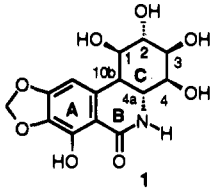
Asymmetric Total Synthesis of (+)-Pancratistatin

Barry M. Trost* and Shon R. Pulley

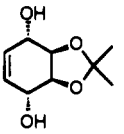
Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received July 6, 1995

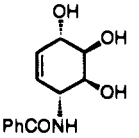
The promising biological activity and low natural abundance of (+)-pancratistatin (**1**) has made it a target for total synthesis.[1] Prior to initiation of our program, only a racemic synthesis had been accomplished.[2,3] Very recently an asymmetric synthesis based upon whole-cell oxidation of bromobenzene with *Pseudomonas putida* 39/D appeared in the literature.[4] The ready availability of diol **2**[5] suggested that an effective strategy might emerge by its palladium-catalyzed desymmetrization using a nitrogen nucleophile.[6] By combining this desymmetrization protocol with a novel cyclization to create the lactam, an effective total synthesis has emerged. By default, this route also resulted in an asymmetric synthesis of (−)-*N*-benzoyl conduramine A-1 (**3**).[7]



1

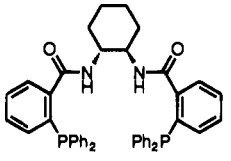


2

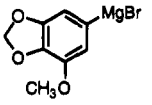


3

Scheme 1 outlines the route. Treatment of diol **2** with 2 equiv of *n*-C_4H_9Li in THF at 0 °C followed by quenching with methyl chloroformate gives dicarbonate **4**[8] (87% yield). The desymmetrization utilizes a palladium complex derived from the chiral ligand **5**[6] and π-allylpalladium chloride to give azide **6**[8] in 83% isolated yield. To establish the ee, azide **6** was converted to

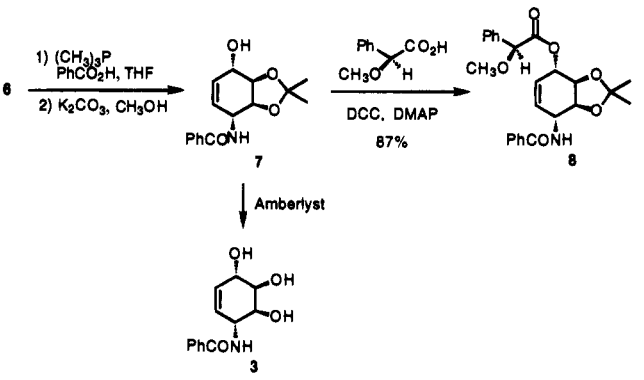


5



9

(−)-*N*-benzoyl conduramine A-1 derivative **7**[7b,9] by reduction with trimethylphosphine in the presence of benzoic acid followed by hydrolysis. To verify the absolute configuration as depicted and establish the enantiohomogeneity (>95%), **7** was esterified with *O*-methylmandelic acid to give **8**. In addition, the acetonide was removed to give (−)-*N*-benzoyl conduramine A-1 **3**, ($[\alpha]^{25}_D$) = −138° (*c* 1.31, CH_3OH).[9]



With enantiopure monoazide **6** in hand, the stage was set for regio- and diastereocontrolled introduction of the aryl group by S_N2' chemistry via organocuprates. All attempts to preform the organocuprate led to disappointing results, which we attributed to the instability of the arylcuprate. On the other hand, addition of the Grignard reagent **9**[10] to a mixture of the azide **6** and cuprous cyanide gave reproducibly the desired adduct **10**, for which the vicinal coupling J_{ab} = 10 Hz (δ_a 3.10, δ_b 3.36) confirms the regio- and diastereochemistry. Difficulty associated with purification of **10** led to its immediate *cis*-dyhydroxylation to give **11**[8] in 62% overall yield from **6**. The NMR coupling constants fully confirm the assigned regio- and stereochemistry (δ_a 2.83, δ_b 3.51, δ_c 4.01, J_{ab} = 12 Hz, J_{ac} = 10.3 Hz).

For formation of the final lactam B ring, we envisioned conversion of the azide to an isocyanate followed by intramolecular acylation. Surprisingly, all attempts to effect cyclization of the isocyanate derived from **10** onto the electron rich aromatic ring failed. The resultant products, which were not characterized, appear to have lost the acetonide, implying that the ether oxygen of the acetonide is more nucleophilic than the aromatic ring. To increase the nucleophilicity of the aromatic ring, a σ-rather than π-nucleophile was contemplated. Thus, the electron rich aromatic ring was brominated ortho to the methoxy group with a positive halogenating agent, NBS, to give **11c**. The regioselectivity was confirmed by correlation to the product obtained by bromination of a free phenol under conditions known to ortho-brominate.[11] The successful completion of the total synthesis confirms this assignment.

The isocyanate **12** was formed by straightforward means. Its treatment with 2 equiv of *tert*-butyllithium led to metal halogen exchange being faster than addition to the isocyanate. The resultant aryllithium undergoes spontaneous intramolecular addition to form the desired lactam **13a**[8] in 65% yield. Deblocking the vicinal diol generates the acetonide of the *O*-methyl ether of 1-isopancratistatin, **13b**[8] (δ_a 2.83, δ_b 3.39, δ_c 4.29, J_{ab} = 13.7 Hz, J_{ac} = 8.1 Hz).

(1) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Swaga, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018. 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.

(2) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

(3) For synthetic approaches, see: Park, T. K.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 195. Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295. Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1993**, *34*, 4751. Lopes-Rosangela, S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775. Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076. Clark, R. D.; Souchet, M. *Tetrahedron Lett.* **1990**, *31*, 193.

(4) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.

(5) From benzoquinone, see: Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Synth. Commun.* **1989**, *19*, 537. From 1,3-cyclohexadiene, see: Dumortier, L.; Liu, P.; Dobbelaere, S.; Van Der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243. Also see: Dangschat, G.; Fischer, H. O. *Naturwissenchaften* **1939**, *45*, 756. We prepared **2** in five steps and 69% overall yield from benzoquinone by the method of Cambie.

(6) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.

(7) (a) Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111. (b) Johnson, C. R.; Plé, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388 and references cited therein. (c) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

(8) Satisfactory characterization has been obtained for this compound.

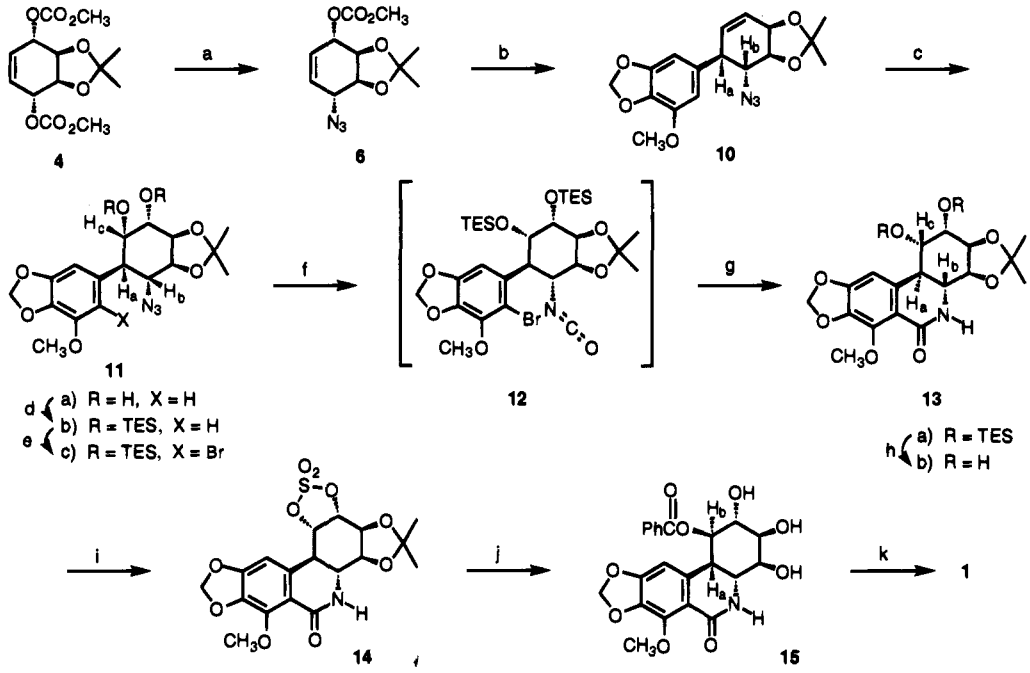
(9) Our rotations for **3** and **7**, $[\alpha]^{25}_D$ = −129° (*c* 1.15, $CHCl_3$), are higher than those recorded in the literature[7b] (**3**, $[\alpha]^{25}_D$ = −126° (*c* 1.29, CH_3OH); **7**, $[\alpha]^{25}_D$ = −107° (*c* 1.0, $CHCl_3$)), although the melting points are the same. We further verified our rotational data by converting **7** to its corresponding *O*-methyl mandelic ester, which showed a single diastereomer.

(10) For precursor aryl bromide, see: Shirasaka, T.; Takuma, Y.; Imaki, N. *Synth. Commun.* **1990**, *20*, 1223. Dallacker, F.; Sanders, J. *Chem.-Ztg.* **1984**, *108*, 186.

(11) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.

0002-7863/95/1517-10143$09.00/0

Scheme 1. Asymmetric Synthesis of (+)-Pancratistatin[a]



[a] (a) 0.5 mol % $(\pi\text{-}C_3H_7PdCl)_2$, 0.75 mol % **5**, $TMSN_3$, CH_2Cl_2, room temperature, 82% yield; (b) **9**, CuCN, THF, ether, 0 °C; (c) cat. OsO_4, $NMO{\cdot}H_2O$, CH_2Cl_2, room temperature, 62% yield (two steps); (d) $TESOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, quantitative; (e) NBS, DMF, 75% yield; (f) (i) $(CH_3)_3P$, THF, H_2O; (ii) $COCl_2$, THF, $(C_2H_5)_3N$; (g) *t*-C_4H_9Li, ether, −78 °C, 62−65% yield (three steps). (h) TBAF, THF, −78 to 0 °C; (i) (i) $SOCl_2$, $(C_2H_5)_3N$, (ii) cat. $RuCl_3{\cdot}H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temperature, 72%; (j) $PhCO_2Cs$, DMF, then workup with THF, H_2O, cat. H_2SO_4, 85% yield; (k) (i) CH_3OH, K_2CO_3, room temperature, (ii) LiI, DMF, 80 °C, 85% yield.

Completion of the synthesis requires inversion at C-1, which anticipates that S_N2 substitution proximal and syn to the acetonide, i.e., at C-2, is less favorable than at C-1 for electronic reasons in spite of the fact it does not involve a *trans*-diaxial ring opening of the cyclic sulfate **14** in a chair conformation. Furthermore, molecular mechanics calculations indicate that a twist-boat conformation in which C-1 is readily attacked is slightly lower in energy (0.5 kcal/mol) than the chair conformation. Indeed, nucleophilic attack occurs with complete selectivity to give only **15**,[8] in which the acetonide cleaves simultaneously with hydrolysis of the alkyl sulfate (δ_a 3.39, δ_b 5.76, J_{ab} = 2.4 Hz). Simple removal of the benzoyl and methyl ether groups completes the synthesis of (+)-pancratistatin, $[\alpha]^{25}_D$ = +44.0° (*c* 1.0, DMSO), whose spectral properties are in full agreement with those of the natural product.[1,4] The overall yield of (+)-pancratistatin from diol **2** is 11%.

The successful application of the palladium-catalyzed approach to desymmetrization illustrates its extension to highly functionalized ring systems. Use of azide introduces nitrogen in the equivalent of a "protected" form since it survives many types of reactions as illustrated herein. The resultant product provides a versatile juxtaposition of functionality for further structural elaboration as illustrated by the syntheses of both *N*-benzoyl conduramine A-1 and pancratistatin. Furthermore, either enantiomer is available by this route. The power of this new lactam-forming reaction is highlighted by its succeeding in the present case where conventional methods failed. Several anomalies of the pancratistatin ring system have also been revealed. The present route also indicates several shortcomings of current methodology that, once resolved, will provide further streamlining of this route to pancratistatin and its analogues.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Fellowship support for part of the stay of S.R.P. from the American Cancer Society is gratefully acknowledged. Mass spectra were provided by the Mass Spectrometry Facility at the University of California—San Francisco. We are indebted to Johnson Matthey Alfa Aesar for their generous loan of palladium salts.

Supporting Information Available: Characterization data for **4**, **6**, **10**, **11**, and **13**−**15**, experimental procedures for the preparation of **6**, **10**, and **13a**, and molecular mechanics structures for conformations of **14** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA952216K