Aryl Radical Additions to Enamides. Construction of the Hydroapoerysopine Ring System via a 7-Endo Cyclization Process

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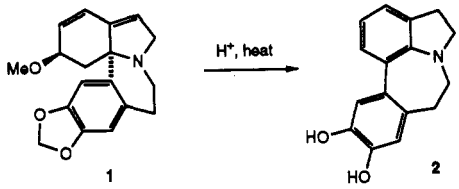
The *Erythrina* alkaloids are a widely distributed family of structurally interesting and biologically active natural products.[1] An early observation that proved to be crucial to establishing the spiro-amine nature of the erythrinane skeleton was the acid-mediated rearrangement of erythraline (1) to apoerysopine (2).[2] We wish to report a facile entry into the apoerysopine-type ring system based on a relatively rare 7-endo radical cyclization process.



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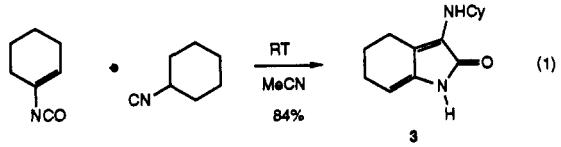
Numerous synthetic approaches into the erythrina ring system have been developed and a prominent theme for elaborating the fully substituted carbon center at the BC ring fusion has been trapping of *N*-acyliminium ion intermediates with electron-rich aryl rings.[3] Several syntheses of the apoerysopine ring system have also been reported.[4] Recently, we disclosed an efficient entry into highly functionalized hydroxindole intermediates based on a novel [1 + 4] cyclization of vinyl isocyanates with alkyl isocyanides.[5] Thus a model for the AB ring substructure of both the erythrina alkaloids and the derived apoerysopine system can be readily fashioned employing this technology (eq 1).



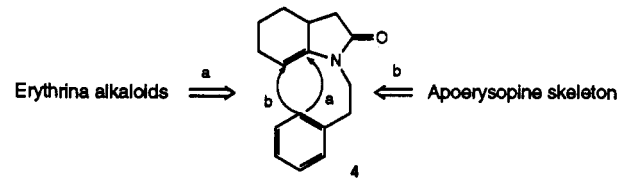
3 (1)

Cy = cyclohexyl

It was envisioned that the enamide function in compound 3 could be useful for facilitating bond construction at several locations in the molecule. From the N-alkylated species 4, for example, selective access to either ring type via a common intermediate could, in principle, be achieved by appropriate selection of cyclization conditions (Scheme I).

Several reports have demonstrated that intramolecular Heck-type reactions on enamide functions somewhat

Scheme I



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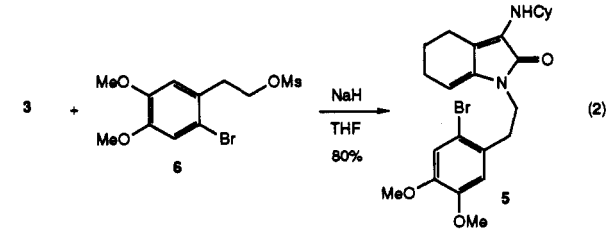
related to the one in intermediate 4 give primarily spirocyclic products.[6] To test the viability of this pathway as an entry into the erythrinane ring system, compound 5 was prepared in straightforward fashion (eq 2). Selective



(2)

formation of the endocyclic enamide anion of 3 with sodium hydride followed by addition of the readily available bromo mesylate 6[7] delivered the key N-alkylated lactam 5 in 80% yield. Numerous palladium-mediated cyclization conditions were examined to effect the requisite spirocyclization, but without success. There was no evidence for the presence of the desired spirocyclic material and in most instances complex mixtures of products were obtained from these reactions.[8]

Attention then turned to the corresponding radical cyclization process. Once again considerable precedent in related systems pointed to spiro-ring formation as a predominant reaction pathway, at least when a 5-exo cyclization was available. A number of investigators have demonstrated that spirocyclic oxindole products prevail in many intramolecular additions of aryl radicals to enamides.[9] However, the bridgehead center in 5 is more sterically encumbered than in these examples and, in light of the decelerating influence that strategically placed substituents can have on the exo cyclization mode,[10] bond formation via the more accessible 7-endo pathway may be preferred in compound 5.

Treatment of 5 with tri-*n*-butyltin hydride and AIBN in refluxing benzene afforded only the hydroapoerysopine derivative 7 in 65% yield based on recovered starting material. None of the corresponding product derived from

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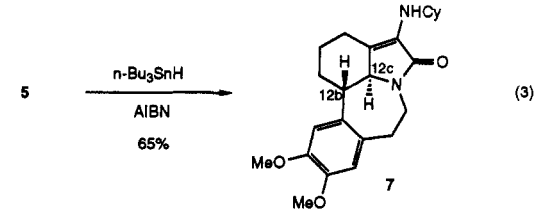
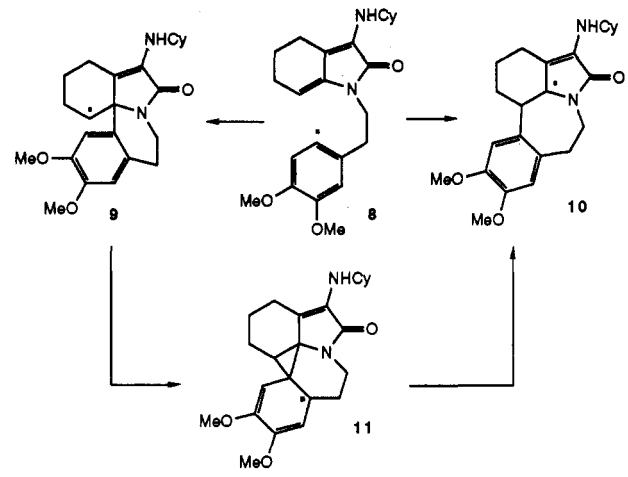


a 6-exo pathway was detected. The structural assignment for **7** rests on several points. DEPT experiments revealed the presence of five methine carbons, two of which were situated in the aromatic region of the spectrum. This observation is consistent only with structure **7** since the alternative formulation derived from a 6-exo cyclication would exhibit one nonaromatic methine carbon. Additionally, no aliphatic quaternary carbon signals were evident in the ^{13}C NMR spectrum of this compound. The appearance of a doublet centered at δ 3.36 (assigned to H_{12c}), which is typical of a proton attached to a carbon substituted with a heteroatom, was again inconsistent with the erythrinane structure. Irradiation of this signal caused a broad ddd centered at δ 2.60 to become a broad doublet. This signal was attributed to the benzylic proton at C-12b. Assignment of a trans-ring fusion derives from the H_{12b}–H_{12c} coupling constant of 10.2 Hz, which correlates well with the value expected from the Karplus equation for a trans relationship.[11a] Furthermore, this coupling constant is consistent with the corresponding trans-ring fusion in the closely related lycorane alkaloids in which the relevant coupling constants range between 10 and 12 Hz.[11b-d] The related cis-fused species exhibit coupling constants of 4–7 Hz.[11b]

The outcome of this cyclization reaction is noteworthy in several respects. Although there exists a marked proclivity for the exo mode of closure for 5-hexenyl and 6-heptenyl radicals, this inclination can be altered by the presence of steric congestion at the normally favored bond-forming site.[10] Furthermore, appropriately positioned activating groups have been reported to accelerate the endo pathway in several instances.[12] The relatively efficient production of a seven-membered ring in this cyclization is also of interest in that the rate constant measured for 7-endo closure in the simple heptenyl radical is near the lower limit for synthetic utility ($k_{7\text{-endo}} \sim 7 \times 10^2$ s^{-1}) and as a consequence, seven-membered ring formation via radical cyclization is relative rare.[13,14] Scheme II depicts the possible events occurring during this cyclization process. Bromine atom abstraction from **5** affords the aryl radical **8**, which could undergo either 6-exo cyclization to give **9** or 7-endo addition to provide **10**. It seems unlikely that the secondary radical **9** is involved to any significant degree since rapid trapping would be anticipated under the reaction conditions employed. On the other hand, the 7-endo pathway would afford the highly stabilized radical **10**.[15,16] An alternative pathway would involve initial 6-exo addition to afford radical **9** followed by an aryl group migration via intermediate **11** to afford radical **10**.[17] This rationale, while it cannot be excluded, seems unlikely at the concentrations employed in these reactions, since the rate constant of a typical neophyl radical rearrangement at 25 °C is 9×10^2 s^{-1} [18a] while hydrogen transfer from *n*-Bu_3SnH to cyclohexyl radicals is 1.8×10^6 M^{-1} s^{-1} at the same temperature.[18b]

Scheme II



The unusual stereochemical course of this transformation also deserves comment. In most related radical cyclization processes, the stereochemistry of hydrogen transfer is under steric approach control wherein trapping of the postcyclization radical occurs from the face opposite to the newly formed carbon–carbon bond.[9b,c,19,20] This normally provides a cis-ring fused product. In contrast, radical **10** may be sufficiently persistent[15] that the initial cyclization conformer can relax to a more stable arrangement (aryl substituent in an equatorial orientation) faster than hydrogen transfer. Trapping of this nearly planar radical intermediate could then occur from an axial direction to afford the observed trans-ring fusion.[21]

The clean stereochemical course of this transformation, if general in nature, is a significant feature that will emerge as an important factor for planning future synthetic

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applications for this chemistry. Additional investigations are currently underway to exploit radical additions to related enamide species for the construction of other alkaloid systems.

Experimental Section[22]

3-(Cyclohexylamino)-5,6-dihydro-2-oxo-4*H*-indole (3). To a solution of 1-cyclohexenecarboxylic acid[23] (10.0 g, 80.0 mmol) in toluene (35 mL) at rt was added triethylamine (8.0 g, 80.0 mmol) followed, after 20 min, by the addition of diphenyl phosphorazidate (DPPA) (21.7 g, 80.0 mmol) over a period of 20 min. After an additional 30 min, the solution was passed through a plug of silica gel to give, after solvent evaporation under reduced pressure, the acyl azide (10.0 g, 67.0 mmol). This material was immediately dissolved in acetonitrile (50 mL) and heated at reflux for 30–40 min affording the corresponding isocyanate, which after cooling to rt, was treated with freshly prepared cyclohexyl isocyanide[24] (7.3 g, 67.0 mmol). The resulting solution was allowed to stir at rt for 15 h. At this time, the precipitate that formed was filtered (suction) and recrystallized from acetonitrile to afford product (11.9 g, 84%): mp 145–146 °C (CH_3CN); IR (KBr) ν 3372, 3182, 2940, 1685, 1665, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09–1.33 (m, 5H), 1.61 (m, 1H), 1.72–1.81 (m, 4H), 1.95 (m, 2H), 2.24 (q, J = 5.4 Hz, 2H), 2.60 (dd, J = 6.0, 6.0 Hz, 2H), 3.29 (m, 1H), 3.94 (d, J = 9.3 Hz, 1H, exchangeable) 5.32 (t, J = 4.5 Hz, 1H), 7.73 (s, 1H, exchangeable; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.7, 23.8, 24.7, 25.7, 34.3, 52.1, 104.5, 106.5, 130.4, 136.7, 168.4; MS, m/z (rel inten) 232 (M^+, 100), 189 (64), 150 (98), 135 (15), 122 (15); HRMS, calcd for $C_{14}H_{20}N_2O$: 232.1575, found 232.1578. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.39; H, 8.67; N, 12.06. Found: C, 72.38; H, 8.61; N, 12.09.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-[(methylsulfonyl)oxy]ethane (6). In a modification of the procedure of Barthel and Alexander,[7a] 2-(3,4-dimethoxyphenyl)ethanol[7b] (8.0 g, 44.0 mmol) was dissolved in acetic acid (15 mL), and bromine (8.8 g, 55.0 mmol) was added at a rate so as to maintain the reaction temperature at around 20 °C. After 1 h, water (120 mL) was added and the aqueous layer extracted with chloroform (3 × 120 mL). The chloroform layer was washed with saturated aqueous sodium bicarbonate solution (2 × 70 mL) and brine (2 × 50 mL) and dried over the anhydrous magnesium sulfate. Chromatography (silica gel; hexanes/ethyl acetate, 4:1) afforded the brominated ester in quantitative yield. This material (9.5 g, 32.0 mmol) was dissolved in methanol (120 mL), and potassium carbonate (8.7 g, 63.0 mmol) was added. After 30 min, the methanol was removed under reduced pressure and the residue was dissolved in dichloromethane (250 mL). The organic layer was washed with water (125 mL) and brine (2 × 50 mL) and dried over anhydrous magnesium sulfate. No further purification was performed.

The resultant bromo alcohol (9.2 g, 35.0 mmol) was dissolved in dichloromethane (180 mL), and triethylamine (7.1 g, 70.0 mmol) was added and the mixture cooled to 0 °C at which time methanesulfonyl chloride (5.6 g, 49.0 mmol) was added. The reaction mixture was allowed to stir at this temperature for 45 min and then at rt for 30 min. Water (90 mL) and dichloromethane (120 mL) were then added and the layers separated. The aqueous layer was extracted with dichloromethane (100 mL), and the organic layers were combined and washed with saturated aqueous sodium bicarbonate solution (70 mL) and brine (2 × 100 mL) and dried over anhydrous magnesium sulfate. Solvent evaporation under reduced pressure followed by passing the crude reaction mixture through a plug of silica gel afforded the sensitive mesylate (9.0 g, 76% yield): mp 92–95 °C; IR (Nujol) ν 1601, 1575, 1260, 1216, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 3H), 3.11 (t, J = 6.9 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.39 (t, J = 6.9 Hz, 2H), 6.77 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 37.2, 56.1, 68.7, 113.8, 114.1, 115.5, 127.2, 148.4, 148.7; MS, m/z (rel inten) 340 (34), 338 (M^+, 32), 244 (100), 242 (100), 231 (73), 229 (85), 151 (18), 120 (16); HRMS, calcd for $C_{11}B_{15}BrO_5S$ 337.9824, found 337.9829.

3-(Cyclohexylamino)-1-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-5,6-dihydro-2-oxo-4*H*-indole (5). To a suspension of sodium hydride (0.24 g of 60% dispersion in mineral oil, 6.0 mmol, rinsed with pentane) in DMF (34 mL) was added compound 3 (1.0 g, 4.3 mmol) in DMF (11 mL) at rt over 10 min. After 25 min, a solution of the mesylate 6 (2.13 g, 6.3 mmol) in DMF (7 mL) was added over a period of 5 min. The reaction was complete as judged by TLC, after 4 h of stirring at rt. Water (180 mL) and ether (120 mL) were added, and the aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined and washed with water (3 × 100 mL) and brine (2 × 50 mL) and dried over anhydrous magnesium sulfate to give the crude product after solvent evaporation under reduced pressure. Chromatography, (silica gel, hexanes/ethyl acetate, 4:1) afforded compound 5 (1.64 g 80% yield): mp 100–102 °C (ethyl acetate); IR ($CDCl_3$) δ 3367, 3080, 2931, 1687, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08–1.37 (m, 5H), 1.56 (m, 1H), 1.67–1.69 (m, 4H), 1.94 (m, 2H), 2.20 (q, J = 5.4 Hz, 2H), 2.56 (dd, J = 6.3, 6.3 Hz, 2H), 2.91 (dd, J = 7.5, 7.5 Hz, 2H), 3.29 (m, 1H), 3.72 (dd, J = 7.5, 7.5 Hz, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 3.92 (d, J = 9.0 Hz, 1H, exchangeable) 5.32 (t, J = 4.5 Hz, 1H), 6.66 (s, 1H), 6.97 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.6, 23.9, 24.7, 25.6, 34.3, 35.1, 38.9, 52.0, 55.9, 56.1, 102.9, 104.7, 113.6, 114.0, 115.3, 129.8, 130.1, 138.5, 148.2, 148.3, 166.6; MS, m/z (rel inten) 476 (9), 474 (M^+, 9), 395 (100), 313 (12), 245 (11), 190 (8); HRMS, calcd for $C_{24}H_{31}BrN_2O_3$ 474.1518, found 474.1523.

4-(Cyclohexylamino)-3a,4-didehydro-10,11-dimethoxy-1,2,7,8,12b,12c-hexahydro-5-oxo-*trans*-3*H*-indolo[7,1-*ab*][3]benzazepine (7). To a degassed refluxing benzene (8 mL) solution of compound 5 (0.38 g, 0.8 mmol) and AIBN (0.018 g) was added n-Bu_3SnH (0.47 g, 1.6 mmol) in benzene (4 mL) over a period of 1.5 h. The resultant reaction mixture was allowed to reflux for 15 h. The benzene was the removed under reduced pressure and the residue was dissolved in ether, followed by stirring for 6 h with a 60% aqueous KF solution. The resultant mixture was filtered, and the aqueous layer was extracted with ether (2 × 15 mL). The combined ether layers were washed with brine (1 × 50 mL) and dried over anhydrous magnesium sulfate. Chromatography (silica gel, hexanes/ethyl acetate, 2:1) afforded tetracycle 7 (0.175 g, 56%, 65% based on recovered starting material): mp 144–145 °C (ethyl acetate); IR (KBr) δ 3355, 2930, 1682, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02–1.49 (m, 7H), 1.59–1.87 (m, 4H), 1.98–2.21 (m, 4H), 2.60 (br ddd, J = 11.1, 10.2, 3.6 Hz, 1H), 2.69–2.77 (m, 1H), 2.80–2.92 (m, 2H), 3.28 (m, 1H), 3.36 (d, J = 10.2 Hz, 1H), 3.81 (m, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 3.96 (m, 1H exchangeable), 4.56 (m, 1H), 6.68 (s, 1H), 6.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 25.1, 25.7, 25.9, 26.5, 29.4, 33.8, 34.4, 36.4, 41.9, 46.4, 52.8, 56.0, 56.3, 63.8, 110.6, 113.2, 116.8, 129.7, 133.9, 134.9, 147.3, 167.4; MS, m/z (rel inten) 396 (M^+, 23), 256 (21), 178 (23); HRMS, calcd for $C_{24}H_{32}N_2O_3$ 396.2412, found 396.2408. Anal. Calcd for $C_{24}H_{32}H_2O_3$: C, 72.70; H, 8.14; N, 7.07. Found C, 72.58; H, 8.25; H, 6.57.

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Supplementary Material Available: Copies of NMR spectra of 5 and 6 (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) For a recent example of an aryl radical cyclization onto an enamine double bond wherein some trans-fused products were obtained in a 6-endo addition, see: Glover, S. A.; Warkentin, J. *J. Org. Chem.* **1993**, *58*, 2115. For a related example, see: Ponaras, A. A.; Zaim, O. *Tetrahedron Lett.* **1993**, *34*, 2879.

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