Tandem Radical Cyclizations Initiated with α-Carbonyl Radicals: First Total Synthesis of (+)-Paniculatine

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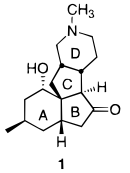
Paniculatine (**1**), magellanine (**2**), and magellaninone (**3**), isolated from club mosses paniculatum and magellanicum, belong to a subclass of *Lycopodium* alkaloids.[1−3] These compounds, possessing unique tetracyclic frameworks with 5−7 stereogenic centers, have been challenging targets for total synthesis since their isolation. Several promising synthetic approaches toward construction of the tetracyclic skeleton have been reported.[4] In 1994, total syntheses of magellanine (**2**) and magellaninone (**3**) were accomplished independently by Overman via a Prins pinacol rearrangement[5] and by Paquette via a tandem Michael−Michael addition.[6] However, to date, the total synthesis of paniculatine (**1**) has not been reported.



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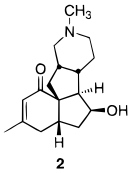

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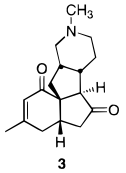
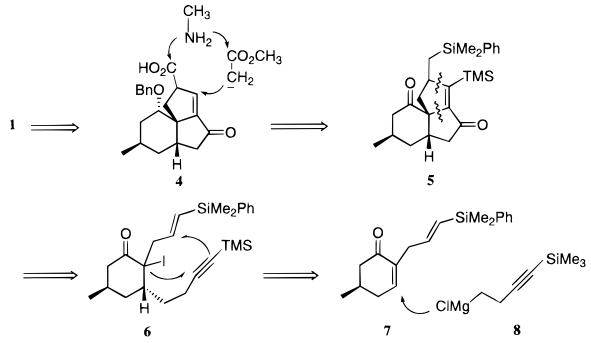


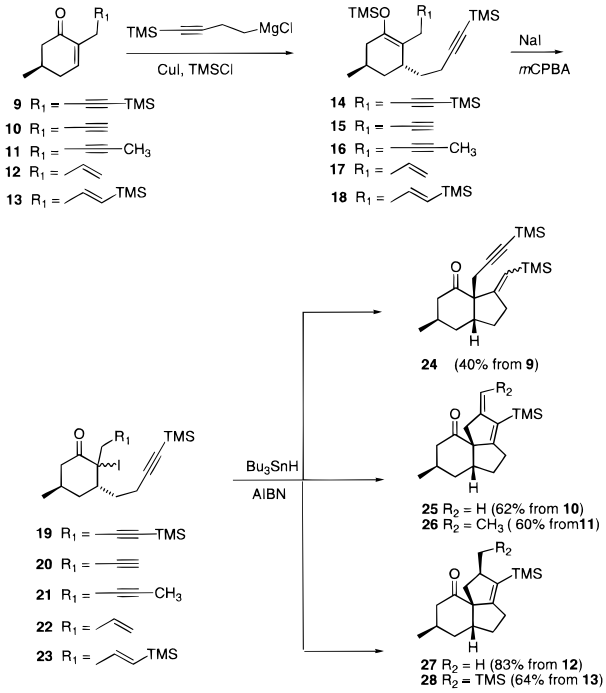
3

In our previous work, we have demonstated that α-carbonyl radical cyclization reactions can serve efficiently as key steps in total syntheses of several natural products, including (±)-modhephene, (−)-dendrobine and (−)-5-oxosilphiperfol-6-ene.[7] As an extension of our work in this area, we herein report the tandem radical cyclizations[8] initiated with α-carbonyl radicals as well as their application to the first total synthesis of (+)-paniculatine (**1**). The retrosynthetic analysis is shown in Scheme 1. α-Iodo ketone **6** could be prepared from enone **7**[9] by the conjugate addition and iodination method developed in our laboratories.[7] Grignard reagent **8** would add to enone **7** from the α-face with stereoelectronic control.[10] This conjugate addition would establish the desired stereochemistry at C(3) in **6**. Radical generated from iodo ketone **6** would undergo a tandem radical cyclization reaction to produce the angularly fused tricyclic ketone **5**. Subsequent modification of **5**, including allylic oxidation and desilylation, should furnish enone **4**. Furthermore, we anticipate that 1,4-addition of an acetate unit to the enone moiety in **4** would occur from the less hindered convex α-face of the BC ring and would thus provide a handle to control the stereochemistry of the center at the CD ring juncture. Introduction of a methylamine unit followed by functional group modification would then afford (+)-paniculatine (**1**).

Scheme 1



Scheme 2



Our work began with a systematic investigation on the feasibility of the α-carbonyl radical-initiated tandem cyclization. CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride (**8**) to chiral enone **9**,[9] followed by trapping the resulting enolate with cholorotrimethylsilane (TMSCl), gave trimethylsilyl enol ether **14**. Without purification, crude **14** was treated with a mixture of NaI and *m*-CPBA to afford the unstable iodo ketone **19**. Treatment of crude **19** with a benzene solution of tributyltin hydride and AIBN, introduced with a syringe pump at reflux, failed to give the expected tandem radical cyclization product. Instead, **24** was produced exclusively (Scheme 2). The radical cyclization apparently proceeded only to the first stage. The expected ensuing radical cyclization failed to occur, presumably because of two bulky trimethylsilyl groups on both side chains in **19**. To minimize this steric hindrance, we decided to

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(9) Compounds **7** and **9**−**13** were prepared from (*R*)-5-methylcyclohexenone according to Baraldi's method: Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G.; Zanirato, V. *Tetrahedron Lett* **1984**, *25*, 4291. (*R*)-5-Methylcyclohexenone was synthesized from (*R*)-pulegone by Caine's method: Caine, D.; Procter, K.; Cassell, A. *J. Org. Chem.* **1984**, *49*, 2647.
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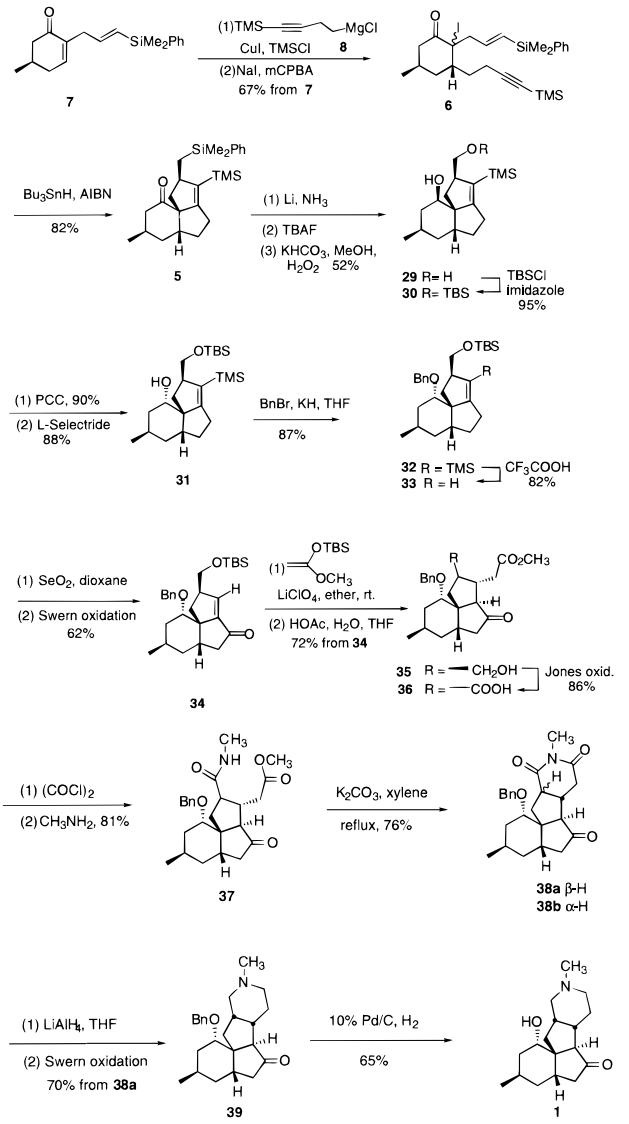
use enones **10**−**12**, having a side chain without a bulky trimethylsilyl group, or enone **13**, with a *E* double bond as starting materials. With the same reaction sequence, iodo ketones **20**−**23** were prepared from enones **10**−**13** via intermediates **15**−**18** (Scheme 2). To our delight, when **20**−**23** were treated with tributyltin hydride and AIBN in benzene via syringe pump addition, tandem radical cyclizations indeed occurred to give the angularly fused tricyclic ketones **25**−**28**. The stereochemical outcome of the tandem radical cyclization was clarified by the X-ray analysis of the crystalline product **28**.[11] We found that all stereogenic centers of **28** are in the same configuration as those of paniculatine (**1**), except that the trimethylsilylmethyl group on the C ring has the wrong stereochemistry, which can, in principle, be corrected during an appropriate stage of the synthesis.

Having established an efficient method to construct the angularly fused tricyclic system, we then proceeded with total synthesis of **1**. Chiral enantiopure enone **7**,[9] containing an *E*-olefinic side chain with a phenyldimethylsilyl group serving as a masked primary alcohol, was chosen as the starting material.[12] CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride (**8**) to **7**, followed by trapping of the resulting enolate with TMSCl and iodination with NaI/*m*-CPBA,[7] yielded iodo ketone **6** (67%) (Scheme 3). When **6** was treated with tributyltin hydride and AIBN in benzene via syringe pump addition, tandem radical cyclization occurred smoothly to afford tricyclic ketone **5** (82%). The phenyldimethylsilyl group in **5** was subsequently converted to a primary alcohol according to Taber's method.[12] Thus, Li/NH_3 reduction of **5**, followed by treatment with Bu_4NF and H_2O_2/$KHCO_3$, gave diol **29** (52%).[12] Treatment of **29** with *tert*-butyldimethylsilyl chloride and imidazole to protect the primary alcohol group furnished **30** (95%). At this stage, in order to invert the β-OH to the α-configuration, **30** was oxidized with pyridinium chlorochromate and then reduced with L-Selectride to give **31** (88% from **30**). Protection of the secondary alcohol in **31** by treatment with KH and benzyl bromide afforded **32** (87%). Desilylation of **32** with CF_3COOH furnished intermediate **33** (82%). Allylic oxidation of **33** with SeO_2, followed by Swern oxidation, afforded enone **34** (62%). Conjugate addition of *tert*-butyldimethylsilyl methyl ketene acetal to **34**,[13] followed by removal of the *tert*-butyldimethylsilyl group on the primary alcohol, yielded intermediate **35** (72%). The 1,4-addition occurred from the sterically less hindered α-face, as expected. Jones oxidation of **35** gave carboxylic acid **36** (86%). At this stage, the stereochemistry of the carboxylic acid group in **36** was not determined. Treatment of **36** with oxalyl choride, followed by addition of methylamine, afforded amide **37** (81%). Heating **37** in xylene in the presence of K_2CO_3 produced imides **38a** and **38b** as two diastereomers (**38a**:**38b** = 6:1, 76%). The major isomer **38a** was separated. Reduction of the imide and the ketone moieties of **38a** with $LiAlH_4$, followed by Swern oxidation of the resulting secondary alcohol in ring B, gave **39** (70%). Finally, removal of the benzyl group of **39** by hydrogenolysis using 10% Pd-on-carbon as a catalyst afforded enantiomerically pure (+)-paniculatine (**1**) (65%). All spectral data of **1** agree satisfactorily with those reported.[1] Furthermore, the HBr salt of **1** was prepared and subjected to a single-crystal X-ray analysis,[11] which unambiguously confirms the structure and stereochemistry of the synthetic product **1**. The optical rotation of this material was determined to be $[\alpha]_D = +66$.[14]

Scheme 3



In summary, we have developed an efficient α-carbonyl radical-initiated tandem cyclization reaction for synthesis of the angularly fused tricyclic ketones. Application of this methodology to the first total synthesis of (+)-paniculatine (**1**) has been achieved. We believe that this tandem radical cyclization will also be an efficient methodology for the total synthesis of other angularly fused polycyclic natural products.

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Supporting Information Available: Experimental procedures and spectral data including molecular drawings and X-ray data of **28** and HBr salt of **1**, and ^1H and ^{13}C NMR spectra of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The molecular drawings and the X-ray data of **28** and the HBr salt of **1** are presented in the Supporting Information.

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(14) In ref 1, the optical rotation of (+)-paniculatine was not reported.