Tetrahedron Letters,Vol.30,No.44,pp 6077-6080,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

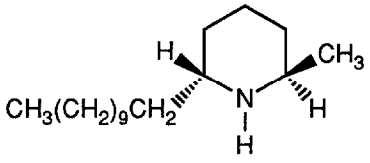
THE IMINE-EPOXIDE REARRANGEMENT IN THE FORMATION OF TRANS-2,6-DISUBSTITUTED PIPERIDINES. A STEREOSELECTIVE SYNTHESIS OF (±)-TENERAIC ACID.

Harry H. Wasserman*, Karen Rodriques and Roman Kucharczyk
Department of Chemistry, Yale University, New Haven, CT 06511 USA

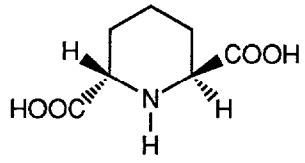
Summary: Teneraic acid, a naturally-occurring *trans*-2,6-piperidine dicarboxylic acid, has been synthesized using the imine-epoxide rearrangement.

The family of *trans*-2,6-disubstituted piperidine alkaloids includes a number of products exhibiting notable biological activity.[1] Despite interest in the pharmacological properties of these compounds, there are few general, stereoselective methods for their synthesis. The reduction of substituted pyridine derivatives[2] or various intramolecular cyclizations[3] have generally yielded product mixtures in which the more stable *cis* isomers predominate. More recent approaches which have demonstrated significant *trans* stereoselectivity have included the hydride reduction of cyclic imines[4], alkene cycloadditions to tetrahydropyridine N-oxides followed by reductive cleavage[5], and the alkylation and reduction of cyanopiperidines[6] or bicyclic carbamates[7].

In recent work, we have shown that the imine-epoxide rearrangement followed by hydride ion reduction provides a mild, efficient method for the formation of *trans*-2,6-disubstituted piperidines[8], and we have used this procedure for the synthesis of the fire-ant venom alkaloid, solenopsin A[9] **1**. To further illustrate the applicability of this methodology, we now report a stereoselective synthesis of teneraic acid **2**. To our knowledge, this is the first synthesis of this *trans*-piperidine-2,6-dicarboxylic acid, recently isolated from the red alga *porphyra tenera*.[10,11]



1

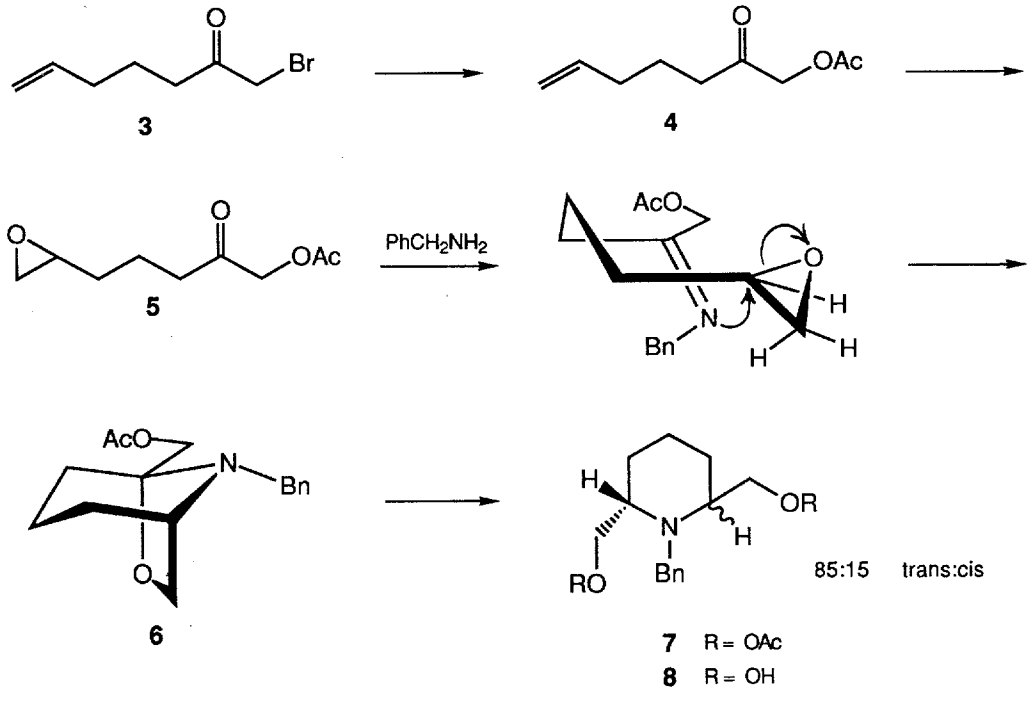


2

The readily available 1-bromo-6-hepten-2-one **3**[12] was heated with KOAc in absolute ethanol to yield the keto acetate **4** (85%) which was then treated with MCPBA to form the epoxide **5** (85%). The keto-epoxide **5** was then heated at reflux for 22 h with benzylamine in the presence of 3Å molecular sieves to form the

oxatropane **6**.[13] Compound **6** then underwent reduction with $NaCNBH_3$ in dry HOAc, followed by workup with acetic anhydride, to yield the pure diacetates **7** (85% from the epoxide **5**). 250 MHz NMR analysis showed the diacetates to be a 85:15 mixture of *trans*:*cis* isomers.[14]

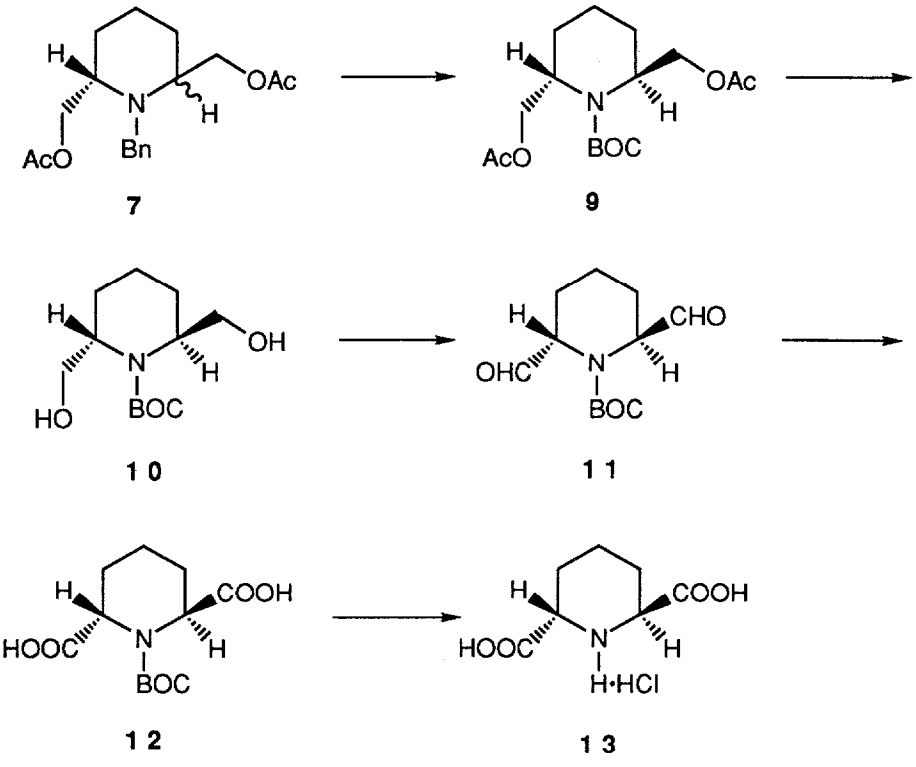
Removal of the acetate protecting groups with K_2CO_3 in MeOH proceeded smoothly, but attempts to oxidize the resulting N-benzyl diol **8** using various oxidizing agents were unsuccessful.[15] This problem was readily solved, however, by replacing the N-benzyl group with the less electron-rich N-BOC group.



In our successful oxidation sequence, the diastereomeric benzyl diacetates **7** were hydrogenated over 10% Pd/C in 10:1 MeOH:AcOH at 30 p.s.i. for 1 h (95%) to remove the benzyl groups, and the resulting *cis* and *trans* amines separated by silica gel chromatography (the *trans*:*cis* ratio remained 85:15). Reaction of the *trans* isomer with di-t-butyl-dicarbonate for 15 h yielded the *trans* carbamate **9** (87%). Removal of both acetate groups as described above provided the diol **10**, which was purified by recrystallization from CH_2Cl_2/hexane (90%).

Standard Swern oxidation conditions (oxalyl chloride, DMSO, -78° C, 1 h, then excess Et_3N) were used to obtain the dialdehyde **11** (90%) which was immediately

oxidized to the diacid **12** in t-BuOH with aqueous $KMnO_4$ in the presence of a pH 4.5 phosphate buffer (60%). Removal of the BOC protecting group was accomplished with trifluoroacetic acid, and treatment with 1 N HCl provided a quantitative yield of **13**. The teneraic acid hydrochloride **13** obtained in this manner was identical in all respects (250 MHz NMR, FTIR and MS) to an authentic sample.[16]



Acknowledgments: This work was supported by NIH grant GM 31350.

Notes and references:

1. Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379.

2. Adkins, H.; Kuick, L.; Farlow, M.; Wojick, B. *J. Am. Chem. Soc.* **1934**, *56*, 2425.

3. For example: Takahashi, K.; Mikajiri, T.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4372.

4. a) Yamamoto, H.; Maruoka, K.; Matsumura, Y. *Tetrahedron Lett.* **1982**, *23*, 1929; b) Yamaguchi, R.; Kawanisi, M.; Nakazono, Y. *Chem. Lett.* **1984**, 1129.

5. a) Carruthers, W.; Williams, M. *Chem. Commun.* **1986**, 1287; b) Tufariello, J.; Puglis, J. *Tetrahedron Lett.* **1986**, *27*, 1489; c) Gallagher, T.; Lathbury, D. *Tetrahedron Lett.* **1985**, *26*, 6249.

6. a) Husson, H.-P.; Bonin, M.; Romero, J.; Grierson, D. *J. Org. Chem.* **1984**, *49*, 2392; b) Takahashi, K.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4368.

7. Ciufolini, M.; Hermann, C.; Whitmire, K.; Byrne, N. *J. Am. Chem. Soc.* **1989**, *111*, 3473.

8. Wasserman, H.; Thyes, M.; Wolff, S.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4973.

9. Wasserman, H.; Rusiecki, V. *Tetrahedron Letters* **1988**, *29*, 4977.

10. Kawauchi, H.; Tukazima, S.; Ota, S.; Murai, A. *Nippon Suisan Gakkaishi* **1978**, *44*, 1371.

11. We were unable to find a report on the biological activity of teneraic acid, although the corresponding *cis* isomer exhibits activity as an anticonvulsant[17] and synaptic depressant.[18]

12. Oppolzer, W. *Tetrahedron* **1981**, *37*, 4359.

13. The oxatropane 6 was purified by silica gel chromatography (95%). ^{1}H NMR: 7.4-7.2 (m, 5H), 4.30 (d, J=11.6 Hz, 1H), 4.19 (d, J=11.6 Hz, 1H), 3.96 (d, J=13.4 Hz, 1H), 4.0-3.9 (m, 1H), 3.80 (d, J=7.4 Hz, 1H), 3.46 (d, J=13.4 Hz, 1H), 3.32 (m, 1H), 2.06 (s,3H), 1.9-1.6 (m, 5H), 1.5-1.4 (m, 1H). HRMS: calcd for $C_{16}H_{21}O_3N$, 275.1522, found 275.1501.

14. The isomeric ratio was determined by using the method of Hill, R.; Chan, T.-H. *Tetrahedron* **1965**, *21*, 2015.

15. Among the oxidizing agents used were: PDC, Jones reagent, $KMnO_4$, and oxalyl chloride/DMSO. It is possible that under the above conditions the N-benzyl tertiary amino group interacts with the newly formed carbonyl groups. Alternatively, the tertiary amino group may undergo oxidation.

16. We thank Professor Minoru Sato of Kitasato University for providing a sample of natural teneraic acid.

17. Croucher, M.; Meldrium, B.; Collins, J. *Neuropharmacology* **1984**, *23*, 467.

18. Davies, J.; Evans, R.; Francis, A.; Jones, A.; Smith, D. A. S.; Watkins, J. *Neurochemical Research* **1982**, *7*, 1119.

(Received in UK 15 September 1989)