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Enantioselective Synthesis of (*R*)-(–)-Cryptopleurine

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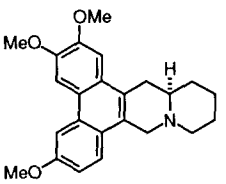
Abstract: An enantioselective synthesis of naturally occurring (*R*)-(–)-cryptopleurine based on highly efficient asymmetric amidoalkylation using a cyclic *N*-acyliminium intermediate is described.

We have currently devised[1] a general procedure for preparing enantiomerically pure derivatives of piperidines via asymmetric addition of carbon nucleophiles to cyclic *N*-acyliminium ions bearing some chiral pyrrolidine auxiliaries. With this enantioselective strategy in hand, we envisioned development of an asymmetric entry to the phenanthroquinolizidine alkaloid (–)-cryptopleurine (**1**). Cryptopleurine[2] continues to attract considerable attention due to its interesting physiological properties including antiviral[3] and antitumor activities.[4] A number of syntheses of racemic cryptopleurine have been documented in the literature,[5] and one optically active synthesis of its antipodal isomer has been published.[6] Herein we report the first enantioselective synthesis of the naturally occurring (*R*)-(–)-enantiomer (**1**) of cryptopleurine using the highly efficient asymmetric amidoalkylation reaction with a silyl enol ether as a nucleophile.

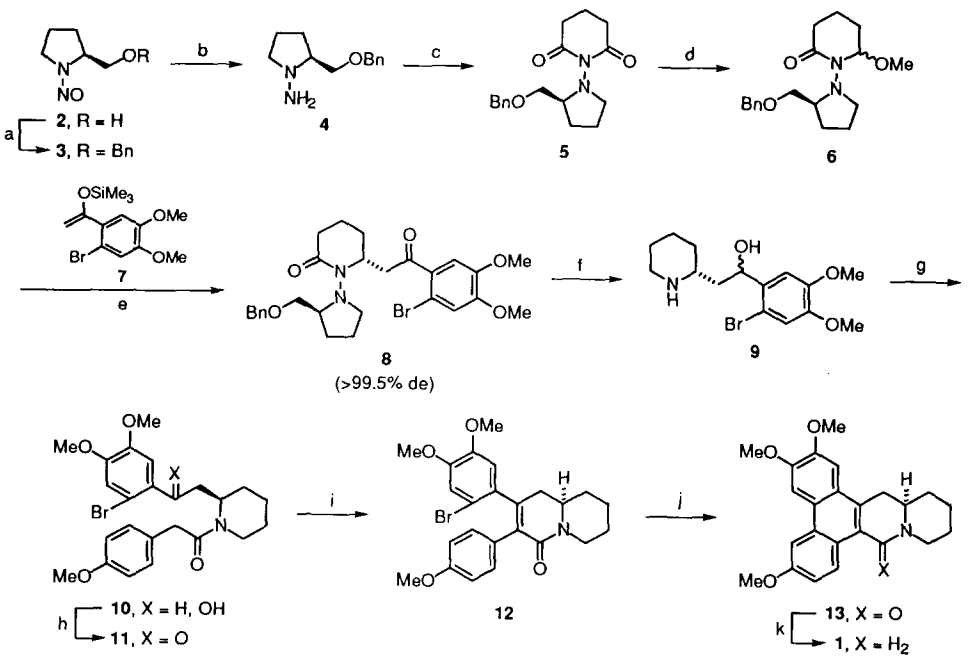


(–)-Cryptopleurine (**1**)

Our previous work[1] revealed that higher levels of asymmetric induction in nucleophilic addition to cyclic *N*-acyliminium ions are obtained using the 2-substituted pyrrolidines as chiral auxiliaries rather than C_2 symmetric 2,5-disubstituted pyrrolidines. Accordingly, we decided to employ the cyclic imide **5** chirally modified by (*S*)-2-benzyloxymethylpyrrolidine to obtain the desired chirality in the reaction process. Thus, (*S*)-*N*-nitrosoprolinol (**2**)[7] was converted to the (*S*)-*N*-aminopyrrolidine **4** via O-benzylation followed by $LiAlH_4$ reduction. Condensation of **4** with glutaric anhydride provided **5** (87% from **2**). Reduction of **5** with $LiBEt_3H$ afforded a *ca.* 4:1 diastereomeric mixture of the alcohols, which was converted to the methoxy lactam **6** (MeOH, PPTS) in 64% yield from **5**. Upon exposure of **6** to the silyl enol ether **7** and BF_3•Et_2O in CH_2Cl_2 at room temperature, the in situ generated *N*-acyliminium ion underwent asymmetric addition of the silyl enol ether **7** to furnish the desired (6*R*)-keto lactam **8** (70%) with virtually perfect diastereoselectivity: based on ^1H NMR no trace of the (6*S*)-epimer could be detected in the product indicating a de of >99.5%.

The keto lactam **8** was treated with the BH_3–THF complex to afford a *ca.* 1:1 diastereomeric mixture of the hydroxy piperidine **9** via a simultaneous process involving reduction of the lactam and ketone carbonyl groups as well as reductive cleavage of the hydrazine moiety to remove the chiral pyrrolidine auxiliary. Compound **9** was transformed into the hydroxy amide **10** (55% from **8**) by N-acylation. Subsequent

oxidation of **10** with pyridinium dichromate gave the keto amide **11** (77%), which underwent intramolecular aldol type condensation under the basic conditions (5% ethanolic KOH, reflux) to form the quinolizidinone **12** in 60% yield. Construction of the phenanthrene nucleus was achieved through photocyclization of **12**, affording 9-oxocryptopleurine **13** in 54% yield. Alternatively, treatment of **12** with Bu_3SnH and AIBN effected intramolecular radical cyclization, leading to significantly higher yield (87%) of **13**. Finally, reduction of **13** with $LiAlH_4$ provided (*R*)-(–)-cryptopleurine (**1**), mp 196–197 °C (lit.[2a] mp 197–198 °C); $[\alpha]^{25}_D$ –96.7° (*c* 0.40, $CHCl_3$) [lit.[2a] $[\alpha]^{18}_D$ –106° (*c* 1.52, $CHCl_3$)]. The spectral data were identical with those of the authentic racemate.[5d]



(a) BnBr, NaH, DMF–THF, r.t. (94%); (b) $LiAlH_4$, THF, reflux; (c) glutaric anhydride, CH_2Cl_2, r.t., then Ac_2O, cat. NaOAc, reflux (93% from **3**); (d) i, $LiEt_3BH$, THF, –78 °C (80%); ii, MeOH, cat. PPTS, r.t. (80%); (e) BF_3•Et_2O, CH_2Cl_2, r.t. (70%); (f) i, BH_3•THF, THF, reflux; ii, 10% NaOH, reflux; (g) *p*-$MeOC_6H_4CH_2COCl$, 5% NaOH, CH_2Cl_2, 0 °C → r.t., then K_2CO_3, MeOH–H_2O, reflux (55% from **8**); (h) PDC, CH_2Cl_2, 4 Å sieves, r.t. (77%); (i) KOH, EtOH, reflux (60%); (j) method A: hv (high-pressure Hg lamp), Et_3N, dioxane (54%); method B: Bu_3SnH, AIBN, benzene, reflux (87%); (k) $LiAlH_4$, THF, reflux (55%).

References and Notes

1. Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 6119.
2. (a) Gellert, E.; Riggs, N. V. *Aust. J. Chem.* **1954**, *7*, 113. (b) Gellert, E. *Aust. J. Chem.* **1956**, *9*, 489.
3. Krmpotic, E.; Farnsworth, N. R.; Messmer, W. M. *J. Pharm. Sci.* **1972**, *61*, 1508.
4. Hartwell, J. L.; Abbott, B. J. *Adv. Pharmacol. Chemother.* **1969**, *7*, 117.
5. For recent syntheses of (±)-cryptopleurine: (a) Crag, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2487. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. (c) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955. (d) Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. (e) Grieco, P. A.; Parker, D. *J. Org. Chem.* **1988**, *53*, 3325.
6. Buckley III, T. F.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222.
7. Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.

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