Communications

A General, Stereocontrolled Route to the Geissoschizine Family of Alkaloids. Concise Synthesis of the Apogeissoschizine Skeleton

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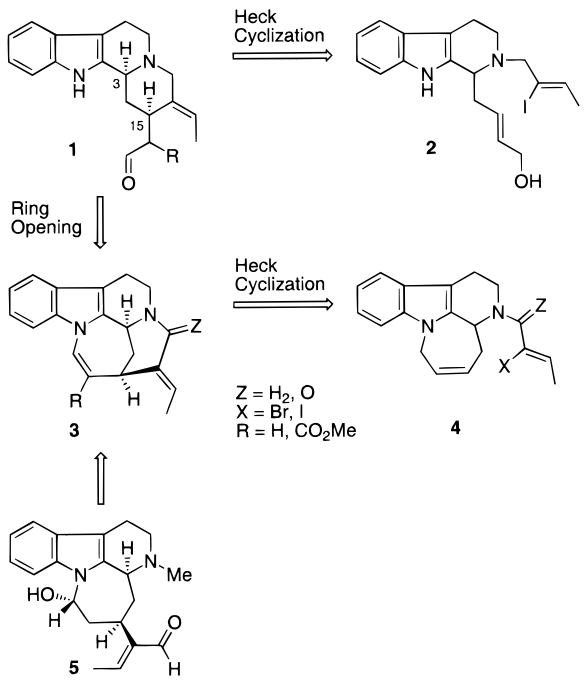
In the course of our synthetic studies on the geissoschizine skeleton (**1**), we found that the Heck cyclization of precursor **2** proceeded with good selectivity (ca. 6:1), but only after extensive examination and optimization of reaction parameters.[1] Although the desired diastereomer was obtained in synthetically useful yield (ca. 50%), the lack of complete diastereocontrol prompted us to devise a strategy that circumvented the stereoselectivity issue altogether. Thus, we designed a precursor that upon cyclization would produce a bridged bicyclic system (**3**), thereby ensuring the cis relationship between hydrogen atoms at C-3 and C-15 (biogenetic numbering, Scheme 1). The pentacyclic framework of **3** is found in apogeissoschizine (**3**, Z = H_2, R = CO_2-Me)[2] and has been encountered in intermediates en route to geissoschizine in previous syntheses.[3,4] Furthermore, structure **3** has the basic carbon skeleton of akagerine (**5**) and some related alkaloids.[5,6] The seven-membered ring in the desired cyclization precursor, **4**, was expected to be formed by ring-closing metathesis[7] of a 1,9-diallylated tetrahydro-β-carboline derivative.

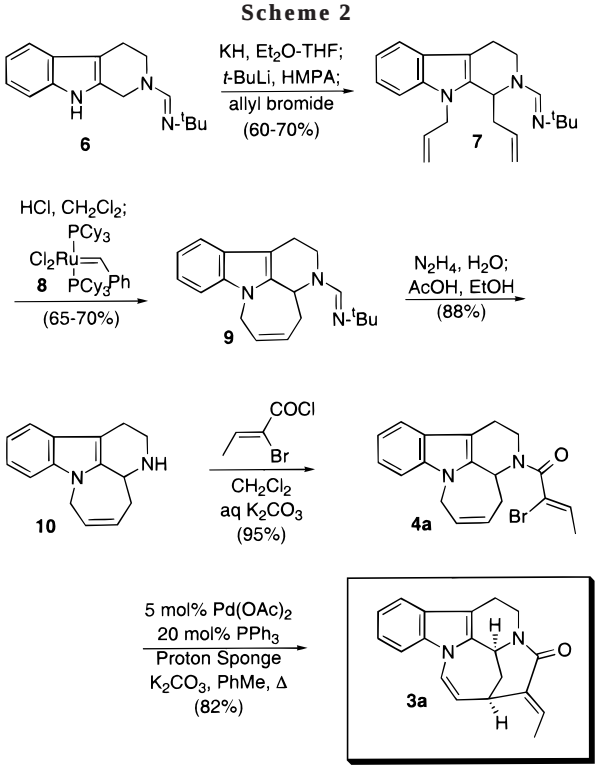
Our first-generation synthesis of the cyclization precursor is outlined in Scheme 2. Tetrahydro-β-carboline *tert*-butylformamidine (**6**) was diallylated using the one-pot procedure developed by Meyers.[8] Although compound **7** did not undergo ring-closing metathesis with Grubbs' catalyst (**8**) under the standard conditions,[7] ostensibly due to the presence of the highly basic formamidine unit, its hydrochloride salt did react in refluxing methylene chloride solution.[7b] The catalyst activity diminished quickly under these conditions, however, which necessitated syringe-pump addition of the catalyst. Hydrazinolysis[8] of the resulting intermediate (**9**) afforded secondary amine **10**. Acylation of **10** with α-bromocrotonoyl chloride[9] gave the cyclization precursor, **4a**.

In contrast to our previous work, in which β-iodoallylic side chains were utilized,[1,10] Jeffery's conditions[11] were found

Scheme 1



Scheme 2



(1) Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219.
(2) Rapoport, H.; Windgassen, R. J., Jr.; Hughes, N. A.; Onak, T. P. *J. Am. Chem. Soc.* **1960**, *82*, 4404.
(3) (a) Benson, W.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 862. (b) Hachmeister, B.; Thielke, D.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3825.
(4) Bennasar, M.-L.; Jimenez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105.
(5) An approach to akagerine via the apogeissoschizine skeleton has been realized: Benson, W.; Winterfeldt, E. *Heterocycles* **1981**, *15*, 935
(6) Isolation of akagerine: Angenot, L.; Dideber, L. O.; Dupont, L. *Tetrahedron Lett.*, **1975**, *16*, 1357
(7) (a) Schwabb, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. For recent reviews of this area, see: (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037.
(8) (a) Meyers, A. I.; Hellring, S. *J. Org. Chem.* **1982**, *47*, 2229. (b) Meyers, A. I.; Loewe, M. F. *Tetrahedron Lett.* **1984**, *25*, 2641. (c) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778.
(9) (a) Berge, J. M.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 2230. (b) Bachman, G. B. *J. Am. Chem. Soc.* **1933**, *55*, 4279
(10) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.
(11) (a) Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffrey, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

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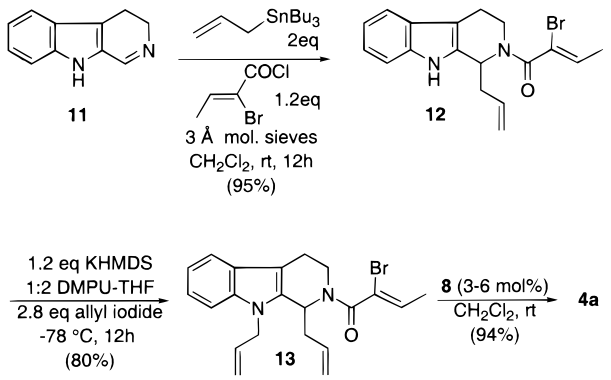
Scheme 3



unsuitable for the cyclization of **4a**.[12] However, the reaction proceeded cleanly under a very "nonpolar" set of conditions [$Pd(OAc)_2$, PPh_3, proton sponge, K_2CO_3, PhMe, 110 °C, 18 h] and afforded the apogeissoschizine pentacycle (**3a**) in 82% yield.[13] This sequence produced the desired pentacyclic skeleton in six steps from commercially available tetrahydro-β-carboline.

While this strategy was appealing in its conciseness and in the simultaneous introduction of the two allyl groups needed for the ring-closing metathesis, it required protection and deprotection steps. Furthermore, intermediates **7** and **9** were obtained in only moderate yields. The critical Heck cyclization step, however, proceeded in high yield and inspired us to devise an even more concise strategy to the key cyclization precursor. Noting that the α-bromocrotonoyl side chain could be introduced simultaneously with an allyl group at C-1[14] and should be sufficiently inert under the metathesis conditions, we decided to eliminate protection−deprotection steps from the sequence completely. The resulting efficient construction of the Heck cyclization precursor is shown in Scheme 3.

Condensation of dihydro-β-carboline **11**[15] with allyltributyltin and α-bromocrotonoyl chloride[9] gave **12** in nearly quantitative yield.[14] Introduction of the allyl group on the indole nitrogen turned out not to be trivial. Conditions typically employed for alkylation of indoles (NaH or KH in THF/DMF) gave at best modest yields, since the anion generated from **12** began to decompose above ca. −40 °C, presumably due to the presence of the vinyl bromide moiety in the molecule. After some experimentation, it was found that by using KHMDS as the base the reaction took place cleanly at −78 °C in a 2:1 THF/DMPU mixture, giving diallyl **13** in 80% yield. Ring-closing metathesis,[7] which now proceeded under the standard, relatively mild conditions, smoothly converted **13** into the cyclization precursor **4a** in high yield.

This improved sequence is noteworthy in that it (a) generates the syn relative stereochemistry needed for a large group of alkaloids with complete stereocontrol, (b) requires no protecting groups, and (c) produces the apogeissoschizine pentacycle in only four steps from dihydro-β-carboline, in 58% overall yield. Transformation of pentacycle **3a** into the geissoschizine and akagerine families of natural products is currently under investigation in our laboratories.[16]

Acknowledgment. We are grateful to the National Institutes of Health (R01-GM-55998) for generous support of this program. Pfizer Inc. and Merck Research Laboratories are also thanked for financial assistance.

Supporting Information Available: Experimental procedures and compound characterization data, including copies of NMR spectra for all new compounds (29 pages).

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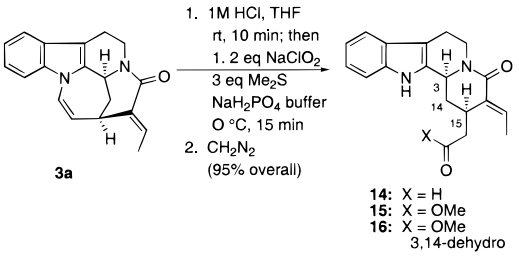
(12) A cyclization precursor having the 2-iodocrotyl side chain (**4**, X = I, Z = H_2) underwent dealkylation when subjected to Jeffrey's conditions.

(13) In the absence of potassium carbonate, the reaction stopped after reaching ca. 20% conversion with 10 mol % catalyst loading (or 55% with 30 mol % catalyst loading), presumably because the bromide anion inhibited the reaction. Addition of silver phosphate or carbonate also resulted in high conversions, but the reaction mixtures were not clean.

(14) Yamaguchi, R.; Otsuji, A.; Utimoto, K.; Kozima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 298. See also: Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925.

(15) Whittaker, N. *J. Chem. Soc. C* **1969**, 85.

(16) In preliminary experiments, pentacycle **3a** was converted into the known methyl 21-oxogeissoschizoate **15**,[3,17] which has previously been utilized en route to geissoschizine.[3b] This transformation was accomplished as follows. Compound **3a** in THF hydrolyzed quickly and quantitatively into 21-oxogeissoschizal **14** upon addition of a drop of 1 M aqueous HCl. The addition of buffered sodium chlorite solution to this reaction mixture, using dimethyl sulfide as the hypochlorous acid scavenger,[18] cleanly oxidized the aldehyde to the acid. Treatment of the crude 21-oxogeissoschizoic acid with diazomethane afforded methyl 21-oxogeissoschizoate (**15**, mp 210.5−211.5 °C (lit.[3b] mp 213 °C, lit.[17] mp 210−211 °C) in 95% overall yield, after chromatography. The spectral data of the product matched those found in the literature.[17,20]



(17) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804.

(18) When the oxidation was performed in the presence of 4 equiv of resorcinol, a commonly used HOCl scavenger,[19] methyl 21-oxogeissoschizoate was obtained in only 60% overall yield, along with 18% of the 3,14-dehydro compound (**16**) and several minor unidentified products. By contrast, 3 equiv of Me_2S completely prevented overoxidation of the indole substrate, without consuming the chlorite. The use of Me_2S as a HOCl scavenger has not previously been reported and represents a useful modification of the standard sodium chlorite oxidation of aldehydes to carboxylic acids.

(19) For a comparative listing of HOCl scavengers employed in chlorite oxidation, see: Hase, T.; Wähälä, K. in *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, p 4533.

(20) We thank Professor Stephen F. Martin (University of Texas, Austin) for generously providing an authentic sample of **15** for direct comparison.