c* 0.52, MeOH), (97%), (Scheme 4). The *tert*-butyl ester of **13** was then hydrolyzed to the acid **14** with 50% TFA in CH_2Cl_2 (94%). Conversion of *L*-Cbz-(O*t*-Bu)-Asp-OH to the corresponding Weinreb's *N,O*-dimethylhydroxyamide was accomplished using *iso*-butyl chloroformate, *N*-methyl morpholine to form a mixed anhydride, followed by coupling with *N,O*-dimethylhydroxyamine hydrochloride (81%). The product was catalytically hydrogenated in THF to remove the Cbz group to give the intermediate **C** (83%). Standard peptide coupling of **14** and **C** employing reagents BOP, HOBt, DIPEA in CH_2Cl_2 as solvent gave compound **15** in 84%

yield. The reduction of the *N,O*-dimethylhydroxyamide **15** using $LiAlH_4$ (1.0 M solution in ether), at -40 °C, in ether-THF gave aldehyde **16** in 51% yield. Higher or lower reaction temperature, or excess amount of THF gave more over/under reduction products.[11] The method to synthesize aldehyde **1** from its corresponding acid **14** as described in the patent literature using Bu_3SnH and $(Ph_3P)_2PdCl_2$ catalyst failed to give the expected product in our hands.[4a,12] Finally, careful hydrolysis of *tert*-butyl ester **16** with 30% TFA in CH_2Cl_2 gave the expected compound **1**, as a white solid in 90% yield, mp 116-118° C, [α] -109.2° (*c* 0.52, MeOH). The overall yield of this 18-step total synthesis was 9.8%.

Scheme 4
Synthesis of Compound 1



(a) PhCOCl, $NaHCO_3$ (aq), 97%; (b) 50% TFA in CH_2Cl_2, 94%; (c) 1. $ClCO_2i$-Bu, NMM; 2. HN(OMe)Me•HCl, 81%; (d) H_2, Pd/C (20%), THF, 83%; (e) BOP, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 84%; (f) $LiAlH_4$ (1.0M in Et_2O), -40 °C, Et_2O-THF, 51%; (g) 30% TFA in CH_2Cl_2, 30 min, 90%.

In conclusion, PD 194035, a previously described peptidomimetic ICE inhibitor of the pyridazinodiazepine class, has been synthesized in a stereoselective manner using Evan's chiral auxiliary. This modified scheme is more efficient and provides a better overall yield than the published procedure.

References and Notes

1. (a) Sleath, P. R.; Hendrickson, R. C.; Kronheim, S. R.; March, C. J.; Black, R. A. *J. Biol. Chem.* **1990**, *265*, 14526. (b) Thornberry, N. A.; Bull, H. G.; Calaycay, J. R.; Chapman, K. T.; Howard, A. D.; Kostura, M. J.; Miller, D. K.; Molineaux, S. M.; Weidmer, J. R.; Aunins, J.; Eliistonk, K. O.; Ayala, J. M.; Casano, F. J.; Chin, J.; Ding, G. J.-F.; Egger, L. A.; Gaffney, E. P.; Limjuco, G.; Palyha, O. C.; Raju, S. M.; Rolando, A. M.; Salley, J. P.; Yamin, T.; Lee, T. D.; Shively, J. E.; MacCross, M.; Mumford, R. A.; Schmidt, J. A.; Tocci, M. J. *Nature* **1992**, *356*, 768.
2. (a) Ator, M. A.; Dolle, R. E. *Curr. Pharm. Des.* **1995**, *1*, 191. (b) Schwartz, L. M.; Milligan, C. E. *Trends Neurosci.* **1996**, *19*, 555.
3. Dolle, R. E.; Prasad, C. V. C.; Prouty, C. P.; Salvino, J. M.; Awad, M. M. A.; Schmidt, S. J.; Hoyer, D.; Ross, T. M.; Graybill, T. L.; Speier, G. J.; Uhl, J.; Miller, B. E.; Helaszek, C. T.; Ator, M. A. *J. Med. Chem.* **1997**, *40,* 1941.
4. (a) Batchelor, M.J.; Bebbington, D.; Bemis, G. W.; Fridman, W. H.; Gillespir, R. J.; Golec, J. M. C.; Gu, Y.; Lauffer, D. J.; Livingston, D. J.; Matharu, S. S.; Mullilcan, M. D.; Murckl, M. A.; Murdoch, R.; Nyce, P. L.; Robidoux, A. L. C. **1997**, WO 97/22619; *Chem. Abstr.* **1997**, *127*, 122000. (b) Dolle, R. E.; Chaturvedula, P. V.; Morgan, R. T.; Schmidt, S. J. U.S. Pat. 5,552,400, 1996; *Chem. Abstr.* **1996**, *124,* 261732.
5. Hale, K. J.; Cai, J.; Delisser, V.; Manaviazar, S.; Peak, S. S.; Bhatia, G. S.; Collins, T. C.; Jogiya, N. *Tetrahedron* **1995**, *52*, 1047.
6. Decicco, C. P.; Leathers, T. *Synlett*, **1995**, 615.
7. Adams, C. E.; Aguilar, D.; Hertel, S.; Knight, W. H.; Paterson, J. *Synth. Comm.* **1988**, *18*, 2225.
8. Attwood, M. R.; Hassall, C. H.; Krohn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1011.
9. McArthur, C. R.; Worster, P. M.; Okon, A. U. *Synth. Comm.* **1983**, *13*, 311.
10. Literature[4a] reported: mp 182-185° C, $[\alpha]_D$ -80.0° (*c* 0.5, MeOH).
11. The reaction gave mainly unreacted starting material below -60 °C, and over reduced alcohol above -20 °C. A minimum amount of THF was used to enhance the solubility of compound **15** in ether. The use of excess THF led to over reduction. The yield reported here is not optimized.
12. Chapman, K. T. *Bioorg. Med. Chem. Lett.* **1992,** *2*, 613.