

A DIASTEREOSELECTIVE SYNTHESIS OF *trans, trans*-OCTAHYDRONAPHTHOQUINOLIZINE

Hai Mi and David I. Schuster*

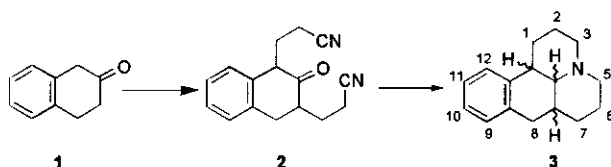
Department of Chemistry, New York University, New York, NY, 10003-6603, USA

Abstract - A facile approach involving stereospecific reduction of an enamine moiety in a tetracyclic system has made it possible to synthesize diastereospecifically the biologically active octahydronaphthoquinolizine with *trans, trans* stereochemistry.

The rigid tetracyclic systems of octahydronaphthoquinolizines (OHNQ) are close structural analogues of compounds which are known to be biologically active due to specific interactions at neuroreceptor sites in the central nervous system.^{1,2} In particular, OHNQ's show specific affinity for sigma receptor binding sites.³ Sigma receptors in the central nervous system and the periphery have been implicated in a variety of physiological processes, and may represent links between the nervous, endocrine and immune systems.³ Octahydronaphthoquinolizines present a synthetic challenge since they possess stereogenic centers at three contiguous ring junction carbons. The approaches to this system which have been reported previously produce a mixture of diastereomers with a low percentage of the biologically most active *trans, trans* isomer.⁴

As shown in **Scheme I**, Cai made all stereoisomers of OHNQ in a simple three-step reaction. All four diastereomers were separated and characterized by X-ray crystallography and NMR spectroscopy. In this

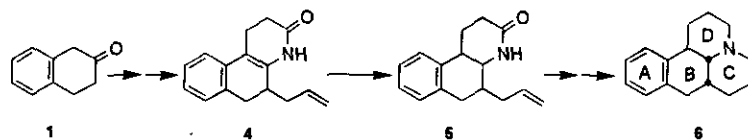
Scheme I



synthesis, there is no control of stereochemistry at the ring closure step, and the major product is the biologically inactive *cis, cis* isomer.⁵

Katerinopoulos and Kouvarakis took another route which gave the *trans, cis* OHNQ isomer (6) as the major product,⁶ as shown in **Scheme II**. The key step in which stereogenic centers are created is the ionic hydrogenation^{7,8,9} of 4 with trifluoroacetic acid and triethylsilane to yield 5. Approach of the proton takes

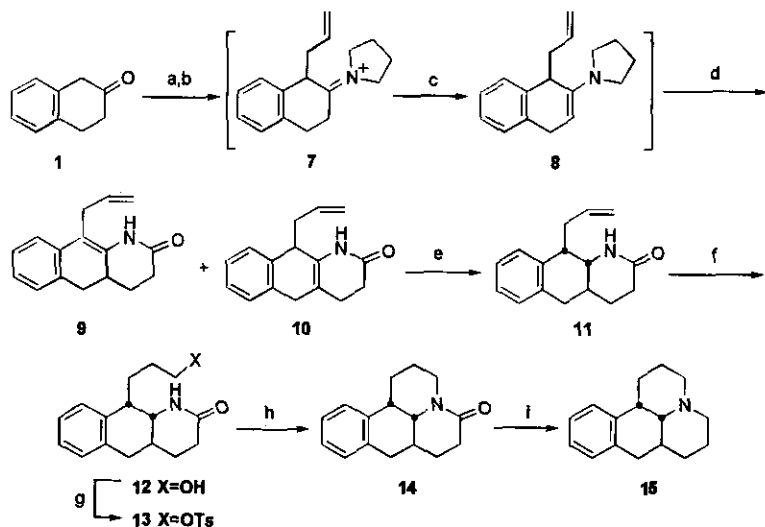
Scheme II



place from the less hindered side, *anti* to the allylic moiety, leading to *cis* fusion of rings B and C. Hydride is then delivered to the benzylic cation *via anti* addition, leading to *trans* B/D ring fusion in **6**.

Starting with β -tetralone, tricyclic compounds (**9**) and (**10**) were easily obtained in a one-pot reaction in 80% yield, as shown in Scheme III. The ratio of **9** to **10** is 3 to 2. After alkylation with allyl bromide, the

Scheme III



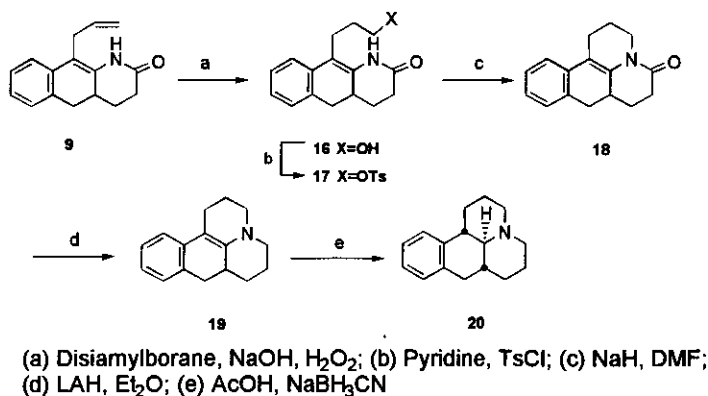
(a) Pyrrolidine, Benzene; (b) $\text{CH}_2=\text{CHCH}_2\text{Br}$, Dioxane; (c) Et_3N ; (d) $\text{CH}_2=\text{CHCONH}_2$;
 (e) Et_3SiH , CF_3COOH ; (f) Disiamylborane, then NaOH , H_2O_2 ; (g) Pyridine, TsCl;
 (h) NaH , DMF; (i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Borane dimethyl sulfide complex, THF.

intermediate iminium cation (**7**) was trapped by a second equivalent of base, triethylamine or dicyclohexylamine, to give enamine (**8**).^{10,11} Addition with acrylamide followed by cyclization afforded **9** and **10** directly. Without separation, **9** and **10** were subjected to ionic hydrogenation which gave a single compound (**11**) in 85% yield. Since ionic hydrogenation with triethylsilane and trifluoroacetic acid is reputed to proceed by *anti*-addition across the tetrasubstituted double bond,^{7,8,9} we hoped that *trans, trans* fusion of B/D and B/C rings could be furnished at this stage. The closure of ring D was carried out by using disiamylborane to transform the terminal double bond to primary alcohol (**12**) in 80% yield, formation of tosylate (**13**), followed by treatment with sodium hydride, to give the tetracyclic amide (**14**). The two steps from **12** to **14** have a combined yield of 70%. Reduction of this amide^{12,13} gave the tertiary amine (**15**) in 75% yield, which was identified as *cis, trans* OHNQ by comparison of its spectra (¹H and

^{13}C nmr) with those reported previously by Cai.⁴ The stereochemistry was further confirmed by X-ray crystallographic data of **11** and **14**.

In order to attempt to change the steric preference, the closure of ring D was carried out prior to ionic hydrogenation, as shown in **Scheme IV**. The intrinsic difference in reactivity of the two double bonds in **9** towards hydroboration was utilized to produce primary alcohol (**16**) in 90% yield. Using conventional methods, primary alcohol (**16**) was transformed to tetracyclic unsaturated amide (**18**) in 89% yield. However, treatment with triethylsilane-trifluoroacetic acid did not effect reduction of the conjugated double bond in **18**, which was therefore treated with lithium aluminum hydride to give enamine (**19**). The conjugated double bond in the tetracyclic system (**19**) was reduced successfully by treatment with acetic acid and sodium cyanoborohydride, a well known protocol to reduce enamines and iminium ions.^{14,15} The yield from **18** to **20** is 40%. The low yield is attributed to the lability of the intermediate enamine (**19**) and the difficulties in reducing a cyclic tertiary amide. Not only was the enamine moiety easily reduced, but the three stereogenic centers were simultaneously generated diastereospecifically in the desired *trans-trans* configuration. Spectroscopic comparison (^1H and ^{13}C nmr) with data previously reported by Cai⁴ confirmed **20** to be the desired *trans, trans* OHNQ.

Scheme IV



The stereochemistry from ionic hydrogenation of **4**, **9** and **10** is dictated by both the conformation of the intermediate cation and the configuration at the carbon bearing the allyl substituent, such that formation of the *trans, trans* product is impossible as long as the allyl group is conformationally unrestricted. Cyclization prior to hydrogenation changes the molecular conformation such that formation of the *trans, trans* product becomes feasible.

With a simple stereospecific route to *trans, trans* OHNQ's now available, it will be possible to prepare substituted analogs which should have even greater affinity and selectivity for sigma receptor binding sites than the parent compound.^{3,4}

REFERENCES

1. J. M. Walker, W. D. Bowen, F. O. Walker, R. R. Matsumoto, B. de Costa, and K. C. Rice, *Pharmacol. Rev.*, 1990, **42**, 355.
2. B. L. Largent, H. Wikstrom, A. L. Gundlach, and S. H. Snyder, *Mol. Pharmacol.*, 1987, **32**, 772.
3. Y. Itzhak, 'Sigma Receptors,' Academic Press, Inc., San Diego, 1994.
4. B. Cai, 'Ph. D. Dissertation,' New York University, 1994.
5. B. Cai, Y. Pan, J. C. Dewan, D. J. Wink, R. B. Murphy, and D. I. Schuster, *Tetrahedron Lett.*, 1993, **34**, 2067.
6. A. Kouvarakis and H. E. Katerinopoulos, *Synth. Commun.*, 1995, **25**, 3035.
7. D. N. Kursanov, Z. N. Parnes, G. I. Bassova, N. M. Loim, and V. I. Zdanovich, *Tetrahedron*, 1967, **23**, 2235.
8. D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.
9. D. N. Kursanov, Z. N. Parnes, M. I. Kalin, and N. M. Loim, 'Ionic Hydrogenation and Related Reactions,' Harwood Academic Publishers, Amsterdam, 1985.
10. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 1963, **85**, 207.
11. A. G. Cook, 'Enamines: Synthesis, Structure, and Reactions,' M. Dekker, New York, 1969.
12. H. C. Brown, and P. Heim, *J. Org. Chem.*, 1973, **38**, 912.
13. H. C. Brown, S. Narasimhan, and Y. M. Choi, *Synthesis*, 1981, 996.
14. Y. Nakagawa and R. V. Stevens, *J. Org. Chem.*, 1988, **53**, 1871.
15. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.

Received, 12th August, 1996