A Short Synthesis of (±)-13-Deoxyserratine**

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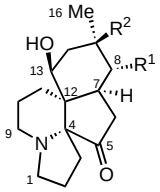
Dedicated to Professor Pierre Potier

Lycopodium alkaloids[1] exhibit a fascinating structural complexity and have emerged as challenging synthetic targets in recent years. In the serratinane subgroup, with the exception of (±)-serratinine (**1a**)[2] and the corresponding 8-deoxy derivative,[3] both of which have been synthesized previously by a long and low-yielding route, not much attention has been paid to other alkaloids of this structural family. So far, only one approach to serratine (**1b**)[1, 4] has been reported by Livinghouse and Luedtke.[5]



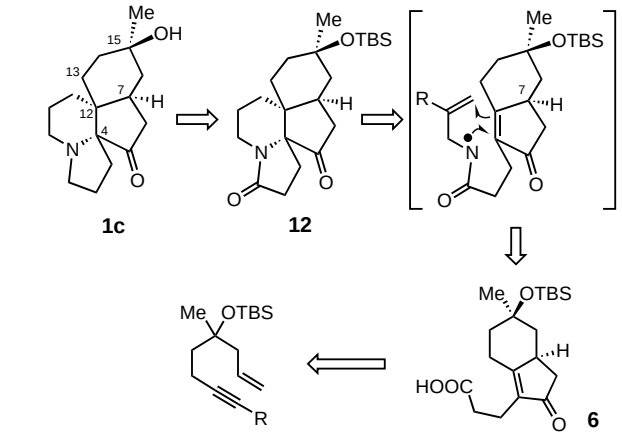
1a: R^1=OH, R^2=H

1b: R^1=H, R^2=OH

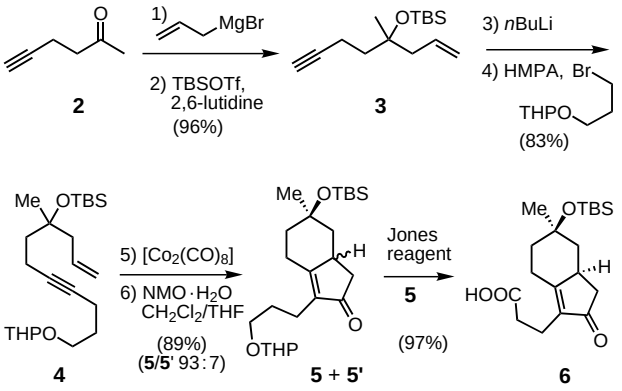
We recently developed several processes for generating various types of nitrogen-centered radicals, which can be captured by internal olefins to give a variety of nitrogen-containing heterocycles.[6, 7, 8] Our interest in the synthesis of (±)-serratine (**1b**) was therefore stimulated by the possibility that the indolizidine framework could be introduced by using a cascade of radical cyclizations starting with an amidyl radical. We report herein the successful implementation of this strategy to the synthesis of (±)-13-deoxyserratine (**1c**).

As shown in Scheme 1, our synthetic plan hinges on two key steps that allow the stereocontrolled introduction of the four stereogenic centers at C4, C7, C12, and C15. A diastereoselective Pauson–Khand[9] reaction would allow easy access to the key bicyclo[4.3.0]nonenone intermediate **6**. The concave shape of this molecule will then control the stereochemistry in the cascade sequence to give **1c**.

The synthesis started with the alkylation of 5-hexyn-2-one (**2**) allylmagnesium bromide. The resulting tertiary alcohol was treated with TBSOTf to afford the protected alcohol **3** in 96% yield. Subsequent deprotonation with *n*BuLi followed by alkylation with THP-protected 3-bromopropanol furnished precursor **4** for the Pauson–Khand reaction. Treatment of the [alkyne–$Co_2(CO)_6$] complex derived from **4** with NMO·H_2O[10] resulted in a rapid conversion into the desired bicyclo[4.3.0]nonenone as a 93:7 mixture of diastereoisomers **5** and **5′** in 89% yield. The major isomer **5** was submitted to Jones oxidation to give the key intermediate acid **6** (64% from 2) (Scheme 2).



Scheme 1. Retrosynthetic analysis of (±)-13-deoxyserratine (**1c**).



Scheme 2. Synthesis of key intermediate acid **6**. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, HMPA = hexamethyl phosphoramide, THP = tetrahydropyran, NMO = 4-methylmorpholine *N*-oxide.

The high diastereoselectivity (93:7)[11] observed in the Pauson–Khand reaction may be explained by considering the relative stability of the intermediates that lead to **5** and **5′**.[12] The preferred conformers of the [alkyne–$Co_2(CO)_6$] complex can be regarded as **A** and **B** in which the TBSO group lies in a pseudo-equatorial position. A weaker repulsion between H7 and the pseudo-axial methyl group in **A** than that between H6 and the axial-like methyl group in **B** favors cyclization through the conformer **A** (Scheme 3).

O-Benzoyl-*N*-allylhydroxamine **7** was chosen as a suitable precursor for the crucial radical cyclization, since the addition of tributylstannyl radical to the oxygen atom of the benzoate group would induce cleavage of the weak N–O bond and formation of the desired radical **8** (Scheme 5).[7] Successive treatment of **6** with isobutylchloroformate, *N*-allylhydroxylamine,[13] and benzoyl chloride led to the precursor **7** in 78% yield; the intermediates were not isolated (Scheme 4). We

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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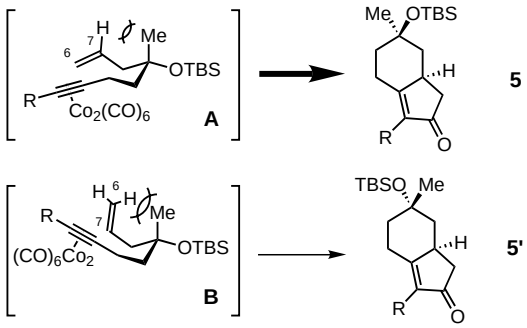
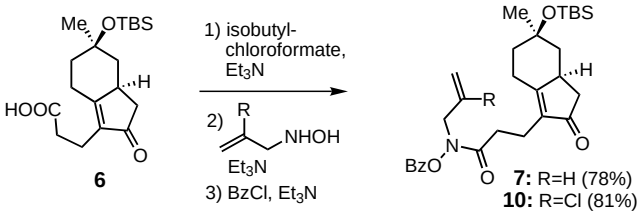
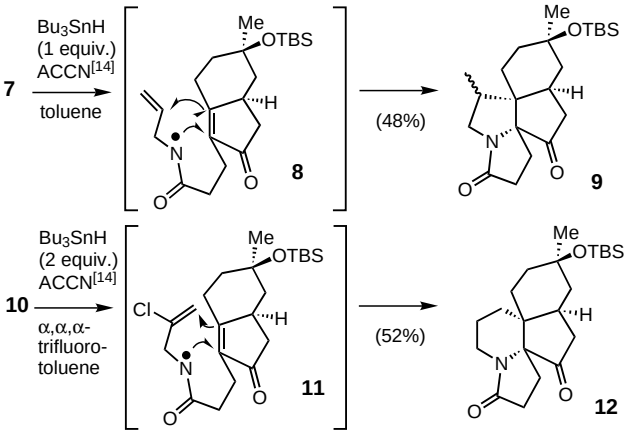


Scheme 3. Conformations of the intermediates in the Pauson–Khand reaction.



Scheme 4. Synthesis of radical precursors **7** and **10**.

were delighted that a cyclization cascade occurred upon slow addition of Bu_3SnH and ACCN[14] to a refluxing solution of **7** in toluene. However, the product was identified as pyrrolidine **9**, which resulted from a 5-*exo*/5-*exo* cyclization mode (48%), despite our expectation that 5-*exo*/6-*endo* mode should have been favored by considering steric factors in the intermediate carbon-centered radical (Scheme 5).

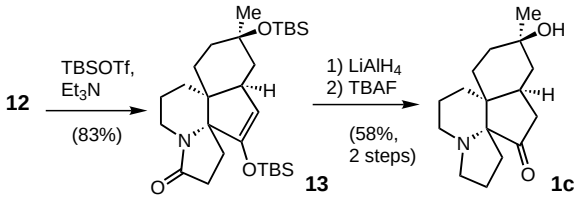


Scheme 5. Synthesis of pyrrolidine **9** and indolizidine **12**.

Clearly, as is usually the case with radical cyclizations, closure of the intermediate amidyl radical occurred from the least hindered convex face of the molecule, thus fixing the relative stereochemistry of **9**. Even though the 13-deoxyserratine skeleton could not be constructed by using **7** as a precursor, amidyl radical **8** proved to be a powerful intermediate since two bonds and two adjacent quaternary centers were created in a stereoselective manner.

To overcome the formation of the second five-membered ring, a small structural modification was performed, inspired by the earlier work of Knapp et al and Smith and coworkers.[15] A chlorine atom was thus placed on the olefinic trap to discourage a 5-*exo* closure without hindering the desired 6-*endo* mode. The new radical precursor **10**, obtained by using *N*-(2-chloroallyl)hydroxylamine instead of *N*-allylhydroxylamine (81%) (Scheme 4), was therefore treated with Bu_3SnH (2 equiv) in α,α,α-trifluorotoluene.[16]

A second equivalent of Bu_3SnH was necessary to reductively remove the chlorine atom in situ after the cascade process. As expected, indolizidine **12**,[17] which contains the correct skeleton of compound **1c**, was isolated as the major product (52%) (Scheme 5). Finally, protection of **12** as the *tert*-butyldimethylsilyl enol ether followed by reduction of the lactam moiety with $LiAlH_4$[18] and deprotection of the alcohol with TBAF completed the synthesis of (±)-13-deoxyserratine (**1c**) in 48% yield over the last three steps (Scheme 6).



Scheme 6. Synthesis of 13-deoxyserratine (**1c**).

In summary, we have in hand a concise (10 steps) and efficient (12% overall yield) synthesis of (±)-13-deoxyserratine (**1c**). The use of an amidyl radical intermediate allowed us to create the two adjacent quaternary centers at C4 and C12 in *one* step, with the correct relative stereochemistry. The presence of these centers in the serratine skeleton has considerably hampered previous approaches. Moreover, the radical cascade can be directed at will to produce either an indolizidine or a pyrrolizidine framework, both of which are found in a large number of alkaloids.

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Synthesis and Characterization of a Digermanium Analogue of an Alkyne**

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The heavier Group 14 element analogues of alkynes, in which one or both carbon atoms of the triple bond are replaced by silicon, germanium, tin, or lead, are a unique compound class that has attracted considerable discussion and interest.[1, 2] Over the last decade, a rapidly growing series of computational papers[3–26] have predicted a *trans*-bent structure[27] for heavier-element analogues that carry organic substituents.[16–26] With the exception of the lead compound 2,6-Trip$_2$H$_3$C$_6$PbPbC$_6$H$_3$-2,6-Trip$_2$ (Trip = C$_6$H$_2$-2,4,6-*i*Pr$_3$),[28] which has a planar, *trans*-bent CPbPbC core (Pb-Pb-C = 94.26(4)° and a long, essentially single Pb–Pb bond (Pb–Pb = 3.1881(1) Å),[14, 28] no stable Group 14–Group 14 heavier analogues of alkynes have been described. Various experiments[29–34] have indicated the existence of alkyne-like transient species but none of these has been isolated and no structural details are available. The synthesis, structural characterization, and reaction chemistry of such compounds would provide valuable bonding information, especially in view of the current debate on the nature of multiple bonds between heavier main group elements.[35–39] An additional feature of interest is that these potentially triple-bonded systems have been described as "a final challenge" in the area of main-group multiple bonding.[2] The isolation and structural characterization of a germanium alkyne analogue 2,6-Dipp$_2$H$_3$C$_6$GeGeC$_6$H$_3$-2,6-Dipp$_2$ (**1**; Dipp = C$_6$H$_3$-2,6-*i*Pr$_2$) are now described.

2,6-Dipp$_2$H$_3$C$_6$GeGeC$_6$H$_3$-2,6-Dipp$_2$ **1**

Compound **1** was synthesized by the reaction of Ge(Cl)C$_6$H$_3$-2,6-Dipp$_2$ with potassium in THF or benzene. It was isolated as orange-red crystals which were characterized by ^{1}H and ^{13}C NMR, IR, and UV/Vis spectroscopy and by single-crystal X-ray crystallography.[40] The UV/Vis spectrum displays three relatively intense absorptions at 280, 371, and 501 nm which may be the result of $\pi-\pi^*$ and $n-\pi^*$ transitions. The X-ray structure revealed a centrosymmetric molecule (Figure 1) that has a planar *trans*-bent C1-Ge1-Ge1A-C1A core array as required by symmetry. The

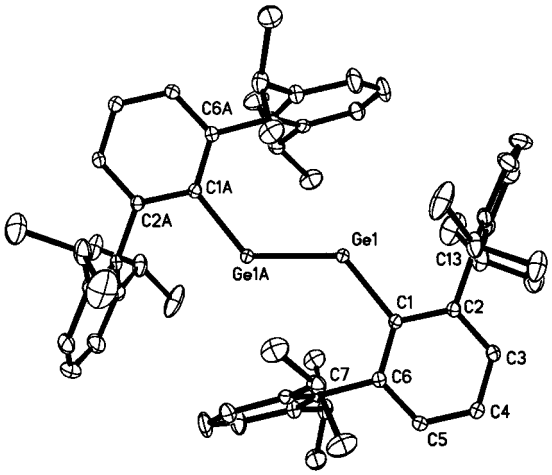

Figure 1. ORTEP plot of **1**, thermal ellipsoids set at 30% probability, H atoms are not shown. Selected bond lengths [Å] and angles [°]. Ge1-Ge1A 2.2850(6), Ge1-C1 1.996(3), C1-C2 1.412(4), C1-C6 1.408(4); Ge1A-Ge1-C1 128.67(8), Ge1-C1-C2 116.9(2), Ge1-C1-C6 124.6(2), C1-C2-C6 118.5(3).

Ge1–Ge1A and Ge1–C1 bond lengths are 2.2850(6) and 1.996(3) Å, and the Ge1-Ge1A-C1A angle is 128.67(8)°. The central aryl ring of the terphenyl ligand is essentially coplanar (torsion angle 0.4°) with the C1-Ge1-Ge1A-C1A array, and the planes of the flanking aryl rings are oriented at approximately 82° with respect to the central aryl ring. The Ge1-C1-C2 and Ge1-C1-C6 angles differ by 7.7° and there is a 4.0° angle between the Ge1-C1 bond and the C1···C4 vector. A cyclic voltammogram of the compound in THF solution displays a reduction wave at −1.38 V and an oxidation at +0.7 V versus the saturated calomel electrode (SCE).

Compound **1** is a stable digermanium analogue of an alkyne. The Ge–Ge distance is considerably shorter than a normal Ge–Ge single bond (ca. 2.44 Å)[41] and indicates the presence of considerable multiple-bonding character. The

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