Synthesis of Cularine and Sarcocapnine *via* Enium Ions and a New, Highly Diastereoselective Reductive Methylation

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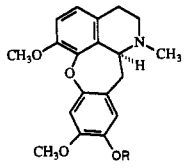
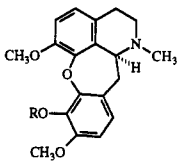
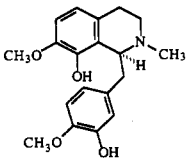
The cularines are isoquinoline alkaloids which contain a dihydrooxepine ring system[1] and occur mainly in the Fumaraceae family.[2a] Some members are muscle relaxants.[2b] A number of syntheses of (+)-cularine (**1a**)[3] and of the isomeric (+)-sarcocapnine[2,4] have appeared. (+)-Sarcocapnidine (**2b**) and *O*-demethyl-**1** (**1b**) were obtained in very low yield by the K_3-$Fe(CN)_6$ oxidation of crassifoline (**3**).[2,4d,f] We now report a new



1 (a: R = CH_3 b: R = H)



2 (a: R = CH_3 b: R = H)



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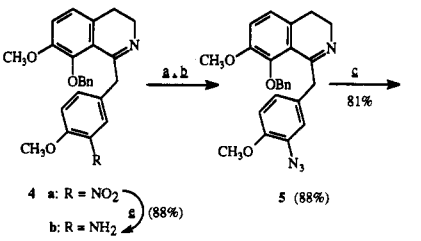
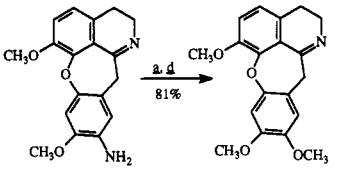
and better route to these alkaloids using arylnitrenium or -oxenium ions, and a new diastereoselective reductive methylation of the imine precursors which yields very high enantiomeric excesses of the desired alkaloids.

The starting materials were appropriately substituted 1-benzyl-8-(benzyloxy)-7-methoxy-3,4-dihydroisoquinolines (**4**), whose preparation by a novel method is described elsewhere.[5]. The nitro derivatiave (**4a**) was converted to the azide (**5**) *via* the amine (**4b**), and the arylnitrenium ion was generated at the same time that the benzyl group was removed[6] using CF_3SO_3H in CCl_4 at −5 °C[7] to give the intramolecular trapping product (**6**)[8a] para to the nitrenium ion, having the desired dihydrooxepine structure.[9]



4 a: R = NO_2 b: R = NH_2 (88%)

5 (88%)



6 7

a: $NaNO_2/H_2SO_4$/0°C. b: NaN_3 c: CF_3SO_3H, CCl_4, -5°C.
d: (i) H_2O ⟶ 60°C, 2h; (ii) CH_2N_2 e: $NaHSO_3$/EtOH/80°, 1h

The presence of the primary arylamine function opens up the possibility of preparing a wide variety of substituted derivatives *via* diazonium ion chemistry. Thus, **6** was converted to the corresponding phenol, which was methylated (CH_2N_2) to give (±)-didehydronorcularine **7**[10] [the spectral data were similar to those for **6** except for the bands corresponding to the NH_2 group and the presence of an additional OCH_3 group: ^1H, δ 3.89; ^{13}C, δ 58.6; *m/z* 325 ($M^{\bullet+}$, 35.9), 310 (100), 294 (69.7)]. Arylnitrenium ions have previously been used to prepare seven-membered rings,[11] but this is the first example of oxepine formation by this route. The yield of the cularine-type ring system so produced is appreciably higher than has been reported for other ring-closure methodologies.

A shorter, more convenient and novel approach involves using **4c** (R = OCH_3)[5] as the starting material and converting it to the corresponding aryloxenium ion, a species known to lead to inter-[12] and intramolecular[8b,13,14] C–O–C bond formation. Oxidation of phenols by hypervalent iodine compounds has been reported recently.[8b,14,15] As far as we can tell, intramolecular arylations have involved only C–C bond formation, and these in low yields. The present report emphasizes C–O–C bond formation in which electrophilic aromatic substitution by the oxenium ion takes place.

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(4) (a) Kametani, T.; Fukumoto, K. *J. Chem. Soc.* **1963**, 4289. (b) Noguchi, I.; McLean, D. B. *Can. J. Chem.* **1975**, *53*, 15. (c) Kametani, T.; Fukumoto, K.; Shibuya, S.; Nakano, T. *Chem. Pharm. Bull.* **1963**, *11*, 1299. (d) Kametani, R.; Fukumoto, K.; Fujihara, M. *J. Chem. Soc., Chem. Commun.* **1971**, 352. (e) de Lera, A. R.; Saá, J. M.; Suau, R.; Castedo, L. *J. Heterocycl. Chem.* **1987**, *24*, 613. (f) Boente, J. M.; Castedo, L.; Cuadros, L.; de Lera, A. R.; Saá, J. M.; Suau, R.; Vidal, M. C. *Tetrahedron Lett.* **1983**, *24*, 2303. (g) Jackson, A. H.; Stewart, G. W.; Charnock, G. A.; Martin, J. A. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1911.

(5) *Via* aza-Wittig reactions between the appropriate β-phenethyliminophosphorane and arylketene to give the ketenimine, which cyclizes: Rodrigues, J. A. R.; Carrasco, G. L.; de Sousa, J. D. F. Paper submitted.

(6) Abramovitch, R. A.; Chinnasamy, P.; Evertz, K.; Huttner, G. *J. Chem. Soc., Chem. Commun.* **1989**, 3.

(7) The yields of cyclization products were found to increase dramatically as the temperature was decreased from 25 °C (28%) to −5 °C (81%) under otherwise constant experimental conditions. If this effect is general, it will represent a great improvement in such arylnitrenium ion cyclizations.

(8) (a) Abramovitch, R. A.; Rodrigues, J. A. R.; Trombetta, T. R. Unpublished results on the intramolecular trapping of phenolic OH by arylnitrenium ions (1986). (b) See also: Tamura, Y.; Yakura, T.; Haruta, J.; Kita Y. *J. Org. Chem* **1987**, *52*, 3927.

(9) **6**: IR (KBr) 3555–3450 (NH_2), 1625 cm^{-1} (C=N); NMR ($CDCl_3$) ^1H, 2.37 (t, 2H), 2.54 (t, 2H) 3.05 (s, 2H), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.78 (s, 2H, NH_2), 6.50 (s, 1H), 6.76 (d, 1H, *J* = 8.6 Hz), 6.80 (s, 1H), 6.82 (d, 1H, *J* = 8.6 Hz); ^{13}C, 22.8, 40.2, 45.7, 58.1, 60.1 , 118.1, 118.9, 119.5, 123.1, 129.8, 132.1, 132.4, 148.1, 149.8, 150.1, 151.8, 152.3; MS *m/z* 310 ($M^{\bullet+}$, 19.9), 295 (100), 279 (49.3), 159 (15.8). Correct microanalytical combustion data were obtaind for all new compounds reported here.

(10) Like cularine, compounds, **6**, **7**, **10**, and **11** are folded about the O···CH_2 axis and are therefore axially chiral.

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(14) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993** 1891. The mechanism of this reaction has not been established.

(15) (a) Kosar, G. F.; Wettach, R. H. *J. Org. Chem.* **1977**, *42*, 1476. (b) Szántay, C.; Blaskó, G.; Bárczai-Beke, M.; Péchy, P.; Dörnyer, G. *Tetrahedron Lett.* **1980**, 3509. (c) White, J. D.; Carovatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi. A. *Tetrahedron* **1983**, *39*, 2393. (d) Vanderlaan, D. G.; Schwartz, M. A. *J. Org. Chem.* **1985**, *50*, 743. (e) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300. (f) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990** 431. (g) Kita, Y.; Yakura, T.; Tolma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119. (h) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

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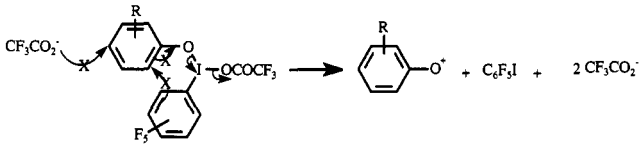
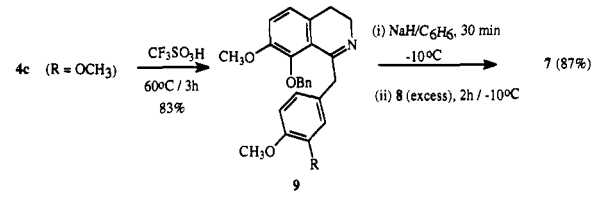
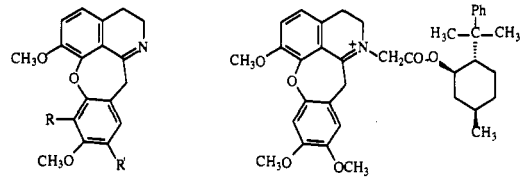
To generate a free aryloxenium ion from Ar–OX$^+$ it is necessary that X be a very good leaving group. Also, any counterion present should be a very weak nucleophile if it is not to intercept the very reactive ArO$^+$. To that end, we choose to use $C_6F_5I(OCOCF_3)_2$ (**8**):[16] not only is the $C_6F_5I^+(OCOCF_3)$ group a good leaving group and $CF_3CO_2^-$ a poor nucleophile, but also C_6F_5 is not likely to undergo intramolecular C–C bond formation:

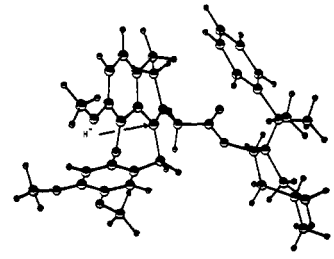


While it has occasionally been used as an oxidizing agent, no reports of its use in the oxidation of phenols were found. In the event, **4c** was debenzylated and the phenol treated with NaH followed by **8** at –10 °C to give (±)-**7** (87%) (this and the examples below appear to be the highest yields reported for intramolecular cyclizations of phenols using hypervalent iodine compounds). A similar reaction with **4d** (R = OBn) gave **9b** (R = OH) (89%), mp 127–128 °C (quite stable; cf. ref 17 concerning the instability of an isomer of **9b**), which was converted to a mixture of **10** (36%) and **11** (58%) (isolated yields).[18] The somewhat preferred attack ortho to the phenolic group over that para to it is noteworthy.[19]

(±)-**7** was *N*-methylated with CH_3I and the methiodide reduced ($NaBH_4$) to give (±)-cularine (89%), mp 113–114 °C.[19] The optically active compound was prepared by treating (±)-**7** with a chiral auxiliary, (+)-8-phenylmenthyl chloroacetate, in methanol, with stirring at room temperature for 10 h, followed by the slow additon of $NaBH_4$ and stirring for 4 h, to give (+)-cularine (**1a**) (94%), mp 114–115 °C, $[\alpha]^{25}_D$ 284.3° (*c* 0.8, MeOH) [lit.[20] $[\alpha]^{25}_D$ 285° (*c* 0.8, MeOH)], corresponding to an ee >99% (based on optical rotation values). (±)-Phenol **10** could be reductively *N*-methylated similarly to yield (+)-*O*-demethylcularine (**1b**) (95%), mp 127–128 °C (lit.[4g] mp 126–127 °C), $[\alpha]^{25}_D$ 323.5°, which, on methylation, gave **1a** (98%), $[\alpha]^{25}_D$ 283.8° (*c* 0.8, MeOH). Finally, (±)-**11** was converted to (+)-sarcocapnidine (**2b**) (93%), mp 125–126 °C, $[\alpha]^{25}_D$ 384° (*c*, 0.0696 MeOH) (lit.[4f] 126–127 °C; 385.4°), ee >99%,[19] which was *O*-methylated to (+)-sarcocapnine (**2a**) (97%); hydrochoride mp 212–213 °C, $[\alpha]^{25}_D$ 217° (*c* 0.3, EtOH) (lit.[21] 213–215 °C; 218°), ee >99%.[19] The high yield of (+) products, starting from racemic imine,[10]







12b

requires a highly diastereoselective reduction and prior or subsequent kinetic resolution, followed by an unprecedented facile hydrolysis and decarboxylation.[22] Clearly the (+)-8-phenylmenthyl group must shield one side of the dihydroisoquinoline much more efficiently than the other. Molecular modeling of **12a**[23] suggests that the heat of formation of the minimum energy conformer shielding the convex side (which results in hydride approach to give the desired *S* configuration) is 3 kcal/mol lower than that of the one shielding the concave side. A ball and stick model is shown in **12b**.

The methodology described here should have applicability to many other systems, some of which we are currently studying.

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(18) Separated by thick layer chromatography on silica gel.
(19) This could be owing to the slightly different steric effects of OH and OCH_3, to a change in which OH group is oxidized in **9d**, or to other factors not presently understood. All the compounds so formed had the expected IR, NMR, and mass spectra and gave correct microanalytical values.
(20) Bhacca, N. S.; Cymerman Craig, J.; Manske, R. H. F.; Roy, S. K.; Shamma, M.; Slusarchyck, W. A. *Tetrahedron* **1966**, *22*, 1467.
(21) Campello, M. J.; Castedo, L.; Saá, J. M.; Suau, R.; Vidal, M. C. *Tetrahedron Lett.* **1982**, *23*, 239.
(22) The mechanism of this reaction is being studied. Since HCl is liberated in the first step, it may be possible that protonation of the tetrahydroisoquinoline nitrogen takes place, which may facilitate decarboxylation. We are in the process of isolating the phenylmenthyl byproduct and will report the results in the full paper.
(23) Using PC Model from Serena Software and the MMX force field derived from MM2 (QCPE-395, 1977) of N. L. Allinger, with the π-VESCF routines from MMPI (QCPE-318), also by N. L. Allinger, as modified by J. McKelvey and J. J. Gajewski.