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A Short Synthesis of the Erythrina Skeleton and of (±)-α-Lycorane

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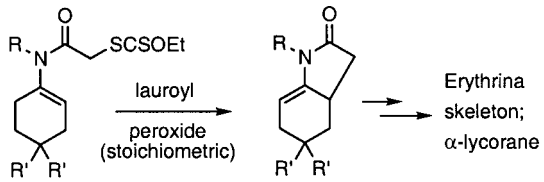
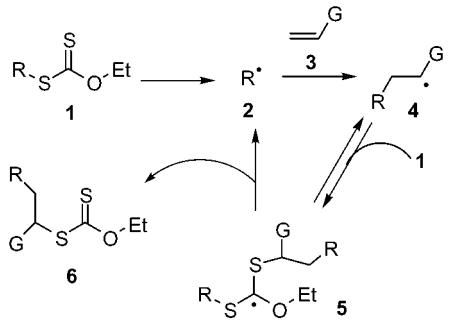
ABSTRACT



A new nonchain 5-*endo* radical cyclization starting with xanthates was exploited in a short synthesis of (±)-α-lycorane and the erythrina ring system.

We have shown, over the past few years, that xanthates and related derivatives were clean and efficient precursors of a variety of free radicals.[1] The underlying mechanism of the addition of an *O*-ethyl xanthate such as **1** to olefin **3** is outlined in Scheme 1. The process offers many advantages, most notably the absence of heavy metals and the possibility of performing both intra- and, especially, intermolecular additions to nonactivated olefins. It is important, if a chain is to be sustained, that the initial radical **2** be at least as—and preferably—more stable than adduct radical **4**, to drive the equilibrium in the last two propagating steps forward. In other words, if radical **2** is more stable than radical **4**, intermediate radical **5** will evolve easily into the desired product **6** and radical **2**, which propagates the chain. This limitation may, however, be lifted by designing a nonchain sequence where the peroxide is used in stoichiometric amounts, becoming a full-fledged reagent rather than a mere initiator.

Scheme 1



Starting with a xanthate such as **7**, we considered using this latter feature to combine a 5-*endo* ring closure with a cyclization onto an aromatic ring. This nonchain sequence would lead in one step to the erythrina skeleton **10**, as pictured in Scheme 2. Radical *5-endo-trig* cyclizations involving enamides have been extensively explored.[2] Most are tin hydride-mediated reactions, whereby the stabilized

(1) (a) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur, Silicon* **1999**, *153*−*154*, 137−154; *J. Chin. Chem. Soc.* **1999**, *46*, 139−145 (b) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672−685.

(2) (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725−28. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399−2407. (c) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2531−2538. (d) Ikeda, M.; Ohtami, S.; Okada, M.; Minakuchi, E.; Sato, T.; Ishibashi, H. *Heterocycles* **1998**, *47*, 181−186. (e) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75−78. (f) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763−1768. (g) Goodall, K.; Parson, A. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3257−3259. (h) Goodall, K.; Parson, A. F. *Tetrahedron* **1996**, *52*, 6739−6758. (i) Goodall, K.; Parson, A. F. *Tetraedron Lett.* **1997**, *38*, 491−494. (j) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1115−

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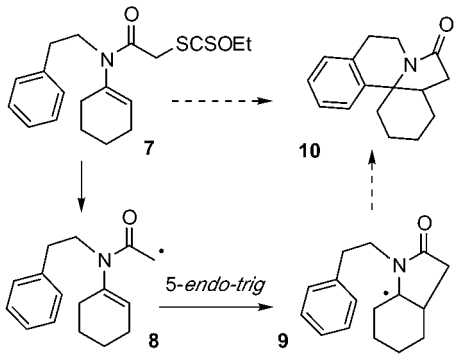
Scheme 2



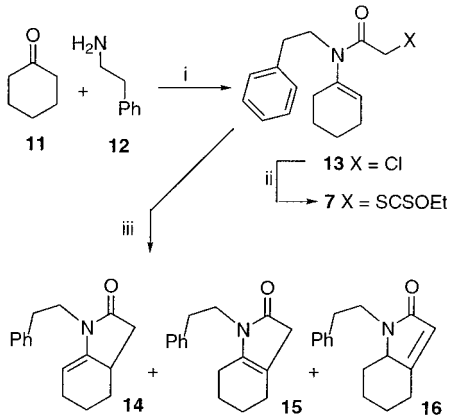
α-amino radical intermediate is ultimately reduced, affording saturated γ-lactams. We have, in contrast, succeeded in obtaining γ-lactams containing a diene system by starting with trichloroacetenamides and generating the radical by electron transfer from metallic nickel in combination with a weak acid such as acetic acid.[3]

We have used this transformation as the key step in the synthesis of γ-lycorane[4] and 3-demethoxyerythratidinone.[5] Oxidative termination of the radical sequence has recently been accomplished using Mn(III)- and Cu(II)-based reagents.[6]

In the present study, it seemed to us that once the *5-endo-trig* closure takes place, the subsequent xanthate transfer from the starting xanthate **7** to the stabilized, tertiary radical **9** would probably be unfavorable, and in any case quite reversible. We hoped therefore that this would allow cyclization of radical **9** onto the aromatic system to give ultimately compound **10** possessing the complete framework of the erythrina alkaloids, many members of which exhibit interesting biological activity (Scheme 2).[7]

The starting material for xanthate **7** was the corresponding chloroacetenamide **13**, prepared by heating cyclohexanone **11** and phenethylamine **12** in refluxing toluene using a Dean−Stark apparatus, followed by trapping the corresponding imine with chloroacetyl chloride. Displacement of the chloride with commercially available potassium *O*-ethyl xanthate proceeded in excellent yield. However, when xanthate **7** was exposed to the action of a stoichiometric amount of lauroyl peroxide (added portionwise) in refluxing 1,2-dichloroethane, none of the desired tetracyclic derivative **10** was found. Instead, we isolated two isomeric lactams **14** and **15** in 62 and 20% yield, respectively (Scheme 3). When

Scheme 3[a]



[a] Conditions: (i) toluene, reflux, 3 h, then Et_3N, chloroacetyl chloride, CH_2Cl_2, rt; (ii) KSC(S)OEt, CH_3CN, rt; (iii) lauroyl peroxide, dichloroethane, reflux, 3 h.

the reaction mixture was heated for longer than 3 h, a more polar compound became more and more visible. It was identified as conjugated isomer **16**, presumably the most thermodynamically stable of the three isomers. By conducting the reaction in refluxing 2-propanol, lactam **16** was rapidly produced and could be isolated in 78% yield. The faster proton exchange in the more protic solvent allows the isomerization process to occur within the addition time of the peroxide.

The formation of unsaturated lactams **14**−**16** may occur through direct oxidation by the peroxide of the intermediate, ring-closed radical **9** into the cationic species **17**, which then loses a proton (Scheme 4). Compound **14** is kinetically the most favored product, but it readily evolves into **15** and ultimately **16** depending on the exact reaction conditions. Alternatively, the formation of the olefinic bond may arise from the disproportionation of the tertiary radical **9**, upon collision with another radical in the medium. Finally, if a xanthate transfer did indeed take place, a xanthate such as **18** would be expected to be thermally labile with respect to elimination of xanthic acid. Which of these processes is actually operating or is the dominant pathway remains at this point a matter of speculation.

Although we could not accomplish the ring closure onto the aromatic ring, the presence of the olefinic bond in the product could be exploited in a more classical Friedel−Crafts type approach to the erythrina framework.[4,7] Moreover, by

1120. (k) Ikeda, M.; Hamada, M.; Yamashita, T.; Ikegami, F.; Sato, T.; Ishibashi, H. *Synlett* **1998**, 1246−1248. (l) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949. (m) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803−1806. (n) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95−102. (o) El Bialy, S. A. A.; Ohtani, S.; Sato, T.; Ikeda, M. *Heterocycles* **2001**, *54*, 1021.

(3) (a) Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1397−1400. (b) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029−1040. (c) Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **2000**, 471−474.

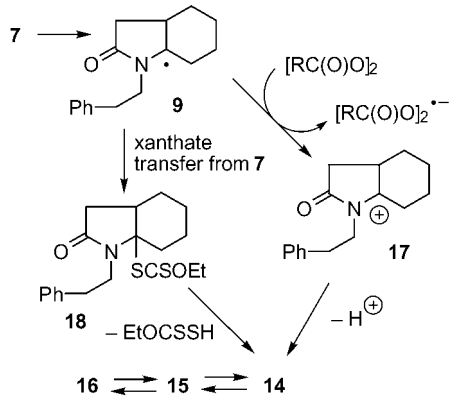
(4) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501−503.

(5) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995−8998.

(6) (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1998**, *39*, 4397−4400; **1999**, *40*, 8615−8618; *Tetrahedron* **2000**, *56*, 3941−3949. (c) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619−8622. (d) Clark, A. J.; Filik, R. P.; Haddleton, D. M.; Radigue, A.; Sanders, C. J.; Thomas, G. H.; Smith, M. E. *J. Org. Chem.* **1999**, *64*, 8954−8957. (e) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901−2904. (f) Ishibashi, H.; Toyao, A.; Takeda, Y. *Synlett* **1999**, 1468−1470. (g) Toyao, A.; Chikaoka, S.; Takeda, Y.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Tetrahedron Lett.* **2001**, *42*, 1729−1732.

(7) For a review of Erythrina alkaloids, see: Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. 48, pp 249−337.

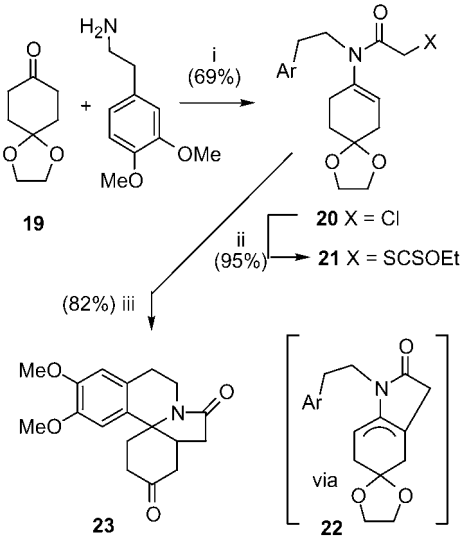
Scheme 4



modifying the substitute on the nitrogen atom, a simple entry into the galanthan skeleton of the lycoranes could be implemented.

For the synthesis of the erythrina system, we started with commercially available monoprotected 1,4-cyclohexanedione **19**, which when condensed with homoveratrylamine and the intermediate Schiff base directly converted into chloroacetenamide **20** by treatment with chloroacetyl chloride (Scheme 5). The corresponding xanthate **21**, obtained by

Scheme 5[a]



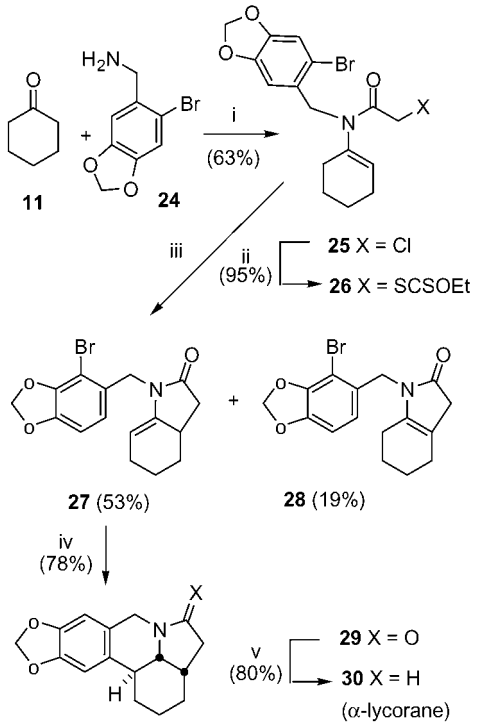
[a] Conditions: (i) toluene, reflux, 3 h, then chloroacetyl chloride, Et_3N; (ii) KSC(S)OEt, acetonitrile, rt; (iii) lauroyl peroxide, 1,2-dichloroethane, reflux, 3 h, then *p*-toluensulfonic acid, catalytic, reflux 30 min.

displacement of the chloride with potassium *O*-ethyl xanthate, was heated in refluxing1,2-dichloroethane with a portionwise addition of a stoichiometric amount of lauroyl peroxide. A catalytic amount of *p*-toluenesulfonic acid was then added to induce the Friedel−Crafts ring closure onto the aromatic ring. There was thus no need to isolate the mixture of the isomeric, intermediate unsaturated lactams **22** since they both give the same iminium ion in the presence of acid. The dioxolane ring does not survive these acidic conditions, and it is ketone **23** (mp 162−165 °C) that is ultimately isolated in good overall yield (82% from xanthate **21**). As far as we are aware, this three-step sequence represents the shortest route to an erythrina derivative.

A concise approach to (±)-α-lycorane could also be implemented by simply modifying the substituent on the nitrogen atom and by combining the first 5-*endo* ring closure with the *6-endo* radical cyclization described a few years ago by Rigby and Mateo.[8] We have applied a similar ring closure to a short synthesis of the epimeric (±)-γ-lycorane.[4]

α-Lycorane **30** belongs to the large class of Amarylidacea alkaloids, which have attracted much attention due to the wide spectrum of biological activity exhibited by many of its members.[9] Our synthesis of (±)-α-lycorane begins with the condensation of cyclohexanone with bromobenzylamine **24** and direct chloroacetylation of the resulting Schiff base to give chloroacetenamide **25** in 63% overall yield (Scheme 6). Displacement of the chloride with the xanthate salt

Scheme 6[a]



[a] Conditions: (i) toluene, reflux 3 h, then chloroacetyl chloride, Et_3N; (ii) KSC(S)OEt, acetonitrile, rt; (iii) lauroyl peroxide, 1,2-dichloroethane, reflux 3 h; (iv) *n*-Bu_3SnH, AIBN, benzene; (v) $LiAlH_4$, THF.

furnished the radical precursor **26**, which was subjected to the action of lauroyl peroxide in refluxing 1,2-dichloroethane, to induce the key oxidative cyclization. As anticipated, this

(8) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569−10582.

operation produced a mixture of the isomeric tetrahydroindolones **27** and **28** in 53 and 19% yield, respectively. In accord with the literature,[8] reaction of the major isomer with tributyltin hydride and AIBN in boiling benzene gave the desired tetracyclic structure **29** in 78% yield. Finally, reduction with $LiAlH_4$ completed the synthesis of (±)-α-lycorane **30** (mp 152−155 °C from CH_2Cl_2/hexane; lit.[8] mp 155−156 °C). This expeditious synthesis is, as far as we are aware, the shortest route to this substance.

(9) For a review of Amaryllidaceae alkaloids, see: Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, pp 323−424.

In conclusion, the present routes to the erythrina ring system and to (±)-α-lycorane underscore the synthetic potential of this new xanthate-mediated tin-free cyclization. The essentially neutral, mild reaction conditions are in principle compatible with a wide variety of functional groups. Extension to more complex structures is currently under investigation.

Supporting Information Available: Experimental details and full spectral data for the main new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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