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Regioselective 6-Endo Cyclizations of 2-Indolylacyl Radicals: Total Synthesis of the Pyrido[4,3-*b*]carbazole Alkaloid Guatambuine

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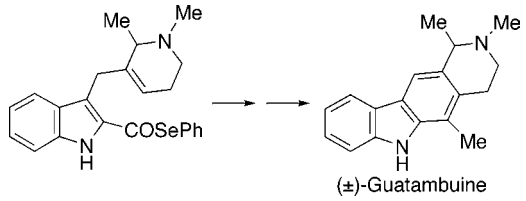


A regioselective 6-endo reductive cyclization of 2-indolylacyl radicals constitutes the key step of a straightforward synthetic entry to the olivacine skeleton, illustrated by a total synthesis of the tetrahydropyridine alkaloid guatambuine.

The pyrido[4,3-*b*]carbazole alkaloids, exemplified by the fully aromatic components ellipticine and its isomer olivacine (Figure 1), constitute a small subgroup of naturally occurring biologically active compounds that have been known for more than 40 years.[1] Owing to their well-established anticancer properties, ellipticine and, to a lesser extent, olivacine have been the objective of many total syntheses using a great variety of approaches.[1−3] However, despite the intensive synthetic work, radical methodologies have been scarcely used to assemble the linear pyridocarbazole skeleton of these alkaloids.[4,5]

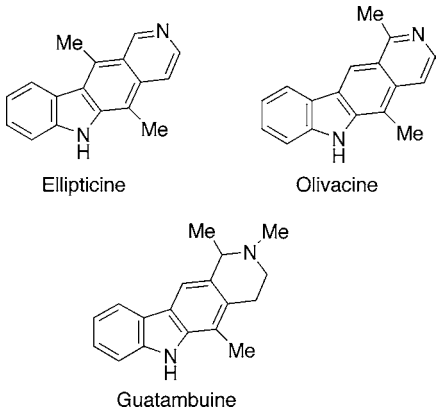
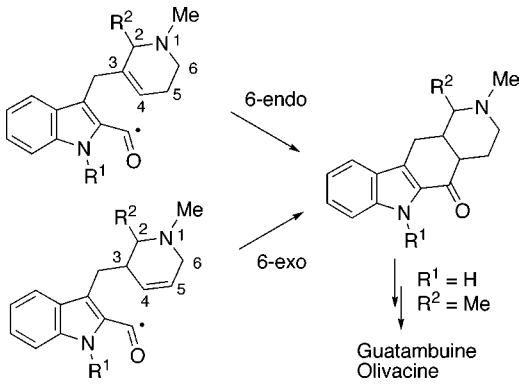


FIGURE 1. Pyrido[4,3-*b*]carbazole alkaloids.

SCHEME 1. Synthetic Strategy



Our previous experience in the inter-[6] and intramolecular[7] reactions of 2-indolylacyl radicals with alkenes under reductive conditions led us to envisage a straightforward approach to the olivacine skeleton hinging on the cyclization of 3-(tetrahydro-3-pyridylmethyl)-2-indolylacyl radicals (Scheme 1). This paper deals with our work in this area, including a concise total synthesis of the pyridocarbazole alkaloid (±)-guatambuine, a tetrahydro derivative of olivacine isolated from several *Aspidosperma* species.[8,9]

Radical reactions have become an important tool for the construction of nitrogen heterocycles.[10,11] In this context, there are several reports in the literature concerning radical cyclizations upon tetrahydropyridines, most of them leading to structures with the nitrogen atom in the newly formed ring.[12,13]

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(4) For a radical cascade protocol leading to ellipticine, see: Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615−10618.

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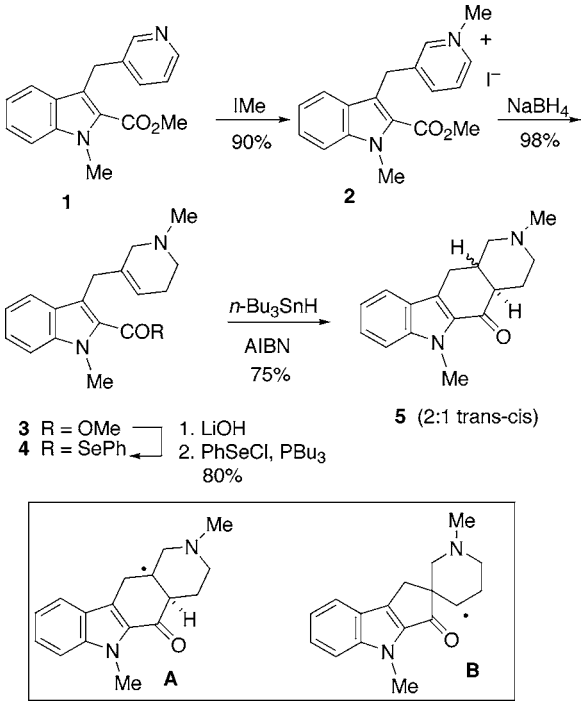
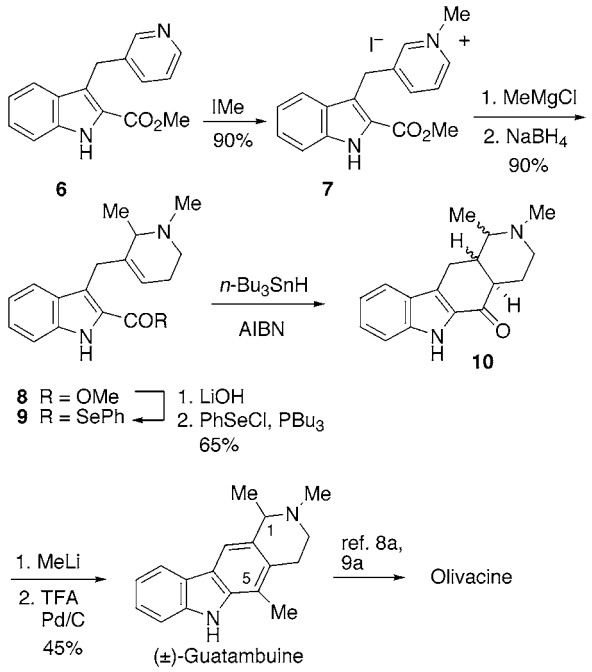
SCHEME 2. Model Studies



SCHEME 3. Synthesis of (±)-Guatambuine



In our initial design there were two distinct ways to close the central carbocyclic ring, namely, a 6-endo cyclization of a 5-hexenoyl radical (1,2,5,6-tetrahydropyridine) or a 6-exo cyclization of a 6-heptenoyl radical (1,2,3,6-tetrahydropyridine). As the required starting substrates appeared to be more accessible from pyridine derivatives through conventional reductive protocols, we focused our attention on the first approach. Considering the precedents on related cyclizations involving acyl radicals,[7,14] we expected that the higher alkene substitution at the 3-position of the ring would probably retard the competitive 5-exo cyclization mode, thus favoring the desired formation of the 6-membered ring.

We first carried out a model study to probe the feasibility of the proposal using selenoester **4**, which incorporated the required 1,2,5,6-tetrahydropyridine moiety, as the radical precursor (Scheme 2). As anticipated, this compound was easily accessible from the known pyridylmethylindole **1**[5] by quaternization with methyl iodide, reduction of the resulting pyridinium salt **2** with $NaBH_4$ in a protic solvent (EtOH), and the subsequent phenylselenation of the tetrahydropyridine methyl ester **3** through the corresponding carboxylic acid. We were pleased to find that selenoster **4** upon exposure to the standard reductive conditions (tributyltin hydride−AIBN, benzene, reflux, slow addition, final concentration 0.06 M) led to the expected pyrido[4,3-*b*]carbazole **5** as a 2:1 mixture of trans−cis stereoisomers in 75% yield. No 5-exo cyclization product was detected by NMR.

This regiochemical outcome is probably the result of a direct 6-endo cyclization of the initially formed acyl radical to give the fused radical adduct **A**, although a partial 5-exo attack followed by ring expansion of the highly strained radical adduct **B** cannot be completely ruled out under the reaction conditions.[15] Further hydrogen abstraction of the bridgehead radical **A** from tributyltin hydride in an incompletely stereoselective way would account for the formation of the trans−cis mixture **5**. This mixture could be quantitatively transformed into the thermodynamically more stable trans-fused piperidine compound by treatment with sodium methoxide in methanol.

At this point, the synthesis of the pyridocarbazole alkaloid guatambuine required the extension of the chemistry outlined above to related substrates unsubstituted at the indole nitrogen. Additionally, at some stage, we had to be able to introduce the C-1 and C-5 methyl groups of the alkaloid. To this end, we focused our attention on pyridylmethylindole **6**[5] (Scheme 3), which was converted as above into *N*-methylpyridinium salt **7**. Reaction of **7** with methylmagnesium chloride efficiently accomplished the introduction of the first (C-1) methyl group. Significantly, the addition of the organometallic reagent took place in a totally regioselective manner at the C-2 position of the ring[16] to give, after reduction of the intermediate 2,3-disubstituted 1,2-dihydropyridine with $NaBH_4$, tetrahydropyridine **8** as the sole product in a yield as high as 90%. Its subsequent hydrolysis followed by phenylselenation led to

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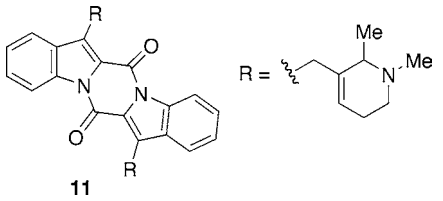
(14) For a review, see: Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem.—Eur. J.* **1997**, *3*, 376−387.

(15) For a discussion on the origin of this regioselectivity, see: (a) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672−3679. For a recent example, see: (b) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520.



11

FIGURE 2. Diketopiperazine **11**.

selenoester **9**, which was subjected to the radical protocol previously used in the model series (tributyltin hydride, AIBN, slow addition) with the hope that the initially formed 2-indolylacyl radical would initiate the desired 6-endo cyclization without interference from the indole NH group.[17]

Owing to the lower solubility of **9** in benzene, the first attempts were performed using a 1:1 mixture of benzene−acetonitrile as the solvent system. However, under these conditions, a fast dimerization of the substrate took place, most likely through a ketene intermediate, to give diketopiperazine **11** (Figure 2) as the only product in 63% yield.[18] The presence of the polar solvent was clearly responsible for this unwanted process[19] since when we worked with more diluted benzene solutions of **9** (final concentration 0.02 M) the radical reaction took place satisfactorily, giving access to pyridocarbazole **10** (mixture of stereoisomers) in approximately 75% yield. Without further purification, **10** was elaborated into (±)-guatambuine by reaction with methyllithium, which accomplished the introduction of the second (C-5) methyl group, followed by TFA−Pd/C promoted dehydration of the resulting carbinol with concomitant dehydrogenation to the carbazole ring. The overall yield from selenoester **9** was 45%.

Our synthetic material displayed ^{1}H NMR data identical to those previously reported,[8,9] and its ^{13}C NMR and analytical data were in full agreement with the proposed structure. Considering that guatambuine had been transformed into olivacine by further dealkylative aromatization,[8a,9a] the synthesis reported here also constitutes a formal synthesis of this fully aromatic alkaloid.

In conclusion, we have shown that the cyclization of 3-(tetrahydro-3-pyridylmethyl)-2-indolylacyl radicals under reductive conditions takes place with total 6-endo regioselectivity, providing a novel synthetic entry to the pyrido[4,3-*b*]carbazole skeleton characteristic of olivacine.

Experimental Section

2,6-Dimethyl-1,2,3,4,4a,6,11,11a-octahydropyrido[4,3-*b*]carbazole-5-one (5). *n*-Bu_3SnH (0.16 mL, 0.61 mmol) and AIBN (8 mg, 0.05 mmol) in C_6H_6 (3 mL) were added over a period of 1 h (syringe pump) to a heated (reflux) solution of selenoester **4** (0.20 g, 0.47 mmol) and AIBN (8 mg, 0.05 mmol) in C_6H_6 (5 mL). After an additional 2 h at reflux, the solution was concentrated, the resulting residue was partitioned between hexanes (10 mL) and acetonitrile (10 mL), and the polar layer was washed with hexanes (3 × 10 mL). The solvent was removed, and the crude product was chromatographed (96:3:1 CH_2Cl_2−MeOH−diethylamine) to give **5** as an oil: 94 mg (75%, 2:1 mixture of trans−cis stereoisomers). This mixture was quantitatively converted into the pure trans compound by treatment with MeONa (38 mg, 0.70 mmol) in MeOH (5 mL): ^{1}H NMR (400 MHz) δ 1.62 (qd, J = 4, 12.4, 12.4, 12.4 Hz, 1H), 1.98 (m, 2H), 2.14 (td, J = 2.7, 12, 12 Hz, 1H), 2.31 (m, 2H), 2.32 (s, 3H), 2.62 (dd, J = 11.6, 16, Hz, 1H), 3.05 (m, 2H), 3.06 (dd, J = 3.6, 16 Hz, 1H), 4.06 (s, 3H), 7.13 (ddd, J = 1.2, 7.2, 8 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.38 (ddd, J = 1.2, 7.2, 8 Hz, 1H), 7.61 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 25.5 (CH_2), 26.1 (CH_2), 31.3 (CH_3), 41.1 (CH), 46.2 (CH_3), 50.1 (CH), 55.7 (CH_2), 62.1 (CH_2), 110.2 (CH), 120.0 (CH), 121.0 (CH), 124.5 (C), 126.5 (CH), 127.0 (C), 129.8 (C), 139.7 (C), 192.5 (C). Anal. Calcd for $C_{17}H_{20}N_2O\cdot{}^1/_2H_2O$: C, 73.61; H, 7.63; N, 10.09. Found: C, 73.24; H, 7.39; N, 9.74.

Methyl 3-(1,2-Dimethyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-1*H*-2-indolecarboxylate (8). Pyridinium salt **7** (0.62 g, 1.50 mmol) was added under Ar to a cooled (−78 °C) solution of MeMgCl (3 M in THF, 1.75 mL, 5.25 mmol) in THF (35 mL), and the mixture was stirred at −78 °C for 20 min and at 0 °C for 6 h. The reaction mixture was poured into a 1:1 mixture of 20% NH_4OH and a saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were concentrated to dryness, and the resulting residue (0.47 g) was dissolved in MeOH (35 mL). $NaBH_4$ (0.16 g, 3.95 mmol) was added to the solution, and the mixture was stirred at rt for 4 h. The solvent was removed, and the resulting residue was partitioned between CH_2Cl_2 (30 mL) and a saturated aqueous Na_2CO_3 solution (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were dried and concentrated to give **8** as a brown oil: 0.40 g (90%); ^{1}H NMR (200 MHz) δ 1.28 (d, J = 6.6 Hz, 3H), 1.95−2.10 (m, 2H), 2.34 (s, 3H), 2.44 (dt, J = 5.6, 5.6, 11.8 Hz, 1H), 2.81 (ddd, J = 5.4, 7.2, 12.8 Hz, 1H), 2.94 (q, J = 6.2 Hz, 1H), 3.82 (br s, 2H), 3.93 (s, 3H), 5.27 (m, 1H), 7.10 (ddd, J = 1.8, 6.6, 8.2 Hz, 1H), 7.30−7.35 (m, 2H), 7.66 (d, J = 8 Hz, 1H), 8.91 (br s, 1H); ^{13}C NMR (75.4 MHz) δ 15.5 (CH_3), 24.0 (CH_2), 29.8 (CH_2), 42.4 (CH_3), 46.7 (CH_2), 51.7 (CH_3), 58.4 (CH), 111.7 (CH), 119.6 (CH), 120.0 (CH), 121.5 (CH), 121.6 (C), 123.5 (C), 125.5 (CH), 128.4 (C), 135.9 (C), 139.1 (C), 162.7 (C). Anal. Calcd for $C_{18}H_{22}N_2O_2\cdot H_2O$: C, 68.33; H, 7.64; N, 8.85. Found: C, 68.39; H, 7.26; N, 8.61.

***Se*-Phenyl 3-(1,2-Dimethyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-1*H*-2-indolecarboselenoate (9).** A solution of methyl ester **8** (0.30 g, 1 mmol) and $LiOH\cdot H_2O$ (50 mg, 1.20 mmol) in a 3:1 mixture of THF−H_2O (8 mL) was stirred at 65 °C for 5 h. The reaction mixture was concentrated, acidified with aqueous 1 N HCl until pH = 4, and concentrated to dryness. The resulting residue was digested with anhydrous MeOH. The methanolic solution was concentrated to give the crude carboxylic acid hydrochloride. A suspension of the above carboxylic acid in anhydrous CH_2Cl_2 (7 mL) was treated with Et_3N (2 mmol). After 15 min at rt, the mixture was concentrated under reduced pressure to give the triethylammonium salt.

In another flask, tributylphosphine (1.24 mL, 5 mmol) was added under Ar to a solution of PhSeCl (0.96 g, 5 mmol) in anhydrous THF (7 mL), and the mixture was stirred at rt for 10 min (yellow solution). Then, the above triethylammonium salt in THF (7 mL) was added to this solution, and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O (25 mL) and H_2O (25 mL) and extracted with Et_2O (3 × 15 mL). The solvent was removed, and the crude product was chromatographed (CH_2Cl_2 and 90:9:1 CH_2Cl_2−MeOH−diethylamine) to give selenoester **9** as a brown oil: 0.27 g (65%); ^{1}H NMR (200 MHz) δ 1.39 (d, J = 6.6 Hz, 3H), 2.05 (m, 2H), 2.45 (s, 3H), 2.51 (dd, J = 6, 12 Hz, 1H), 2.87 (dt, J = 5.8, 5.8, 12.2 Hz, 1H), 3.10 (q, J = 6.2 Hz, 1H), 3.79 (br d, J = 17.6 Hz, 1H), 3.96 (br d, J = 16.8 Hz, 1H), 5.17 (br s, 1H), 7.03 (d, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.45 (m, 3H), 7.65 (m, 3H), 9.82 (br s, 1H); ^{13}C NMR (75.4 MHz) δ 16.2 (CH_3), 24.1 (CH_2),

(17) We had observed that the indole NH group inhibited the radical cyclization of a related selenoester upon pyridines, probably by interfering at the rearomatization step: see ref 5.

(18) For a related dimerization involving 2-indolylacyl chlorides, see: Boger, D. L.; Fink, B. E.; Hedrick, M. P. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1019−1020.

(19) Simple heating of selenoester **9** in 1:1 benzene−acetonitrile for 3 h led to a 3:1 mixture of **9** and **11**. In contrast, heating of **9** in benzene for 6 h led to a 10:1 mixture of **9** and **11**.

30.4 (CH_2), 42.7 (CH_3), 47.5 (CH_2), 59.5 (CH), 112.5 (CH), 120.4 (2 CH), 121.2 (C), 121.4 (CH), 125.4 (C), 126.5 (CH), 128.5 (C), 129.1 (CH), 129.4 (CH), 132.5 (C), 136.5 (C), 136.6 (CH), 137.8 (C), 184.4 (C). Anal. Calcd for $C_{23}H_{24}N_2OSe\cdot{}^3/_2H_2O$: C, 61.33; H, 6.04; N, 6.23. Found: C, 61.29; H, 5.66; N, 5.97.

(±) Guatambuine. *n*-Bu_3SnH (0.10 mL, 0.35 mmol) and AIBN (5 mg, 0.03 mmol) in C_6H_6 (5 mL) were added over a period of 2 h (syringe pump) to a heated (reflux) solution of selenoester **9** (115 mg, 0.27 mmol) and AIBN (5 mg, 0.03 mmol) in C_6H_6 (10 mL). After an additional 1 h at reflux, the solution was concentrated, and the resulting residue was partitioned between hexanes (10 mL) and acetonitrile (10 mL). The polar layer was washed with hexanes (3 × 10 mL) and concentrated to give ketone **10**.

A solution of crude **10** in anhydrous THF (7 mL) was added dropwise under Ar to a cooled (−10 °C) solution of MeLi (1.6 M in Et_2O, 2.50 mL, 4.0 mmol) in anhydrous THF (7 mL), and the resulting mixture was stirred at rt for 3 h. The reaction mixture was poured into an ice-cold saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried and concentrated. 10% Pd/C (85 mg) was added to the resulting residue dissolved in TFA (4 mL), and the suspension was stirred at rt for 3 h. The reaction mixture was filtered through Celite, the cake was washed with CH_2Cl_2 (20 mL), and the organic solution was washed with a saturated aqueous $NaHCO_3$ solution (3 × 20 mL). The organic extracts were concentrated, and the crude product was chromatographed (92:7:1 CH_2Cl_2−MeOH−diethylamine) to give (±)-guatambuine: 32 mg (45%); ^{1}H NMR (300 MHz, HSQC and HMBC) δ 1.52 (d, J = 6.3 Hz, 3H, Me), 2.41 (s, 3H, Me), 2.54 (s, 3H, NMe), 2.79 (ddd, J = 5.7, 6, 11.7 Hz, 1H, 3-H), 2.94 (m, 2H, 4-H), 3.19 (ddd, J = 5.7, 6, 11.7 Hz, 1H, 3-H), 3.89 (q, J = 6.3 Hz, 1H, 1-H), 7.19 (ddd, J = 1.2, 6.6, 7.8 Hz, 1H, 9-H), 7.37 (ddd, J = 1.2, 6.6, 8.1 Hz, 1H, 8-H), 7.42 (dd, J = 1.2, 8.1 Hz, 1H, 7-H), 7.70 (s, 1H, 11-H), 7.85 (br s, 1H, NH), 8.00 (d, J = 7.8 Hz, 1H, 10-H); ^{13}C NMR (100.6 MHz, HSQC and HMBC) δ 12.9 (Me), 20.3 (Me), 25.0 (C-4), 42.0 (NMe), 48.1 (C-3), 59.7 (C-1), 110.6 (C-7), 115.9 (C-11), 116.9 (C-5), 119.2 (C-9), 120.1 (C-10), 121.3 (C-10b), 123.7 (C-10a), 125.5 (C-8), 128.8 (C-4a), 130.0 (C-11a), 138.1 (C-5a), 139.9 (C-6a); HRMS calcd for $C_{18}H_{20}N_2$ 264.1626, found 264.1628. Anal. Calcd for $C_{18}H_{20}N_2\cdot$HCl: C, 71.86; H, 7.04; N, 9.31. Found: C, 71.63; H, 6.85; N, 9.08.

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Supporting Information Available: General experimental protocols and detailed experimental procedures for the preparation of synthetic intermediates **2**, **3**, **4**, and **7**. Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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