Pergamon

Tetrahedron Letters 40 (1999) 3081–3084

TETRAHEDRON LETTERS

Total Syntheses of *ent*-Conduramine A and *ent*-7-Deoxypancratistatin.

Hülya Akgün[§,i] and Tomas Hudlicky*[,ii]

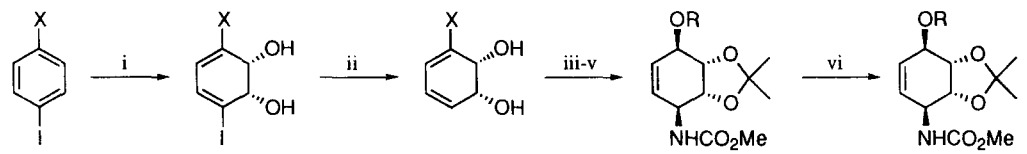
Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA

Received 16 December 1998; revised 19 February 1999; accepted 22 February 1999

Abstract: The first total synthesis of the title alkaloid has been accomplished in fourteen steps form 1-bromo-4-iodobenzene or 1-fluoro-4-iodobenzene via chemoenzymatic production of the antipodal *cis*-diene diols **4**.

The synthesis of Amaryllidaceae alkaloids continues with unabated intensity and interest. In the last three years several asymmetric syntheses of pancratistatin have been completed,[1] the preparation of *ent*-lycoricidine was reported,[2] and the first three total syntheses of narciclasine were achieved.[3] A review has been published which summarizes all but the very recent accomplishments in this area.[4] Our activity in this field has been driven not only by the desire to furnish a practical synthesis of the most active substance, pancratistatin, but also by the interest in biological activity of these compounds. To satisfy the first requirement we have been continuously improving the strategy and execution of synthesis of pancratistatin. The latter issue is being attended to by testing of pancratistatin congeners as well as its unnatural derivatives.[5] In this manuscript we report an improved synthesis of *ent*-7-deoxypancratistatin **1** via **3a**, the protected form of *ent*-conduramine A, **3b**, and the antipodal diol precursors **4**, generated by improved chemoenzymatic means.

Scheme 1



5

4a X = Br
4b X = F

6a X = Br (20% ee)
6b X = F (88% ee)

3a R = H (20% ee)
7 R = Ac (20% ee)

(+)-**3a** R = H (98% ee)
(–)-**7** R = Ac

Reagents: I) *E. coli* JM109 (DTG601); ii) Bu_3SnH, AIBN, THF; iii) DMP, *p*-TsOH; then, $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH; iv) Al(Hg), THF, H_2O; v) Ac_2O, py; vi) PPL lipase, pH 7.

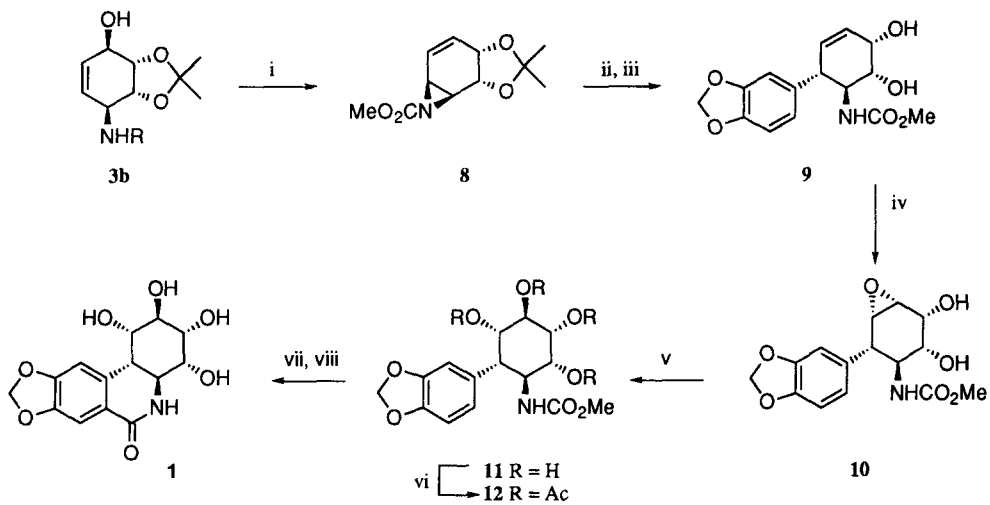
The synthesis of enantiomeric diene diols of type **4** was reported by Boyd, who employed *Pseudomonas putida* strains UV4 and NCIMB 8859 (or NCIMB 11767) in sequence.[6] The former organism responds to the directing effects of the larger iodine substituent and produces a scalemic mixture with ~20% ee in **4a** and 88% in **4b**. These mixtures are hydrogenated to **6a** or **6b** and then subjected to fermentation with the latter strain, which digests the *S,S*-enantiomer and provides the desired *R,R*-enantioner in comparable optical purity to the "normal" metabolite derived from bromeobenzene.[7] This process leads to complete consumption of the other enantiomer and thus precludes applications in enantiodivergent synthesis, as only half of the total mass is carried forward.

[i] hakgun@tr-net.net.tr
[ii] hudlicky@chem.ufl.edu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00434-7

We chose instead to prepare the scalemic mixture of **4a**, transform it to conduramine derivatives **3** by the well documented nitroso Diels–Alder cycloaddition–oxazine reduction sequence,[8] and employ Johnson's lipase resolution method[9] on the acetylated derivative of **3**, as outlined in Scheme 1. In this fashion, both enantiomers of conduramine A derivative become available in an efficient manner. By starting with an already optically enriched mixture (88% ee) instead of the *meso* cyclohexadiene diol used by Johnson the lipase resolution becomes easier and renders a higher yield of the desired enantiomer. In this way we have combined the best of Boyd's and Johnson's protocols and thus maximized the yield. The desired compound **3a** (>98%ee) was then elaborated to the title alkaloid, as shown in Scheme 2. The protected *ent*-conduramine A was subjected to the Mitsunobu protocol, recently reported by Olivo,[10] which has been shown to lead to aziridines of type **8** in much higher yields (>60%) than the previously employed aziridination of the diene systems.[11] The regioselective addition of the aryl cuprate (20–40%) provided, after deprotection (95%), diol **9**, which was subjected to the vanadium oxide catalyzed epoxidation (67%) followed by the stereospecific generation of the tetrol **11** (80%). Acetylation (82%) and exposure of this material to modified Bischler–Napieralski conditions, as reported by Banwell,[12] led to the peracetylated derivative **12** (61%), whose deprotection (72%) furnished the title alkaloid, identical in all respects (with the exception of the optical rotation) to the natural product. The synthesis proceeded in eight steps form *ent*-conduramine A and in 14 steps from 1-bromo-4-iodobenzene with an overall yield of ~1%. The enantiomer, quite surprisingly, showed activity against several cancer cells lines (pancreatic, ovarian, and others).[5e]

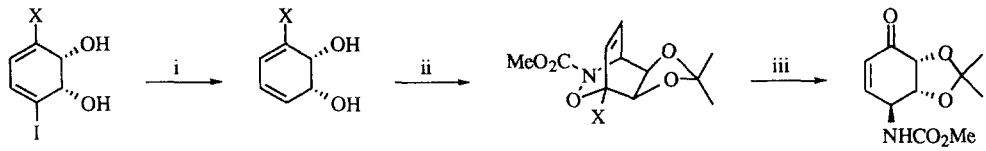
Scheme 2



Reagents: i) PPh_3, DEAD, THF; ii) (3,4-methylenedioxy)bromobenzene, *n*-BuLi, Cu, $BF_3{\cdot}Et_2O$, –78 °C; iii) Dowex-50W, MeOH; iv) $VO(acac)_2$, *t*-BuOH, PhH, 70 °C; v) BzONa, H_2O, 100 °C; vi) Ac_2O, py; vii) Tf_2O, DMAP, CH_2Cl_2, 0 °C; viii) K_2CO_3, MeOH.

When *p*-iodofluorobenzene was oxidized and the resulting diol **4b** subjected to Bu_3SnH reduction, the *ent*-diol **6b** was isolated with 88% ee (a major improvement over the previously reported method that uses biooxidation of fluorobenzene and provides scalemic mixtures requiring enrichment by crystallization).[13] The Diels-Alder reaction of **6b** proceeded with excellent regio- and stereospecificity to afford the fluoroxazine **13** which is not succeptible to the tin-mediated or Al(Hg) reduction of the bridgehead fluorine atom, Scheme 3. Treatment of **13** with either sodium amalgam[14] or $Mo(CO)_6$[10,15] gave the protected amino ketone **14** (*ent*- series) which has been used as a synthon for conduramine and alkaloid synthesis. In conclusion, the preparation of enantiomeric diols[16,17] in an enantiodivergent manner allowed the synthesis of the title alkaloid and the

Scheme3



4a X = Br
4b X = F

6a X = Br (20%ee)
6b X = F (88% ee)

13

14

Reagents: i) Bu_3SnH, AIBN, THF; ii) DMP, *p*-TsOH; then $HONHCO_2Me$, $NaIO_4$, H_2O; iii) Na(Hg) or $Mo(CO)_6$

ent-conduramine synthons in much improved yields.[18] The high yields of the new aziridination and the improved yields of the previously troublesome cuprate addition now furnish the alkaloid in 1-5% overall yield. With several steps in the synthesis performed in an aqueous environment the opportunity for considerations of large-scale synthesis becomes more realistic.

The fact that *ent*-7-deoxypancratistatin displayed activity similar in scope to its enantiomer is both surprising and interesting, although the activity is one order of magnitude less than the natural enantiomer (7-deoxypancratistatin has been found to be 10 times less active than pancratistatin).[5e]

Acknowledgments

The authors thank the National Science Foundation (CHE-9615112), the U.S. Environmental Protection Agency (R862113), and TDC Research, Inc., for generous financial support. Prof. G. R. Pettit and his group (Arizona State Univ.) are thanked for preliminary biological evaluation of the alkaloid.

References and Notes

* To whom correspondence should be addressed.

§ Present address: Faculty of Pharmacy, Hacettepe University, Hacettepe, 06100 Ankara, Turkey.

1. Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643; (b) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143; (c) Doyle, T. J.; Hendrix, M.; Vanderveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153; (d) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341; *Tetrahedron*, **1998**, *54*, 15509, and references within; (e) First synthesis (racemic): Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

   For references to the synthesis of 7-deoxypancratistatin see: (f) Tian, X.; Maurya, R.; Konigsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125; (g) Hudlicky, T.; Tian, X.; Konigsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752; (h) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289; (i) Chida, N.; Jitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. Heterocycles **1996**, *43*, 1385; (j) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164.

2. Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366.

3. Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655; (b) For the second asymmetric synthesis see: Keck, G. E.; Wager, T. T.; Rodriguez, F.; 216th. ACS National Meeting, 1998, Boston; (c) Hudlicky, T.; Gonzalez, D.; Martinot, T. *Tetrahedron Lett.* **1999**, *40*, 3077.

4. Polt. R. in *Organic Synthesis: Theory and Applications*, Hudlicky, T., Ed.; JAI press, 1997; Vol. 3., p. 109.

5. For references to biological activities of these alkaloids see for example: (pancratistatin and 7-deoxypancratistatin) (a) Abou-Donia, A. H.; De Giulio, A.; Evidente, A.; Gaber, M.; Habib, A. A.; Lanzetta, R.; Seif El Din, A. *Phytochemistry* **1991**, *30*, 3445; (b) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat.*

Prod. **1986**, *49*, 995; (c) (lycoricidine) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860; (d) (narciclasine) Ceriotti, G. *Nature* **1967**, *11*, 595; (e) Hudlicky, T.; Pettit, G. R., unpublished observations: Deoxypancratistatin, *ent*- deoxypancratistatin, and several truncated derivatives have been tested by the Pettit group against human cancer cell lines. The full details of the biological profiles will be published in an upcoming full account.

6. Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor , S. C. *J. Chem. Soc., Chem. Commun.* **1995**, 117.
7. Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439.
8. Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.
9. Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1.
10. Olivo, H. F.; Hemenway, M. S.; Hartwig, A. C. Chan, R. *Synlett*, **1998**, 247.
11. For previous syntheses of aziridines of type **2** see reference 1(f), and bibliography cited therein.
12. Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.
13. Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc., Chem. Commun.* **1991**, 61.
14. Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
15. Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602.
16. For references on the use of microbial dioxygenases please consult: (a) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemistry* **1970**, *9*, 1626; (b) Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.
17. For recent reviews on the applications of cyclohexadiene *cis*-diols in enantioselective synthesis see: (a) Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Reports* **1998**, *15*, 309; Hudlicky, T.; Thorpe, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1993; Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, in press.
18. Analytical and spectral data obtained were consistent with the structural assignments of all compounds.