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# Novel 7- and 8-Endo 2-Indolylacyl Radical Cyclizations: Efficient Construction of Azepino- and Azocinoindoles†

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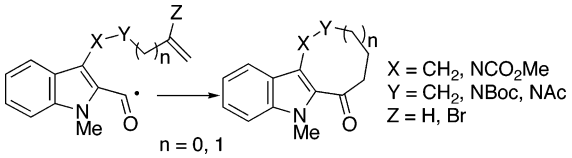
*Received February 16, 2007*




Regioselective 7- and 8-endo cyclizations of selenoester derived 2-indolylacyl radicals upon amino tethered alkenes have been used to synthesize azepino[3,2-*b*]- and azocino-[4,3-*b*]indoles, which are tricyclic subunits present in the indole alkaloids mersicarpine and apparicine, respectively.

Radical cyclizations are recognized as powerful tools in organic synthesis,[1] as is illustrated by numerous reports that deal with the construction of 5- and 6-membered carbo- and heterocyclic rings in the context of the synthesis of complex molecules.[1,2] In contrast with this intense activity, kinetically less favorable cyclizations leading to 7- or 8-membered rings, which can be found in the skeleton of many natural and synthetic compounds, have been comparatively less studied.[3]

As part of a research program aimed at the synthesis of bioactive indole compounds using selenoester derived 2-indolylacyl radicals,[4,5] we have previously reported that valuable 5- and 6-membered indolo 1,2-fused carbocyclic ketones are efficiently assembled by cyclization of *N*-alkenyl substituted 2-indolylacyl radicals under reductive conditions.[6,7] We went on to consider extending the above annulation methodology to the construction of higher homologues, in particular 7- and 8-membered azacycles that are fused to the 2,3-position of the indole ring, which are subunits present in several indole alkaloids[8] such as mersicarpine[9] or apparicine.[10] In this context, we wished to investigate if 2-indolylacyl radicals of general formula **I** (6-heptenoyl radicals) and **II** (7-octenoyl radicals) would undergo regioselective 7- and 8-endo cyclizations upon amino tethered alkenes, which would ultimately lead to the target tricyclic substructures (Scheme 1).

Neither radical process was evident a priori. It is well accepted that the 6-exo ring closure of 6-heptenyl-type radicals is generally preferred to the alternative 7-endo cyclization,[11] although the latter can be competitive and, in some particular substrates, preponderant.[12] Acyl radicals[13] exhibit an even higher tendency to undergo 6-exo cyclizations,[14,15] in particular those intermediates that bear a phenyl group in the tether between the radical and the acceptor,[16] which are closely related to indolylacyl derivatives **I**. More favorable to our purposes, cyclizations of 7-octenyl-type radicals, when feasible, preferentially take place through the 8-endo mode, and several elegant examples, which mainly involve α-carbonyl radicals, have been recently reported.[17] However, the 8-endo cyclization of acyl radicals[13] is rare and is usually limited to conformationally

† Dedicated to Professor Joan Bosch on the occasion of his 60th birthday.

* To whom correspondence should be addressed. Tel: 34 934 024 540, Fax: 34 934 024 539.

(1) For leading reviews, see (a) Renaud, P.; Sibi, M. P., Eds.; *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Gansäuer, A., Ed.; *Topics Current Chemistry*; Radicals in Synthesis I and II; Springer: Berlin; 2006; Vols. 263 and 264.

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(12) For instance, see: (a) Justicia, J.; Oller-López, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911−14921. (b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922−1925.

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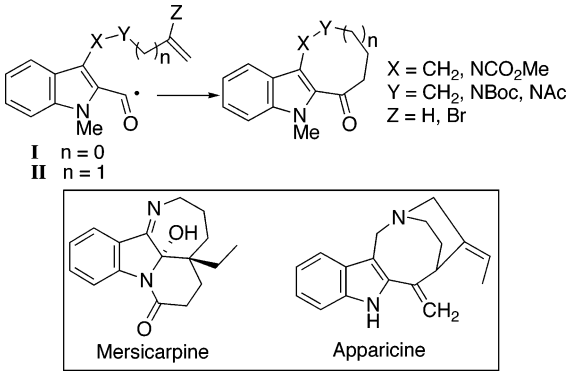
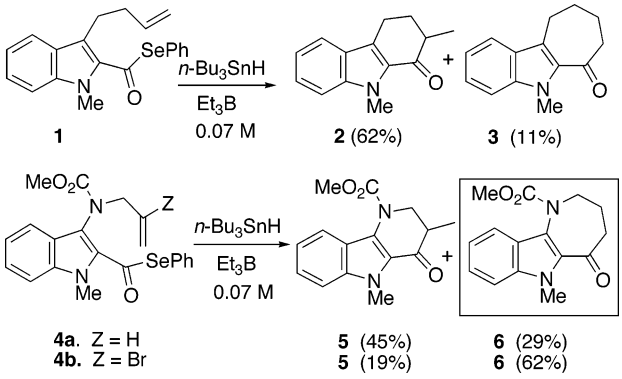
10.1021/jo070322m CCC: $37.00 
Published on Web 05/09/2007

**SCHEME 1**



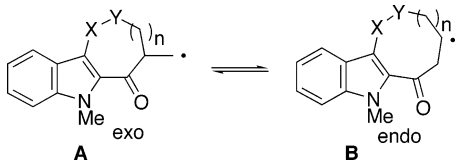

**SCHEME 2. 6-Heptenoyl Radical Cyclizations**




restricted substrates.[18] Most of the reported examples deal with 7-exo cyclizations upon diversely substituted alkenes.[16,19−21]

To examine the behavior of 6-heptenoyl radicals **I** we focused our attention on selenoesters **1** and **4** (Scheme 2), which were prepared from the respective 3-substituted indole-2-carboxylic esters.[22] Consistent with the above precedents as well as with our previous results using the regioisomeric *N*-(3-butenyl)-2-indolylacyl radicals,[6] treatment of the model selenoester **1** with 2 M equiv of *n*-$Bu_3SnH$ with $Et_3B$ as the initiator in benzene (0.07 M) led to the 6-exo carbocyclic ketone **2** as the major product (62% yield), although in this case the 7-endo product **3** could also be isolated from the reaction mixture (11% yield). No evidence of radical reduction (i.e., formation of an aldehyde)

**SCHEME 3**




from the direct hydrogen abstraction from the hydride or from an eventual [1,5]-hydrogen atom transfer was observed.

More satisfactorily, the inclusion of a carbamate nitrogen atom in the connecting chain enhanced the 7-endo regioselectivity, although the formation of the six-membered ring still predominated. Thus, the amino tethered selenoester **4a**, upon subjection to the above protocol, led to a 1.5:1 mixture of exo−endo products, from which the desired azepino[3,2-*b*]indole **6** could be isolated in a significant 29% yield along with pyridoindole **5** (45% yield).[23] At this point, we explored the possibility of increasing the amount of endo product by carrying out the radical cyclization at lower hydride concentrations. Our aim was to shift the equilibration of the initially formed cyclized radicals **A** and **B** (Scheme 3, $n = 0$, X = $NCO_2Me$, Y = $CH_2$) in favor of the thermodynamically more stable endo radical **B** through an intramolecular rearrangement that results in ring expansion.[24] Unfortunately, the exo−endo product ratio was not significantly modified by the hydride concentration (0.07, 0.02, or 0.005 M), so we assumed that such a rearrangement was not included in the reaction pathway.

Finally, the 7-endo closure became the predominant route when a temporary substituent, such as a bromine atom, was introduced at the 6-exo position of the alkene acceptor.[25,26] Treatment of selenoester **4b**, which incorporated a 2-bromo-2-propenyl instead of an allyl moiety, with *n*-$Bu_3SnH$ (2 M equiv) led to a mixture of the same two products **5** and **6** but in a different ratio (approximately 1:3). The excess hydride ensured the final reductive removal of the bromine atom after the cyclization step. In this manner, the tricyclic substructure of mersicarpine (**6**) was isolated as the major product in a synthetically acceptable 62% yield along with minor amounts (19%) of **5**.

Attention was then directed to 7-octenoyl radicals **II** (Scheme 1) with the final aim of achieving the azocino[4,3-*b*]indole substructure of apparicine. The feasibility of the desired 8-endo cyclization was tested using a range of precursor selenoesters, bearing different five-atom chains (4-pentenyl, 3-butenylamino, or allylaminomethyl) at the indole 3-position.[22] In full accordance with our previous results using the regioisomeric *N*-substituted radicals,[6] no cyclization was observed when the model selenoester **7** was treated with *n*-$Bu_3SnH$−$Et_3B$ under different conditions, and only aldehyde **8** could be isolated from the reaction mixtures (60−80% yield, Scheme 4). Reduction

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(22) See the Supporting Information for the preparation of all radical precursors.

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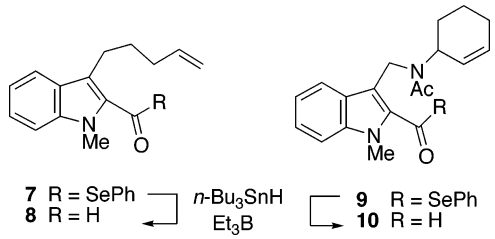
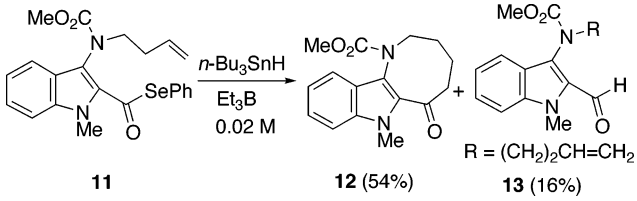
**SCHEME 4. Unsuccessful 7-Octenoyl Radical Cyclizations**




**SCHEME 5. Cyclization of 4-Aza-7-octenoyl Radicals**



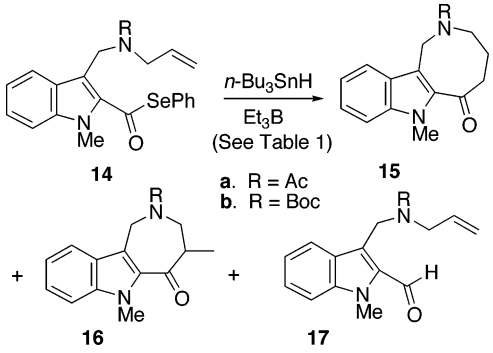

to **8** was also observed when the poorer hydrogen-atom donor $(Me_3Si)_3SiH$ was used as the radical mediator.

After the above unsuccessful result in the carbocyclic series, we were pleased to find that the inclusion of a carbamate or amide nitrogen atom in the chain enabled the cyclization to proceed. Significantly, the regioselectivity of the ring closure depended upon the position of the heteroatom, although the 8-endo route clearly predominated. When selenoester **11**, a precursor of 4-aza-7-octenoyl radicals, was subjected to the usual reductive protocol (*n*-$Bu_3SnH$, $Et_3B$, 0.07 M) the azocino[3,2-*b*]indole **12**, which is a higher homologue of the mersicarpine substructure **6**, was isolated as the only cyclized product (38%) along with minor amounts of aldehyde **13** (21%). Satisfactorily, the premature reduction of the acyl radical could be minimized (16%) by performing the cyclization in a more dilute solution (0.02 M), to give access to **12** in a 54% yield (Scheme 5).

On the other hand, the cyclization of 5-aza-7-octenoyl radicals that were derived from selenoesters **14** followed a different course because it led to mixtures of 8-endo and 7-exo products in ratios that were dependent on the hydride concentration. The results are summarized in Table 1. As can be observed, cyclization of *N*-acetyl selenoester **14a** at a hydride concentration of 0.02 M gave a 3:1 mixture of azocino[4,3-*b*]indole **15a** and azepino[4,3-*b*]indole **16a** (entry 1). Nearly equimolecular amounts (with respect to cyclized products) of the corresponding aldehyde **17a** were also obtained, which indicated that the reduction of the acyl radical was a serious competitor in these series. Significantly, the use of more concentrated solutions (0.14 M, entry 2) not only resulted in a predictable major reduction but also in an increase of the relative amounts of the 7-exo product **16a** with respect to **15a**. In contrast, the use of highly diluted solutions (0.005 M, entry 3) led to a 7:1 mixture of the endo−exo products, from which the tricyclic substructure of apparicine **15a** was isolated in a 55% yield. The analogous tricyclic compound **15b** could also be obtained as the major product by applying this protocol to *N*-Boc selenoester **14b**. The above results clearly indicated that the rearrangement between cyclized radicals **A** and **B** that are depicted in Scheme 3 ($n = 1$, X = $CH_2$, Y = NAc or NBoc) was now included in the reaction pathway and played a key role in the enhancement of the 8-endo regioselectivity.

Gratifyingly, the regioselectivity was completely switched to the 8-endo mode when the alkene acceptor was substituted at

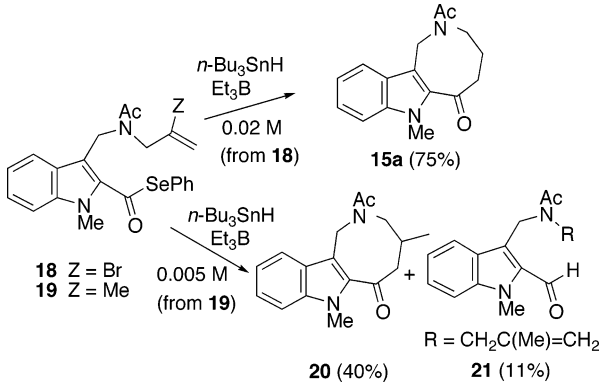
**TABLE 1. Cyclization of 5-Aza-7-octenoyl Radicals[a]**




| entry | radical precursor | concn (M) | endo:exo ratio | endo:exo yield (%)[b] | aldehyde yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **14a** | 0.02 | 3:1 | **15a** (32), **16a** (10) | **17a** (42) |
| 2 | **14a** | 0.14 | 1:1 | **15a** (10), **16a** (10) | **17a** (50) |
| 3 | **14a** | 0.005 | 7:1 | **15a** (55), **16a** (8) | **17a** (25) |
| 4 | **14b** | 0.005 | 4:1 | **15b** (40), **16b** (11) | **17b** (15)[c] |

[a] Reaction conditions: *n*-$Bu_3SnH$ (2 M equiv), $Et_3B$ (2 M equiv), $C_6H_6$, rt. [b] Isolated yields after column chromatography. [c] 5% Unreacted selenoester.

**SCHEME 6. Synthesis of Azocino[4,3-*b*]indoles**




the internal position either by a bromine atom[26] or by a methyl group (Scheme 6). Whereas both substituents sterically prevented the competitive 7-exo attack, the halogen atom also benefited the cyclization, probably by activation of the double bond. Thus, the apparicine substructure **15a** was cleanly obtained (75% yield) from bromovinyl substituted selenoester **18**, without evidence of seven-membered ring formation or premature reduction even when working at 0.02 M. Meanwhile, selenoester **19**, which incorporated a (2-methyl-2-propenyl)amino moiety, gave azocinoindole **20** in a lower yield (40%) along with minor amounts of aldehyde **21** (11%).

Although not directly relevant to our targeted alkaloids, we also examined the behavior of 7-octenoyl radicals that were derived from selenoester **9** (Scheme 4) to see if a tetracyclic system might be constructed after the radical addition to the cyclic double bond. However, both 7-exo and 8-endo routes were too slow for the radical chain to be productive, and only aldehyde **9** was formed.

In conclusion, our study has shown that 7- and 8-endo cyclizations of suitably substituted 2-indolylacyl radicals are viable methods for the construction of 7- and 8-membered rings fused to the 2,3-position of the heterocycle. The presence of a substituted nitrogen atom in the tether is crucial for both the enhancement of the endo regioselectivity and the feasibility of

the ring closure. From the synthetic standpoint, the best yields of azepinoindole **6** and azocinoindole **15a**, related to the alkaloids mersicarpine and apparicine, respectively, are obtained by endo cyclizations that are controlled by vinylic halogen substitution. The application of this work to the synthesis of the natural products is currently underway in our laboratory.

## Experimental Section

**Representative Cyclization Procedure: 2-Acetyl-7-methyl-1,2,3,4,5,7-hexahydroazocino[4,3-*b*]indol-6-one (15a).** *n*-$Bu_3SnH$ (0.16 mL, 0.60 mmol) and $Et_3B$ (1 M in hexanes, 0.60 mmol) were added to a solution of the phenyl selenoester **18** (0.15 g, 0.30 mmol, previously dried azeotropically with anhydrous $C_6H_6$) in anhydrous $C_6H_6$ (30 mL). The reaction mixture was stirred at rt for 2 h with dry air constantly supplied by passing compressed air through a short tube of Drierite. The reaction mixture was concentrated. The residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes (3 × 15 mL). The acetonitrile solution was concentrated, and the crude product was chromatographed (3:7 hexanes−AcOEt) to give **15a** (oil, 60 mg, 75% yield): $^1$H NMR (300 MHz, HSQC and HMBC) $\delta$ 1.94 and 2.16 (2 s, 3H, Me), 2.01 and 2.11 (2 m, 2H, H-4), 2.91 and 3.02 (2 m, 2H, H-5), [3.53 (t, $J$ = 6 Hz) and 3.79 (t, $J$ = 6 Hz), 2H, H-3], 3.86 and 4.05 (2 s, 3H, NMe), 4.92 and 5.13 (2 s, 2H, H-1), 7.20 (m, 1H, H-10), 7.40 (m, 2H, H-8,9), [7.61 (d, $J$ = 8.1 Hz) and 7.82 (d, $J$ = 8.1 Hz), 1H, H-11]; $^{13}$C NMR (75.4 MHz, HSQC and HMBC) $\delta$ 21.7 and 22.1 (Me), 24.6 and 26.5 (C-4), 31.7 and 32.7 (NMe), 41.0 and 42.2 (C-5), 42.1 and 45.8 (C-1), 45.5 and 46.7 (C-3), 110.2 and 110.5 (C-8), 117.8 and 118.4 (C-11b), 119.3 and 121.0 (C-11), 120.7 and 120.8 (C-10), 124.9 (C-11a), 125.5 and 126.5 (C-9), 133.4 and 134.1 (C-6a), 138.1 and 138.8 (C-6b), 169.9 and 171.0 (NCO), 194.2 and 198.1 (C-6); HRMS $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$ 271.1441, found 271.1447.

**Acknowledgment.** We thank the Ministerio de Educación y Ciencia, Spain, for financial support (project CTQ2006-00500/BQU) and a predoctoral grant (FPU program) to D.G.D.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070322M