A Straightforward Synthetic Entry to the 4,9b-Propanopyrrolo[2,3-*c*]quinoline System by a New Reductive Cyclization of α′-(2-Nitrophenyl) Enones

Daniel Solé,* Silvina García-Rubio,[†] Lluís Vallverdú, and Josep Bonjoch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

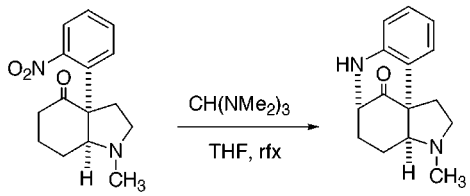
bonjoch@farmacia.far.ub.es

Received April 3, 2001

During the past decade, we have developed a strategy for the synthesis of *Strychnos* alkaloids in which the α-(2-nitrophenyl) ketone moiety is used as a latent form of the indoline nucleus of these alkaloids.[1−3] Interestingly, in the early stages of our studies, we accidentally discovered that, under certain conditions, the α-(2-nitrophenyl) ketone moiety could also be transformed in a tetrahydroquinoline framework.[4,5] Thus, when ketone **1** was treated with $CH(NMe_2)_3$, the bridged tetrahydroquinoline **2** was obtained in good yield (Scheme 1). This unprecedented cyclization implies the reduction of the nitro group and the intramolecular nucleophilic attack of the enolate on a transient intermediate.[4b]

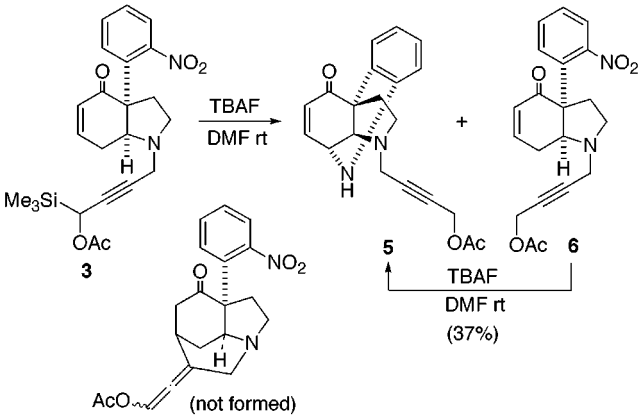
Recently, in the context of the total synthesis of (−)-strychnine,[1b] we prepared several 3a-(2-nitrophenyl)-hexahydroindolones (i.e., **3** and **4**) from which different methodologies for the closure of the piperidine ring were explored. When hexahydroindolone **3** was treated with TBAF (0.4 equiv) in DMF−HMPA,[6] in an attempt to promote the intramolecular conjugate addition of the propargylic silane to the enone,[7] none of the expected cyclization compound was formed, and instead the bridged tetrahydroquinoline **5** and hexahydroindolone **6** were isolated, albeit in low yield (Scheme 2). The latter is the product of direct protodesilylation of **3**, while compound **5** has not only undergone a protodesilylation reaction but also reduction of the nitro group with simultaneous formation of a bond between the γ position of the enone system and the nitrogen.

Scheme 1

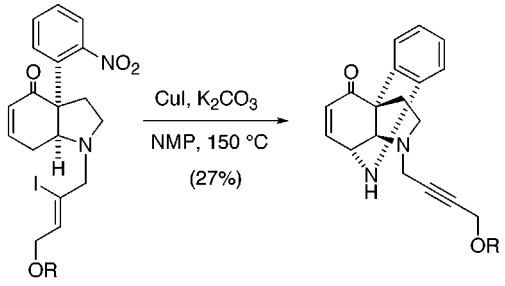


1 **2**

Scheme 2



Scheme 3



4 (R = TBDMS) **7** (R = TBDMS)

Treatment of hexahydroindolone **6** with TBAF (1 equiv), under the same reaction conditions, afforded **5** in 37% yield. This result confirmed that the protodesilylation reaction was independent of the reduction of the nitro group/nitrogen−carbon bond-forming process. The structure of **5** was unambiguously established from its ^1H and ^{13}C NMR data, with the aid of 2D-NMR experiments and NOESY.

On the other hand, in the context of our studies on the intramolecular coupling of vinyl iodides with enones,[1] when hexahydroindolone **4** was heated in *N*-methylpyrrolidinone in the presence of CuI and K_2CO_3,[8] the tetracyclic compound **7** was obtained (Scheme 3) as the only isolable compound (27%). Under the reaction conditions, which also caused the β-elimination of the vinyl iodide, the reduction of the nitro group and the formation of a C−N bond at the γ-position of the enone had taken

[†] Present address: Albany Molecular Research. P.O. Box 11170, Syracuse, NY 13218.

(1) (a) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230−7240. (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655−665.

(2) For a recent procedure for the 2-nitroarylation of ketones, see: Iwama, T., Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673−676.

(3) For the use of 2-nitrophenyl derivatives as precursors of the indoline nucleus in alkaloid synthesis, see inter alia: (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641−2643. (b) Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798−811. (c) Mittendorf, J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 4049−4062. (d) Padwa, A.; Harring, S. R.; Semones, M. A. *J. Org. Chem.* **1998**, *63*, 44−54. (e) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524. (f) Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315−1317.

(4) (a) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 2064−2065. (b) Solé, D.; Parés, A.; Bonjoch, J. *Tetrahedron* **1994**, *50*, 9769−9774.

(5) For the synthesis of tetrahydroquinolines from β-(2-nitrophenyl) ketones, see: Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, S. V. *J. Org. Chem.* **2001**, *66*, 2822−2827

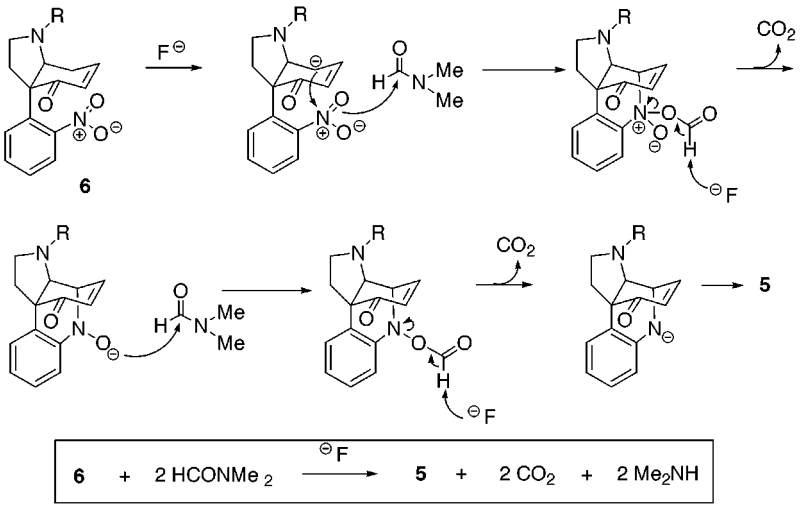
(6) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. *J. Org. Chem.* **1991**, *56*, 3958−3973.

(7) (a) Schinzer, D. *Synthesis* **1988**, 263−273. (b) Schinzer, D. *Stereoselective Synthesis*; Thieme: Stuttgart, 1996; Houben-Weyl, E 21 Vol. 4, D 1.5.2.3, pp 2087−2103.

(8) Iyer, S.; Ramesh, C.; Sarkar, A.; Wadgaonkar, P. P. *Tetrahedron Lett.* **1997**, *38*, 8113−8116.

10.1021/jo015659h CCC: $20.00
Published on Web 06/22/2001

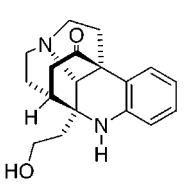
Scheme 4

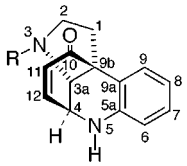


place once again. The structural assignment of **7** was performed by comparison of its spectroscopic data with those of tetrahydroquinoline **5**.

The reductive cyclization of α-(2-nitrophenyl) enones with TBAF−DMF may be tentatively explained by considering a mechanism closely related to that proposed for the transformation of nitro ketone **1** into tetrahydroquinoline **2** by treatment with tris(dimethylamino)-methane.[4b] Thus, the intramolecular nucleophilic attack of the enolate[9,10] on the nitro group would be the first step of the reaction.[11] Formylation of the transient intermediate would shift this otherwise unfavorable reaction. Subsequent reduction with evolution of carbon dioxide would afford a hydroxylamine intermediate from which a further reduction again involving formylation and evolution of carbon dioxide would give the cyclization compound (Scheme 4).[12,13] With respect to the reductive cyclization promoted by CuI, although a similar sequence of reactions, but with Cu^+ as the reducing agent, could work the alternative mechanism involving the previous reduction of the nitro to a nitroso compound and the subsequent nucleophilic attack of the enolate on the latter could be postulated.[14]

Although these reactions have not been fully tested, they will receive further attention because they allow a synthetic entry to the 4,9b-propanopyrrolo[2,3-*c*]quinolinone framework present in the unusual alkaloid strychnochromine.[15]


strychnochromine


5, R : CH_2-C≡C-CH_2OAc

7, R : CH_2-C≡C-CH_2OTBDMS

Interestingly, the above reductive cyclizations are not restricted to enones. Thus, 3a-(2-nitrophenyl)octahydroindol-4-one **1**[16] underwent the reductive cyclization upon treatment with TBAF (1 equiv) in DMF−HMPA to provide the tetrahydroquinolinone **2** in 25% yield, although higher temperatures were required.[17] On the other hand, treatment of α-(2-nitrophenyl) ketone **1** with CuI (1 equiv) and K_2CO_3 (3 equiv) in *N*-methylpyrrolidinone at 150 °C for 4 h also afforded tetrahydroquinolinone **2** in 22% yield.

In conclusion, these unexpected carbon−nitrogen bond-forming processes from (2-nitrophenyl) derivatives provide access to a class of valuable compounds otherwise difficult to obtain and amenable to further elaboration.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were recorded on a Nicolet 205 FT infrared spectrophotometer, and only noteworthy absorptions are listed. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light, iodoplatinate reagent, or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230−400 mesh ASTM). Drying of organic extracts during workup of reactions was performed

(9) The basicity of aprotic solvent solutions of tetraalkylammonium fluorides has been reported to be between that of trialkylamines and alkoxides. For a review about the use of fluoride ion as a base in organic synthesis, see: Clark, J. H. *Chem. Rev.* **1980**, *80*, 429−452.

(10) Intramolecular γ-alkylations of extended dienolates are well-known; see: Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Dekker: New York, 1979; Vol. 1, Chapter 2, pp 85−315.

(11) In fact, it is suspected that the interaction between ketone enolates and the nitro group is responsable for the unusual low yields obtained in reactions (e.g., methoxycarbonylation) involving the enolates of α-(2-nitrophenyl) ketones. See ref 1.

(12) For reduction of formyloxyazacompounds in the presence of a weak base, see: Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1985**, 1517−1520.

(13) Alternatively, before the enolate attack the first reduction could occur in the intermediate arising from the formylation of the nitro group by intramolecular transfer of hydride from the formyl group to the positively charged nitrogen atom. For the intermolecular reduction of nitroaromatic compounds with formate salts, see: Babler, J. H.; Sarussi, S. J. *Synth. Commun.* **1981**, *11*, 925−930. We acknowledge a reviewer's suggestions concerning this question.

(14) Generally, nitroso compounds, which are often postulated as intermediates in the reduction of aromatic nitro compounds, are too reactive to be isolated. However, their formation has been confirmed in some reactions, see: Kim, B. H.; Kim, T. K.; Cheong, J. W.; Lee, S. W.; Jun, Y. M.; Baik, W.; Lee, B. M. *Heterocycles* **1999**, *51*, 1921−1928.

(15) Quetin-Leclercq, J.; Angenot, L.; Dupont, L.; Dideberg, O.; Warin, R.; Delaude, C.; Coune, C. *Tetrahedron Lett.* **1991**, *34*, 4295−4298.

(16) Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013−4028.

(17) No cyclization was observed at room temperature and the starting ketone **1** was recovered even after long reaction times (24 h).

over anhydrous Na_2SO_4. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

***cis*-1-(4-Acetoxy-2-butynyl)-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (6).** To a solution of *cis*-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one·hydrochloride[1a] (0.2 g, 0.68 mmol) in 2-butanone (10 mL) were added 4-acetoxy-2-butynyl iodide (0.24 g, 1 mmol) and anhydrous K_2CO_3 (0.14 g, 1 mmol). The mixture was heated at reflux for 5 h. The solvent was removed in vacuo, and the residue was partitioned between H_2O and CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (from hexane to 1:1 hexanes−EtOAc) to give enone **6** (0.11 g, 43%). ^{1}H NMR (300 MHz): 2.08 (s, 3H, CH_3), 2.47 (dddd, J = 19.3, 5.3, 2.6, 1.5 Hz, 1H, H-7), 2.48 (d, J = 5.8 Hz, 1H, NCH_2), 2.51 (d, J = 5.8 Hz, 1H, NCH_2), 2.79 (ddt, J = 19.3, 5.9, 3 Hz, 1H, H-7), 3.02−3.12 (m, 2H, H-3), 3.52 (m, 2H, H-2), 3.58 (ddd, J = 5.9, 2.6, 1.1 Hz, 1H, H-7a), 4.59 (s, 2H, CH_2O), 6.19 (ddd, J = 10.2, 3, 1.5 Hz, 1H, H-5), 6.84 (dddd, J = 10.2, 5.3, 3, 1.1 Hz, 1H, H-6), 7.41 (ddd, J = 8, 7, 1.4 Hz, 1H, H-4′), 7.50 (dd, J = 8, 1.4 Hz, 1H, H-6′), 7.58 (ddd, J = 8, 7, 1.4 Hz, 1H, H-5′), 7.78 (dd, J = 8, 1.4 Hz, 1H, H-3′). ^{13}C NMR (75 MHz): 20.7 (CH_3), 27.1 (C-7), 36.3 (C-3), 40.2 (CH_2N), 50.0 (C-2), 52.1 (CH_2O), 58.8 (C-3a), 65.6 (C-7a), 79.2 and 81.2 (C≡C), 125.2 (C-3′), 127.8 (C-4′), 128.2 (C6′), 130.1 (C-5′), 132.6 (C-5), 136.6 (C-1′), 146.1 (C-6), 149.1 (C-2′), 170.1 (COO), 197.0 (C-4). IR (film): 1742, 1671, 1527, 1359 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.4): C, 65.21; H, 5.47; N, 7.60. Found: C, 64.90; H, 5.57; N, 7.50.

(3a*RS*,4*RS*,9b*RS*)-3-(4-Acetoxy-2-butynyl)-2,3,3a,4,5,9b-hexahydro-1*H*-4,9b-[2]propenopyrrolo[2,3-*c*]quinolin-10-one (5). Molecular sieves 4 Å (200 mg) were placed in a two-necked flask (25 mL) that was flame-dried in vacuo for 5 min. The flask was purged with argon, and a solution of dry TBAF[18] (45 mg, 0.18 mmol) in DMF (2 mL) and HMPA (0.22 mL, 1.27 mmol) were added. The mixture was stirred at room temperature for 10 min. A solution of nitro ketone **6** (75 mg, 0.2 mmol) in DMF (2 mL) was added dropwise, and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated to give a residue that was purified by chromatography (from CH_2Cl_2 to CH_2Cl_2−MeOH 97:3) to give enone **5** (25 mg, 37%). ^{1}H NMR (500 MHz): 1.72 (m, 1H, H-1), 2.08 (s, 3H, CH_3), 2.89 (m, 1H, H-2), 3.10 (m, 1H, H-3a), 3.14−3.25 (m, 2H, H-1 and H-2), 3.49 (dd, J = 4.6, 2 Hz, 2H, NCH_2), 4.15 (dd, J = 5.6, 2.6 Hz, 1H, H-4), 4.56 (br, 1H, NH), 4.66 (m, 2H, CH_2O), 6.15 (d, J = 9.8 Hz, 1H, H-11), 6.60 (ddd, J = 9.8, 5.6, 2.1 Hz, 1H, H-12), 6.64 (dd, J = 8.1, 1 Hz, 1H, H-6), 6.79 (td, J = 7.5, 1 Hz, 1H, H-8), 7.06 (dd, J = 7.5, 1.5 Hz, 1H, H-9), 7.11 (ddd, J = 8.1, 7.5, 1.5 Hz, 1H, H-7). ^{13}C NMR (75 MHz): 20.7 (CH_3), 27.2 (C-1), 40.4 (CH_2N), 46.1 (C-4), 50.8 (C-2), 52.2 (CH_2O), 55.1 (C-9b), 65.2 (C-3a), 79.3 and 81.0 (C≡C), 115.3 (C-6), 119.3 (C-8), 119.7 (C-9a), 127.5 (C-9), 128.7 (C-7), 129.1 (C-11), 139.5 (C-12), 140.4 (C-5a), 170.2 (COO), 195.3 (C-10). IR (film): 3375, 1744, 1672 cm^{-1}. HRMS: calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1464.

(3a*RS*,4*RS*,9b*RS*)-3-[4-(*tert*-Butyldimethylsilyl)oxy-2-butynyl]-2,3,3a,4,5,9b-hexahydro-1*H*-4,9b-[2]propenopyrrolo-[2,3-*c*]quinolin-10-one (7). A solution of nitro ketone **4**[1b] (80 mg, 0.14 mmol), K_2CO_3 (40 mg, 0.28 mmol), and CuI (28 mg, 0.14 mmol) in *N*-methylpyrrolidinone (6 mL) was heated at 150 °C for 4 h. After cooling, the mixture was poured into brine and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated to give a residue that was purified by chromatography (from CH_2Cl_2 to CH_2Cl_2−MeOH 97:3) to give enone **7** (16 mg, 27%). ^{1}H NMR (200 MHz): 0.08 (s, 6H, $SiMe_2$), 0.88 (s, 9H, CMe_3), 1.69 (m, 1H, H-1), 2.89 (m, 1H, H-2), 3.02−3.25 (m, 3H, H-1, H-2, and H-3a), 3.45 (m, 2H, NCH_2), 4.12 (br, 1H, H-4), 4.29 (m, 2H, CH_2O), 4.50 (br, 1H, NH), 6.16 (d, J = 9.5 Hz, 1H, H-11), 6.50−6.65 (m, 2H, H-6 and H-12), 6.77 (td, J = 7.5, 1 Hz, 1H, H-8), 6.98−7.15 (m, H-7 and H-9). ^{13}C NMR (75 MHz): −5.2 ($SiCH_3$), 18.2 (CSi), 25.8 (CH_3), 27.3 (C-1), 40.3 (CH_2N), 46.2 (C-4), 50.7 (C-2), 51.7 (CH_2O), 55.0 (C-9b), 65.0 (C-3a), 79.0 and 84.0 (C≡C), 115.3 (C-6), 119.3 (C-8), 120.0 (C-9a), 127.5 (C-9), 128.7 (C-7), 129.1 (C-11), 139.5 (C-12), 140.5 (C-5a), 195.5 (C-10). HRMS: calcd for $C_{24}H_{32}N_2O_2Si$ 408.2233, found 408.2227.

Methanopyrrolo[2,3-*e*][1]benzazocine 2.[4b] **Method A.** Operating as in the preparation of **5**, starting from **1** and heating the reaction mixture at 60 °C for 7 h, ketone **2** (25%) was obtained after chromatography (from CH_2Cl_2 to CH_2Cl_2−MeOH 96:4).

Method B. Operating as in the preparation of **7**, starting from **1**, ketone **2** (22%) was obtained after chromatography.

Acknowledgment. This work was supported by the DGES, Spain (project PB97-0877). Thanks are also due to the DURSI, Catalonia, for Grant S.G.R.99-0078 and a fellowship to L.V.

JO015659H

(18) Dry TBAF was prepared by evaporating a solution of TBAF·$3H_2O$ in benzene three times and heating the residue in vacuo at 50 °C for 36 h.