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# An Easy Entry into Berbane and Alloyoyohimbane Alkaloids via a 6-*exo* Radical Cyclization

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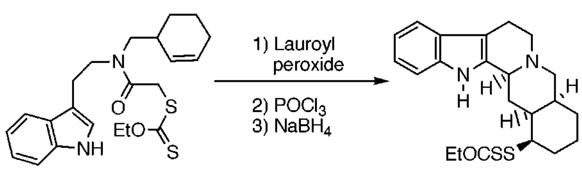
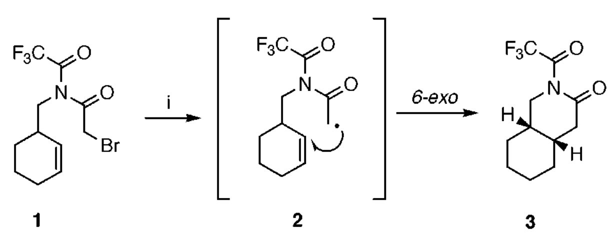
## ABSTRACT




**The pharmacologically important tetracyclic berbane and pentacyclic alloyohimbane structures were prepared efficiently in four steps including a stereoselective 6-*exo* radical cyclization using xanthates as the radical source.**

The development of synthetic methods[1] for constructing the tetracyclic protoberberine-type and the pentacyclic yohimbine-type alkaloids has attracted much attention for several decades because of their important pharmacological properties.[1a,2] The stereoselective 6-*exo*-radical cyclization reported by Stork and Mah[3] a few years ago was of special importance to our synthetic strategy, since this reaction would afford the required *cis*-fused piperidone system (Scheme 1).

**Scheme 1**[a]




[a] Conditions: *n*-Bu$_3$SnH (or Ph$_3$GeH), AIBN, benzene, reflux.

Under the reported tin-mediated reaction conditions, the *cis*-fused piperidone was formed along with a considerable amount of the prematurely reduced, uncyclized product. The proportion of this side product could be decreased by using the slower reducing triphenylgermanium hydride.

Over the past several years, we have shown that xanthates behave as clean and efficient sources of free radicals.[4] The

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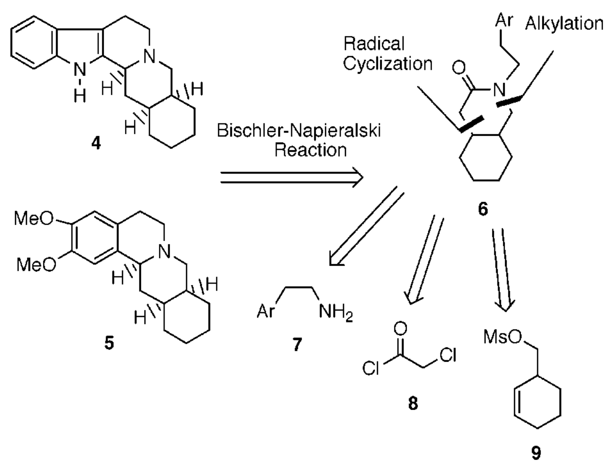
reactions can be conducted in the absence of heavy metals under tin-free conditions, and the premature reduction of the intermediate radicals is easily avoided: intermolecular additions to unactivated olefins and difficult cyclizations can often be readily accomplished.

Building upon these observations, we envisioned a rapid entry into alloyohimbane **4** and berbane **5** systems based on a Stork-like cyclization as the key step and using xanthates as the radical source. Thus, the alloyohimbane system could be assembled in a short sequence by a *6-exo*-radical cyclization followed by Bischler–Napieralski cyclization,[5] in only four steps, from easily available starting materials (Scheme 2).

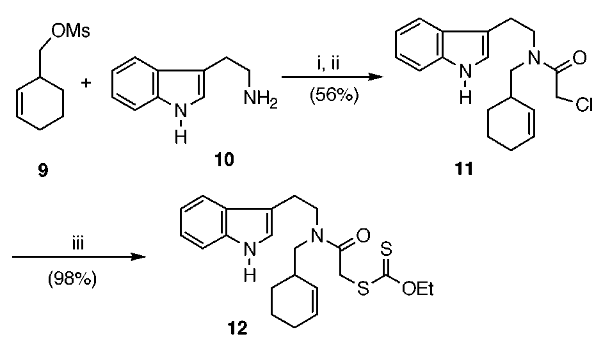
**Scheme 2.** Retrosynthetic Analysis




The required xanthate **12** was assembled by alkylation of tryptamine **10** with the known mesylate **9**,[6] and the resulting secondary amine was trapped with chloroacetyl chloride to afford chloroacetamide **11** in 56% yield. Subsequent substitution of the chlorine atom by the xanthate group was accomplished in nearly quantitative yield using the commercially available xanthate salt (Scheme 3).

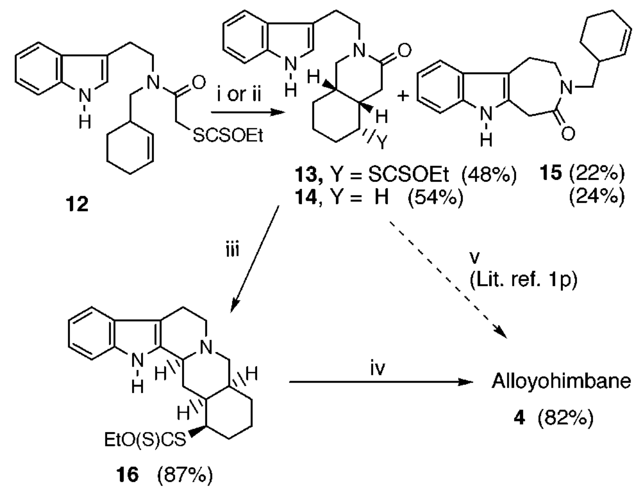
When xanthate **12** was heated in 1,2-dichloroethane in the presence of a small amount of lauroyl peroxide, two major products were formed: the desired product, **13**, derived from *6-exo* cyclization, in 48% yield, and azepinone **15**, derived from competitive ring closure onto the C-2 of the indole system, in 22% yield (Scheme 4).[7] The stereochemistry of xanthate **13** was confirmed by COSY and NOESY NMR experiments.

**Scheme 3**[a]




[a] Conditions: (i) $K_2CO_3$, KI, acetonitrile, reflux, 72 h; (ii) chloroacetyl chloride, $Et_3N$, $CH_2Cl_2$, rt; (iii) EtOC(S)SK, MeOH, rt, 2 h.

**Scheme 4**[a]




[a] Conditions: (i) 1,2-dichloroethane, lauroyl peroxide (20%), reflux, 6 h; (ii) 2-propanol, lauroyl peroxide (120%), reflux, 4 h; (iii) $POCl_3$, benzene, reflux, 2 h; then, $NaBH_4$, ethanol, rt, 0.5 h; (iv) *n*-$Bu_3SnH$, AIBN, benzene; (v) $POCl_3$, then platinum oxide/$H_2$.

The formation of the seven-membered ring seems to occur by a direct ring closure onto the free 2-position of the indole nucleus, rather than through an initial attack at the 3-position to give a spiro intermediate, which then rearranges to azepinone **15**.[7b] Such a rearrangement could in principle give rise to two regioisomers, depending on which bond in the spiro intermediate migrates to the 2-position. None of the other possible isomer was observed. Moreover, in another ancillary study, we have found that a bulky substituent on the indole nitrogen, which hinders position 2 but not position 3 of the indole ring, causes a significant decrease in the proportion of azepinone.

Exposure of compound **13** to the action of phosphoryl oxychloride followed by reduction of the intermediate iminium ion with sodium borohydride resulted in the formation of pentacyclic derivative **16**, possessing the complete alloyohimbane skeleton in 87% yield. Indeed, reductive removal of the xanthate group with tributyltin hydride gave alloyohimbane **4** in 82% yield. Its spectroscopic

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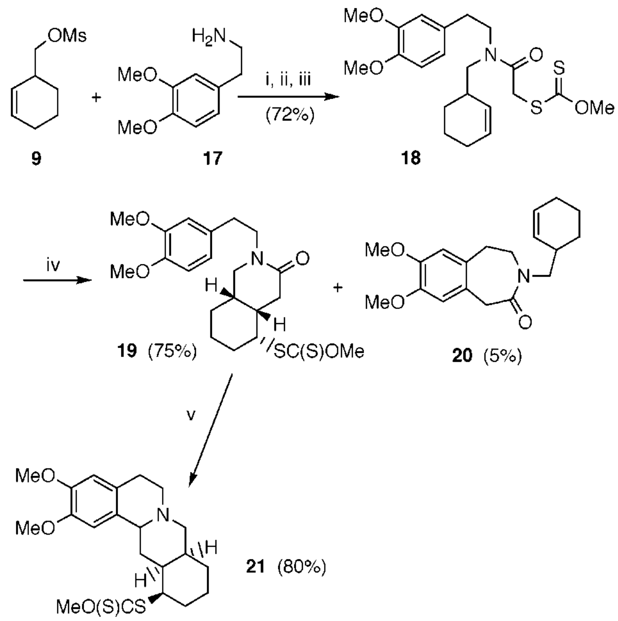
(3) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.
(4) (a) For an overview of this work, see: Quiclet-Sire, B.; Zard, S. Z. *J. Chin. Chem. Soc.* **1999**, *46*, 139. (b) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.
(5) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, p 74.
(6) Walton, J. C.*J. Chem. Soc., Perkin Trans. 2* **1986**, 1641.
(7) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731. (b) We thank a referee for raising this point.

**Scheme 5**[a]




[a] Conditions: (i) $K_2CO_3$, KI, acetonitrile, reflux, 72 h; (ii) chloroacetyl chloride, $Et_3N$, $CH_2Cl_2$, rt; (iii) MeOC(S)SK, MeOH, rt, 2 h; (iv) 1,2-dichloroethane, lauroyl peroxide (20%), reflux, 6 h; (v) $POCl_3$, benzene, reflux, 2 h; then $NaBH_4$, ethanol, rt, 0.5 h.

properties were identical to those published previously[1b] (Scheme 4).

The direct formation of the known piperidone **14**[1p] in 54% yield by simply performing the ring closure in 2-propanol as the solvent, and using stoichiometric amounts of peroxide, illustrates an interesting and important aspect of xanthate technology. 2-Propanol is the source of the hydrogen atom in this case (Scheme 4).[8] Since compound **14** has already been converted into alloyohimbane **4** by a reductive Bishler−Napieralski sequence,[1p] this sequence is one step shorter than through compound **16**. The presence of the xanthate group in intermediate **16** provides however a convenient handle for accessing analogues of potential medicinal interest by exploiting the vast chemistry of sulfur.

This approach was easily extended to the berbane-type alkaloids. Thus, amine **17** was alkylated with mesylate **9** and the resulting secondary amine was acylated with chloroacetyl chloride to give the corresponding chloroacetamide, which was finally converted into xanthate **18** in good overall yield (Scheme 5).

Cyclization of xanthate **18** under the same radical conditions into piperidone **19** proceeded efficiently: only a small amount of azepinone **20** was observed. Finally, exposure of piperidone **19** to the reductive Bischler−Napieralski cyclization furnished the berbane derivative **21** in high yield (Scheme 5).

The present, expeditious approach to the alloyohimbane and berbane skeleton underscores the synthetic potential of the xanthate transfer technology. The use of more functionalized homoallylamide precursors should allow access to the more complex members of this family of alkaloids (e.g., reserpine). Work along these lines is underway.

**Note Added after ASAP:** There was an error in the title of the version posted ASAP August 31, 2001; the corrected version was posted September 17, 2001.

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

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