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A Biomimetic Synthesis of the Pauciflorine A and B Skeleton

Martin E. Kuehne* and Yun-Long Li

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

mkuehne@zoo.umv.edu

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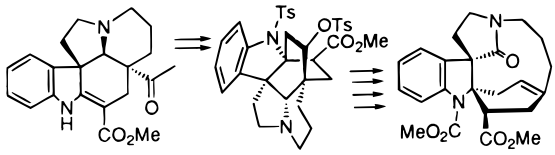
ABSTRACT

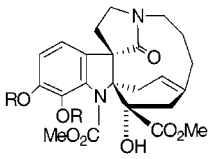


Racemic minovincine (3), following cyclization, reduction, O-tosylation, fragmentation, and carbamate formation, provided the deoxypauciflorine 12.

The pauciflorines A and B (**1** and **2**, Figure 1) were isolated from *Kopsia pauciflora* Hook. f. (Apocyanaceae) in 1996.[1] Their intriguing biological activity of inhibition of melanin biosynthesis in melanoma cells, without cytotoxicity, and their biogenetically unusual structures make these compounds interesting synthetic targets. The relatively novel briged bis-spiroindoline lactam structure of the pauciflorines **1** and **2**, found previously only in kopsijasminilam,[2] includes the additional synthetic challenge of a bridgehead double bond in a ten-membered ring, which also contains two trigonal atoms of a lactam function.

Our approach to the synthesis of this strained pentacyclic ring system was based on its presumed biogenetic derivation from an aspidosperma alkaloid precursor. Thus, racemic minovincine (**3**, 19-oxovincadifformine, Scheme 1), an alkaloid that we had obtained previously by three alternative synthetic routes[3,4] and its cyclization in acid,[5] provided hexacyclic ketone **4**. This compound was envisioned as the key precursor for a fragmentation reaction that would give the pentacyclic skeleton of the pauciflorines, including the bridgehead double bond.

Reduction of hexacyclic ketone **4** with DIBALH at −78 °C provided a 1:4 ratio of two epimeric alcohols **5** and **6**. The alcohols could be chromatographically separated and their stereochemistry defined by an NOE spectrum of epimer **6**, which showed correlations of the hydrogens adjacent to the *tert*-amine (C-3) and the hydroxyl (C-19) groups, as well as a C-3 to C-9 hydrogen correlation. A Swern oxidation of the C-19 *R** hydroxy epimer **5** allowed regeneration of the ketone **4**.



1 pauciflorine A, R = CH_2
2 pauciflorine B, R = Me

Figure 1.

(1) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765.
(2) Ruangrungsi, N.; Likhitwitayawuid, K.; Jongbunprasert, V.; Ponglux, D.; Aimi, N.; Ogata, K.; Yasuoka, M.; Haginiwa, J.; Sakai, S. *Tetrahedron Lett.* **1987**, *28*, 3679.
(3) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707.
(4) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3715.
(5) Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468.
(6) No reaction of **12** with LDA or KH or KHMDS, followed by 2-phenylsulfonyl-3-phenyloxaziridine,[7] or with NaOMe−MeOH and O_2. No reaction of **11** with 2- phenylsulfonyl-3-phenyloxaziridine.
(7) (a) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203. (b) Davis, F. A.; Sherppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (c) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 912.

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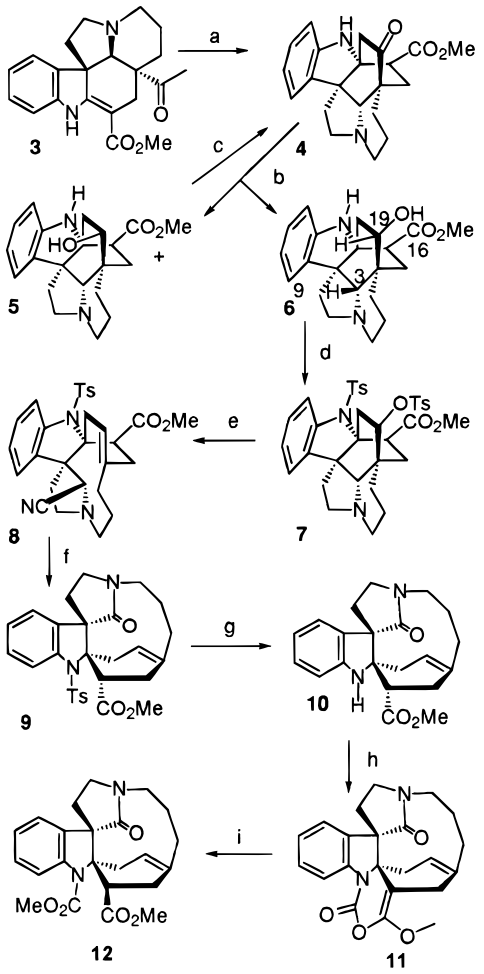
Scheme 1



a: HCl-MeOH, reflux, 44% (85% based on recovery of **4**);
b: DIBALH, THF, -78 °C, **5** : **6** =1 : 4, 72%; Super Hydride, THF, - 78 °C, **5**: **6** = 15 : 1, 85%; c: Swern oxid., 70%; d: Ts_2O, pyd., rt, 89%; e: KCN, EtOH-H_2O, refl., 89%; f: ^tBuOK, THF, O_2, rt, 90%; g: Na naphthalenide, DME, -78 °C, 95%; h: triphosgene, pyr., CH_2Cl_2, 0 °C, MeOH, pyr., 91%; i: NaOMe, MeOH, refl., 92%.

Assignment of the relative stereochemistry of the hydroxyl groups in the alcohols **5** and **6** was also based on the results of subsequent ring fragmentation of the latter.

A reaction of the aminoalcohol **6** with tosyl anhydride in pyridine gave the sulfonamide tosylate **7**. Since elimination of its tosylate function was expected to lead to the stereoelectronically favored desired ring fragmentation, with formation of a hydrolytically sensitive imonium salt, the reaction was carried out in the presence of cyanide. The resulting nitrile **8** was obtained in 89% yield. Oxidation of this α-aminonitrile with potassium *tert*-butoxide and oxygen then furnished the pentacyclic lactam **9** in 90% yield.

The *N*-tosyl substituent of the fragmentation product **9** could be removed with sodium amalgam and NaH_2PO_4, or with sodium naphthalenide. It was also lost in variable yields on formation of the ester enolate with LDA and subsequent aqueous workup, perhaps assisted by bridging to the ester enolate oxygen (see below).

Formation of a carbamate from amine **10** did not occur as easily as the derivatization of amine **4** (methyl chlorocarbonate and K_2CO_3) but required a reaction with triphosgene, followed by treatment with methanol. At 0 °C cyclic ketene acetal−acylal **11** was obtained. Its reaction with sodium methoxide in refluxing methanol provided carbamate ester **12** (demethoxydeoxypauciflorine B).

While oxidation of the enolate anion of the ester **12** or oxidation of the enol derivative **11** was anticipated to provide the 16-α-hydroxy function of the pauciflorines, such an introduction of the hydroxyl group proved to be problematic.[6]

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Supporting Information Available: Experimental procedures, spectroscopic, and analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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