Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Feb 2007.

To cite this article: Antonios Kouvarakis & Haralambos E. Katerinopoulos (1995) A Diastereoselective Synthesis of trans/cis Octahydronaphthoquinolizine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:19, 3035-3044, DOI: 10.1080/00397919508011436

To link to this article: http://dx.doi.org/10.1080/00397919508011436

SYNTHETIC COMMUNICATIONS, 25(19), 3035-3044 (1995)

A DIASTEREOSELECTIVE SYNTHESIS OF TRANS/CIS OCTAHYDRONAPHTHOQUINOLIZINE

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ABSTRACT: The tetracyclic system of 2,3,6,7,7a,8,12b,12c-octahydro-1H,5H-naphtho[1,2,3,i,j]quinolizine with trans/cis fusions of the B/D and B/C rings has been diastereospecifically synthesized in nine steps and in 23% total yield.

Octahydronaphthoquinolizines have been envisioned as potential Central Nervous System (CNS) active compounds binding to dopaminergic[1] adrenergic and sigma[2] receptor sites. This tetracyclic system was recently synthesized in a three step sequence[2,3] involving the preparation of the pyrrolidine enamine of beta tetralone, bis- 2,6 Michael addition to acrylonitrile and reductive cyclization catalyzed by Raney nickel. However this approach yielded a mixture of diastereomers including al four (*cis, cis; trans, trans; cis, trans; and trans, cis*) possible fusions of the B/D and B/C rings. The major product in this synthesis was the *cis, cis* isomer.

Given that activity of phenethylamine analogs requires an antiperiplanar conformation of this moiety,[4] it is imperative to ensure the *trans* fusion of the B

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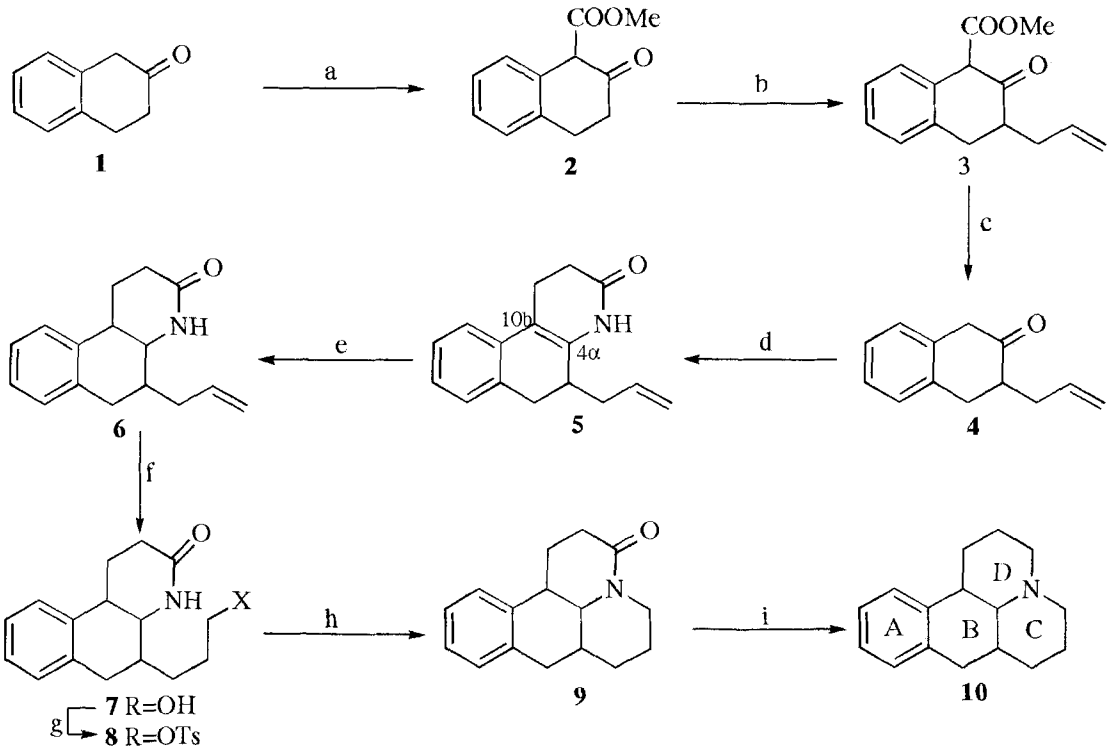
and D rings through a diastereoselective synthesis, thus "locking" the phenethylamine group into the desired conformation. In this report we describe an alternative diastereoselective synthesis of 2,3,6,7,7a,8,12b,12c-octa-hydro-1H,5H-naphtho[1,2,3,i,j]quinolizine with *trans/cis* fusions of the B/D and B/C rings. This tetracyclic system has been constructed in nine steps and in 23% overall yield.

The first stage of this synthetic approach involved the protection of the 1-position of *beta* tetralone[5] (Scheme 1). Reaction of the starting material with dimethyl carbonate in sodium methoxide/methanol yielded the 1-methoxycarbonyl derivative **2**, mainly in its enolic form. Deprotonation by LDA in THF and reaction with allyl bromide introduced the allylic moiety at the desired 3 position. Deprotection at the 1 position was achieved via treatment of **3** with lithium chloride in DMSO-water.[6] The next stage of the synthesis included preparation of the pyrrolidine enamine of **4**, subsequent reaction with acrylamide, hydrolysis of the enamine and cyclization, a process that introduced the D ring of the cystem. Once the unsaturated amide **5** was formed, the problem of the *trans* fusion of the B and D rings was easily resolved by triethyl silane/trifluoroacetic acid "ionic hydrogenation" of the endocyclic double bond.[7,8] The C ring was formed via anti-Markovnikov hydroboration of the allylic double bond using disiamyl borane, and preparation of the tosylate which underwent nucleophilic attack by the amidic anion. At this stage GC/MS analysis of the product revealed the presence of a second, minor (5%) component which was separated by flash chromatography. Reduction of the amidic nitrogen of the major product with BMS/boron trifluoride etherate,[9] yielded a tetracyclic amine which was found by IR, MS, ^{1}H and ^{13}C NMR to be identical to the *trans* B/D, *cis* B/C ring fused octahydronaphthoquinolizine reported

Scheme 1



a) $CO(OMe)_2$ / MeONa/ MeOH; b) LDA/ $CH_2{=}CH_2CH_2Br$; c) LiCl/ DMSO/ H_2O; d) pyrrolidine/ $CH_2{=}CH_2CONH_2$/ C_6H_6; e) Et_3SiH/ CF_3COOH/ CH_2Cl_2; f) Disiamylborane/ NaOH/ H_2O_2; g) Py/ TsCl; h) NaH/ DMF; i) BMS/BF_3Et_2O/THF.

by Schuster's group.[2] The similarly reduced minor product was found to be the *trans, trans* isomer. This stereochemical arrangement was expected since it was controlled by the "ionic hydrogenation" mechanism. Apparently protonation of the C_{10b}-C_{4a} double bond system in **5** takes place at the latter carbon to yield a stabilized benzylic cation. Approach of the proton will take place from the least hindered site, *trans* to the allylic moiety attached to C_5, resulting in the cis fusion of the B and C rings. Attack of the cation by the hydride takes place in the usual *trans* fashion engaging the dopamine moiety into the desired antiperiplanar conformation.

Experimental Section

Chemistry

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1760X FT IR spectrometer. NMR spectra were taken on a Varian FT-80A, 80 MHz and a AC 250 Bruker FT-NMR spetrometer; proton chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were taken on a Hewlett Packard Model 5890 Gas Chromatograph coupled with a Hewlett Packard 5971A Mass Selective Detector. Flash chromatography was performed using Silica Gell 60 230-400 mesh.

Methyl-3,4-dihydro-2-hydroxy-2-naphthalene carboxylate (2).

In a 2 L round bottomed flask were added dry dimethyl carbonate (573 mL), β-tetralone (27.7 g, 0.19 mol). To this system was then added dropwise a solution of sodium methoxide (12.3 g, 0.23 mol) in methanol (50 mL) at 0° C. When the addition was completed the mixture was heated at 80° for 2 h. The system was then cooled to 0°, 1M HCl (330 mL) was added, the mixture was stirred for 5 min, the organic phase was diluted with ethyl acetate (200 mL), washed with sat. NaCl

solution and dried over Na_2SO_4. The solvents were removed under reduced pressure to yield 38.81 g (100 %) of product which was used in the next step without need of further purification. IR: (neat) ν = 1636, 1599, 1568, 1489, 1440, 1385, 1338, 1314, 1226, 752, 666. 1H NMR: ($CDCl_3$) δ = 13.3 (s, 1H), 7.7-7.0 (m, 4H), 3.91 (s, 1H), 3.0-2.4 (m, 4H).

Methyl-3, 4-dihydro-2-hydroxy-3-allyl-naphthalenecarboxylate (3).

To a solution of LDA (34.3 g, 320 mmol) in THF (350 mL) was added a solution of **2** (30.8 g, 151 mmol) in THF (80 mL) dropwise at 0°. The resulting yellow suspention was stirred at 0° for an additional hour. A solution of allyl bromide (22.2 g, 183.3 mmol) in THF (60 mL) was added to this mixture and the system was allowed to warm up to room temperature, stirred for another 45 min period, and cooled to 15° at which point 1M HCl (590 mL), were added dropwise. The mixture was extracted with ethyl acetate (3x100 mL), and the organic phase was washed with sat. NaCl, dried over Na_2SO_4 and the solvents were removed under reduced pressure to give 36.6 g (99.6%) of **3**. IR: (neat) ν = 1714, 1641, 1595, 1567, 1489, 1441, 1337, 1280, 1223. ^1H NMR: ($CDCl_3$) δ = 13.40 (s, 1H), 7.70-7.00 (m, 4H), 5.90-5.40 (m, 1H), 5.10-4.80 (m, 2H), 3.90 (s, 1H), 2.80-1.90 (m, 4H).

3-Allyl-beta tetralone (4).

To a 10 mL round bottomed flask were added compound **3** (1.8 g, 7.4 mmol), DMSO (5.0 mL), LiCl (0.3 g, 6.5 mmol), and water (0.5 mL). The system was heated at 150° for 1 h, the aqueous phase was saturated with NaCl, and the product was extracted with ethyl acetate (2x 50 mL). The organic phase was washed with sat. NaCl solution, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography using

5% ethyl acetate/pet. ether as eluent. The product yield was 1.14 g (83%). IR: (neat) ν = 1736, 1669, 1643, 1451, 1375, 1245, 1046, 999, 920. ^{1}H NMR: ($CDCl_3$) δ = 7.20-6.9 0(br. s, 4H), 5.95-5.30 (m, 1H), 5.15-4.85 (m, 2H), 3.50 (s, 2H), 3.20-1.90 (m, 5H).

5-Allyl-1,4,5,6 - tetrahydrobenzo[f]quinolin-3-(2H)-one (5).

To a Dean and Stark apparatus were placed a solution of 4 (1.87 g, 10.1 mmol), in dry benzene (25 mL), a trace amount of p-toluenesulfonic acid, pyrrolidine (1.1 g, 15.2 mmol), and the solution was heated under reflux for 4 h. The solvent was then distilled and to the residue was added acrylamide (2.41 g, 33.9 mmol) in one portion. The mixture was heated at 90-100° for 38 h, water (8.0 mL) was added and the mixture was stirred at room temperature for 24 h. The product was extracted with ethyl acetate (100 mL), the organic phase washed with sat. NaCl solution (2x 50 mL) dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using 50% ethyl acetate/pet. ether as eluent. The product yield was 0.72 g (30 %) IR: (neat) ν = 3355, 3221, 1679, 1653, 1490, 1382. ^{1}H NMR: ($CDCl_3$) δ = 8.15 (br. s. 1H), 7.27-7.05 (m, 4H), 5.77 (ddd, J= 17,10, and 7.5 Hz, 1H), 5.03 (d, J= 10 Hz, 1H), 5.05 (d, J= 17 Hz,1H), 3.05 (dd, J= 6.5 and 15.5 Hz, 1H), 2.90-2.60 (m, 4H), 2.35-2.00 (m, 4H). GC / MS : m/z: 239 (M+).

5-Allyl-1, 4, 4a, 5, 6, 10b - hexahydrobenzo[f]quinolin-3-(2H)-one (6).

In a 100 mL round bottomed flask were placed a solution of 5 (3.45 g, 14.44 mmol), in dry CH_2Cl_2 (10 mL), and triethyl silane (16.8 g, 144.4 mmol). The system was cooled to 10° and trifluoroacetic acid (49.2 g, 0.43 mol) was added dropwise. The reaction mixture was stirred for 20 h at RT. The volatile components were removed *in vacuo* , the residue was dissolved in CH_2Cl_2,

washed with sat. $NaHCO_3$ solution, the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the product was recrystallized from acetone. The product yield was 2.32 g, (66.7%), mp. 175-177.5°. IR: (neat) ν = 3198, 3073, 2924, 1667, 1487, 1407. ^1H NMR: ($CDCl_3$) δ = 7.33- 7.12 (m, 4H), 5.84 (dddd, J= 18, 12, 10, and 7 Hz, 1H), 5.25 (br s, 1H), 5.08 (d, J= 12 Hz, 1H), 5.02 (d, J= 18 Hz), 3.65 (dd, J= 12.5 and 3 Hz, 1H), 3.03 (dd, J= 18.5 and 6 Hz, 1H), 2.92 (d, J= 18.5 Hz, 1H), 2.83 (t, J= 12.5 Hz, 1H), 2.77- 2.59 (m, 2H) 2.38, (d, J= 6 Hz, 1H), 2.13, (br s, 1H), 1.90 (dd, J= 12 and 6 Hz, 1H), 1.78- 1.71 (m, 1H). GC / MS: m/z: 241 (M+).

5-(3-Hydroxypropyl)-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-(2H)-one (7). In a dry 250 round bottomed flask was placed a saturated solution of **6** (2.32 g, 9.6 mmol) in THF, the system was cooled to 0° and a solution of disiamyl borane (made from 2-methyl-2-butene (3.5 g, 49.8 mmol) and 9.8M BMS (2,45 mL, 24.1 mmol) was added dropwise. After 1.5 h stirring at 0°, a 3N solution NaOH (8 mL) was added followed by immediate addition of 30% H_2O_2 (9.3 mL). After an additional hour stirring at this temperature the mixture was diluted with $CHCl_3$, the organic layer was washed with sat. NaCl solution, dried over Na_2SO_4 and the volatiles were removed *in vacuo* to yield a residue which was purified by flash chromatography using 5% MeOH / CH_2Cl_2 as eluent. The product yield was 2.3 g (92.2%). IR: (neat) ν = 1663. ^1H NMR: ($CDCl_3$) δ = 7.90 (br s, 1H), 7.40- 7.00 (m, 4H), 3.90 (m, 2H), 3.30- 2.50 (m, 7H), 2.30- 1.50 (m, 6H). GC/MS, (as the acetate derivative) m/z: 301 (M+), 242 (M- OAc+).

5-(3-p-toluensulfonyl propyl)-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-(2H)-one (8).

To a solution of **7** (1.14 g, 4.4 mmol) in dry pyridine (20 mL) was added freshly

crystallized tosyl chloride (1.68 g, 8.8 mmol), in small portions at 0°. The solution was stored at this temperature overnight. The solution was then diluted with chloroform, washed with cold 1.5 N HCl, water, sat. NaCl solution, the organic phase was dried over Na_2SO_4 and the volatiles were removed *in vacuo.* This product, 1.76 g (96.8%) was isolated by filtration and used in the next step without further purification. IR: (nujol mull) ν = 3355, 3201, 3063, 2926, 1662, 1358, 1189, 1176. ^1H NMR: ($CDCl_3$) δ = 7.70 (d, J= 8 Hz, 2H), 7.40 (d J=8 Hz, 2H) 7.35-7.00 (m, 4H), 6.80 (br. s, 1H), 4.00 (m, 2H), 3.50 (d, J=10 Hz, 1H), 3.00-2.50 (m, 6H), 2.40 (s, 3H), 2.00-1.40 (m, 6H).

2,3,6,7,7a,8,12b,12c-octahydro-1H, 5H-naphtho[1,2 3,i,j]quinolizin-3-one (9). To a solution of **8** (1.07 g, 2.59 mmol) in dry DMF (25 mL) was added, in small portions, sodium hydride (60% in oil, 0.16 g, 3.89 mmol) at 0°. The mixture was stirred at 0° for 4 h, methanol was added (0.5 mL) the solution was diluted with ethyl acetate (50 mL), washed with water, and sat. NaCl solution, the organic phase was separated, dried over Na_2SO_4, and the volatiles were removed in vacuo to yield 0.59 g (94.5 %) of a residue which, according to GC/MS analysis, comprised of a major (**9a**, 91.4 %) and a minor (**9b**, 3.05 %) component. These components were successfully separated by flash chromatography using 40 % ethyl acetate/pet. ether as eluent. **9a** IR: (neat) ν = 2943, 2927, 1626, 1471, 1455, 1446, 1407, 1260. ^1H NMR: (250 MHz, $CDCl_3$) δ = 7.28-7.17 (m, 4H), 4.60 (dd, J= 15 and 10 Hz, 1H), 3.23 (dd, J=15 and 10 Hz, 1H), 2.94 (dd J= 15 and 5 Hz, 1H), 2.69 (dd J= 15 and 10 Hz, 1H), 2.70-2.60 (m, 1H), 2.62 (dd J= 10 and 5 Hz, 1H), 2.57 (dd, J=10 and 5Hz, 1H), 2.52 (dd J=20 and 5 Hz, 1H), 2.46 (dd J= 15 and 10 Hz, 1H), 2.20-2.10 (m, 1H), 2.02- 1.94 (m, 1H), 1.87 (ddd J= 25, 10, and 5 Hz, 1H),1.67-1.72 (m, 1H), 1.61 (ddd, J= 20, 13 and 8 Hz, 1H), 1.49

(ddd J= 24, 13, and 8 Hz, 1H). GC/MS m/z: 241 (M+). **9b** IR: (neat) ν = 2943, 2927, 1626, 1471, 1455, 1446, 1407, 1260. ^{1}H NMR: (250 MHz, $CDCl_3$) δ = 7.35- 7.10 (m, 4H), 4.84 (br d J=13.5 Hz, 1H), 3.04 (dd J= 17.5 and 6 Hz, 1H), 2.97 (dd J= 20.5 and 10 Hz, 1H), 2.91 (dd J= 22 and 10.5 Hz, 1H), 2.75-2.53 (m, 4H), 2.52 (ddd J= 17.5, 13 and 2.5 Hz, 1H), 1.96 (br d J=13 Hz, 1H), 1.88-1.76 (m, 2H), 1.62 (dd J= 12 and 6 Hz, 1H), 1.5 (ddt J= 26, 13, and 3.5 Hz, 1H), 1.21 (ddd J= 24, 13, and 3.5 Hz, 1H). GC / MS m/z: 241 (M+).

2,3,6,7,7a,8,12b,12c-Octahydro-1H, 5H-naphtho[1,2,3,i,j]quinolizine (10).

To a solution of **9a** (0.32 g, 1.33 mmol) in dry THF (2.0 mL) was added $BF_3{\cdot}Et_2O$ (162.5 μL, 1.33 mmol) at 0°. The solution was then heated under reflux for 10 min. cooled to 0°, a 9.8M solution of BMS in DMS (100 μl., 0.98 mmol) was added dropwise and the solution was heated under reflux for 0.5 h. The solvent was removed in vacuo, and the residue was heated up to 120°. A solution of 6N HCl (223 μL, 0.415 mmol) was added and the system was heated under reflux for 1h. The solution was then cooled to 0°, neutralized by the addition of 6N NaOH (333 μL, 0,623 mmol). The aqueous phase was saturated with K_2CO_3, and the product was extracted with ethyl acetate (4x 20 mL). The organic layer was washed with sat. NaCl solution (2x15 mL) separated, and dried over Na_2SO_4. The solvents were removed *in vacuo* and the product was purified by flash chromatography (10 % MeOH / CH_2Cl_2) to yield 0.23 g (72 %) of **10a**, a compound that was found by its ^{1}H and ^{13}C NMR as well as its MS spectra, to be identical to the *trans* B/D, *cis* B/C ring fused product, reported by Schuster et al.[2] Similar treatment of **9b** gave **10b**, the all *trans* compound according to its spectral analysis.

Acknowledgments

We would like to express our gratitude to Dr A. Politou at the EMBL, Heidelberg, for the High Resolution NMR spectra. This work was supported by grants from the Special Committee for Research, University of Crete and the Greek Ministry of Industry and Research (91ED881).

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(Received in the UK 30 January 1995)