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Synthesis of the *Kopsia* alkaloids (±)-11,12-demethoxylahadinine B, (±)-kopsidasine and (±)-kopsidasine-*N*-oxide

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Abstract

The key intermediate homoannular diene **10** was converted into (±)-11,12-demethoxylahadinine **6** via the conjugate reduction and oxidation of **15** with $Mn(dpm)_2/PhSiH_3/O_2$ at 0°C. Oxidation of **14** with $PhI(OAc)_2$/MeOH followed by reduction gave **17**, which was converted into (±)-kopsidasine **19** and kopsidasine-*N*-oxide **20**. The structure of the latter was confirmed by comparison with an authentic sample, and by X-ray crystallography.

Keywords: kopsane; alkaloids; lahadinine; α-hydroxylation; kopsidasine; kopsidasine-*N*-oxide.

Recently, we reported a plausible biogenetic hypothesis for the conversion of kopsane-like alkaloids **3** into the pauciflorines A and B **1**/**2**, and outlined the synthesis of some key intermediates, Scheme 1.[1] Subsequently, Kuehne and Li have shown the chemical validity of this hypothesis in their synthesis of 16α-deoxy-11,12-didemethoxypauciflorine.[2] During the course of our research on the synthesis of prepauciflorine **3** we had synthesized intermediates that had the potential to be converted into other *kopsia* alkaloids. In 1997 Kam reported the isolation and structure determination of two cyano-substituted indole alkaloids from *Kopsia pauciflora* which were named lahadinine A **4** and lahadinine B **5**, respectively (Scheme 1).[3] They represent the cyano version of 19-deoxyprepauciflorine, and allowed us to investigate the installation of the α-hydroxyester functionality. In this letter we report the synthesis of the 11,12-demethoxy analog **6**, and the related *kopsia* alkaloids kopsidasine **19** and kopsidasine-*N*-oxide **20**, respectively.

Our initial studies were conducted on the demethoxy analog **7** since the 6,7-dimethoxytryptamine required for **5** is considerably more difficult and time consuming to make, and it was expedient to evaluate the strategy on tryptamine itself before committing to the dimethoxy version.[4] In our previous publication we reported that treatment of **7** with triflic anhydride in dichloromethane containing 4-dimethylaminopyridine heated at reflux,[5] gave a deep purple solution of the iminium ion **8**, which on addition of aqueous $NaHCO_3$ gave the homoannular diene **9** (Scheme 2). Attempts to conduct

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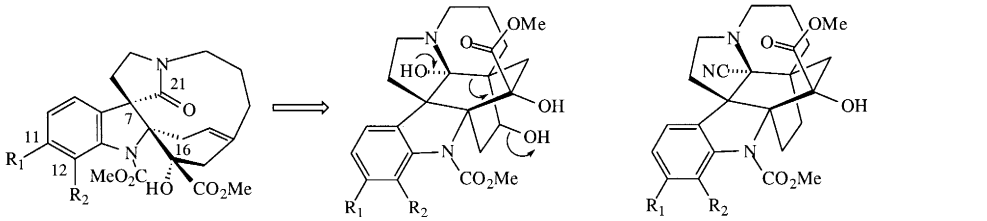
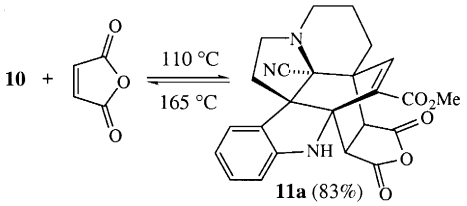
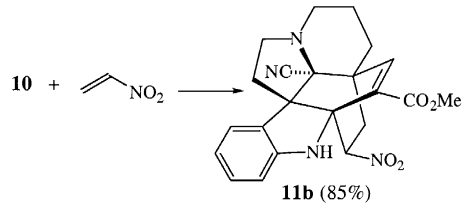


Scheme 1.

Diels–Alder reactions on **9** were uniformly unsuccessful because of competing rearrangement reactions that gave rise to various phenolic carbazoles and cyclohexadienones.[6] It was evident that we needed a less labile version of the homoannular diene that would withstand moderately vigorous conditions to undergo [4+2] cycloaddition chemistry. It was found that treatment of the solution of **8** with trimethylsilyl cyanide gave directly the aminonitrile adduct **10** in 68% yield. The improved stability of the homoannular diene **10** did indeed solve the above problems. For example, treatment of **10** with maleic anhydride in toluene at 100°C for 6 h gave the *endo*-adduct **11a** (83%), Eq. (1). Interestingly, heating **11a** at higher temperatures (165°C) resulted in the retro-Diels–Alder (or retro-Mannich) reaction to give back the starting materials. Also nitroethylene reacted with **10** at 75°C to give **11b** (85%) (X-ray), Eq. (2). Treatment of **11b** with *n*-Bu_3SnH/AIBN(cat)/PhH reflux gave a complex mixture that did not contain (by ^1H NMR) the expected adduct **14**. Consequently, we decided to use the very reactive acryloyl chloride as the dienophile.[7]



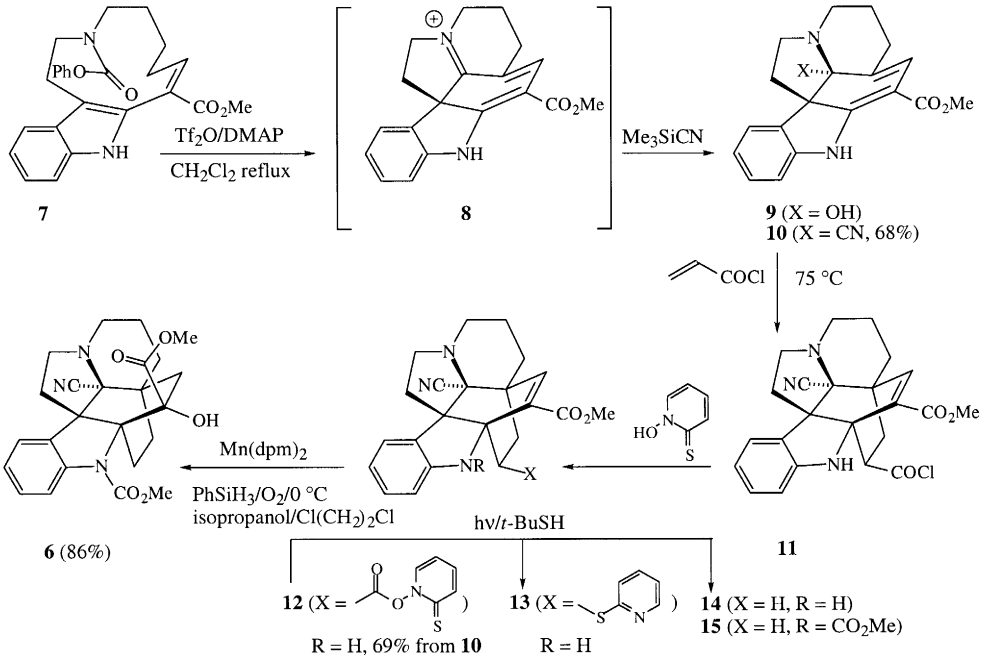
(1)



(2)

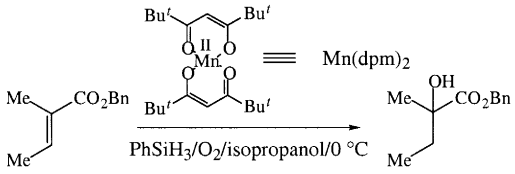
Treatment of **10** with acryloyl chloride (excess) at 75°C gave **11**, which was directly treated with *N*-hydroxy-2-thiopyridone etc., to give **12** (69% from **10**).[8] Irradiation of **12** in the presence of *t*-BuSH resulted in reductive decarboxylation to give **14** and a small amount of the 2-thiopyridyl ether **13**. Protection of the aniline nitrogen in **14** required the use of triphosgene/pyridine followed by methanol, as described by Danishefsky,[9] to give **15** (90%), and was used directly in the next step.

The final step for the conversion of **15** into **6** requires the conjugate reduction of the α,β-unsaturated ester followed by α-hydroxylation of the now saturated ester. In 1990 Isayama et al. reported a single step method for accomplishing the above.[10] They treated a number of simple α,β-unsaturated esters with a catalytic amount of bis(dipivaloylmethanato)manganese (II)[11]/$PhSiH_3/O_2$ in isopropanol at 0°C and obtained the saturated α-hydroxyester in excellent yield, as depicted in Eq. (3). Application of this interesting procedure to the much more complicated and very sterically encumbered α,β-unsaturated



Scheme 2.

ester **15** seemed an optimistic extension, but in the event it worked exceedingly well. Treatment of **15** with $PhSiH_3$(2.5 equiv.)/$Mn(dpm)_2$/*i*-PrOH, $Cl(CH_2)_2Cl$ (2:1)/O_2 gave **6** (crystallized as formed) in 86% yield as a single stereoisomer whose structure and stereochemistry was confirmed by X-ray crystallography, Fig. 1.[12] The overall yield from **12** to **6** is 51%.



(3)

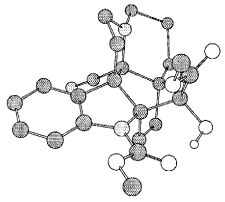
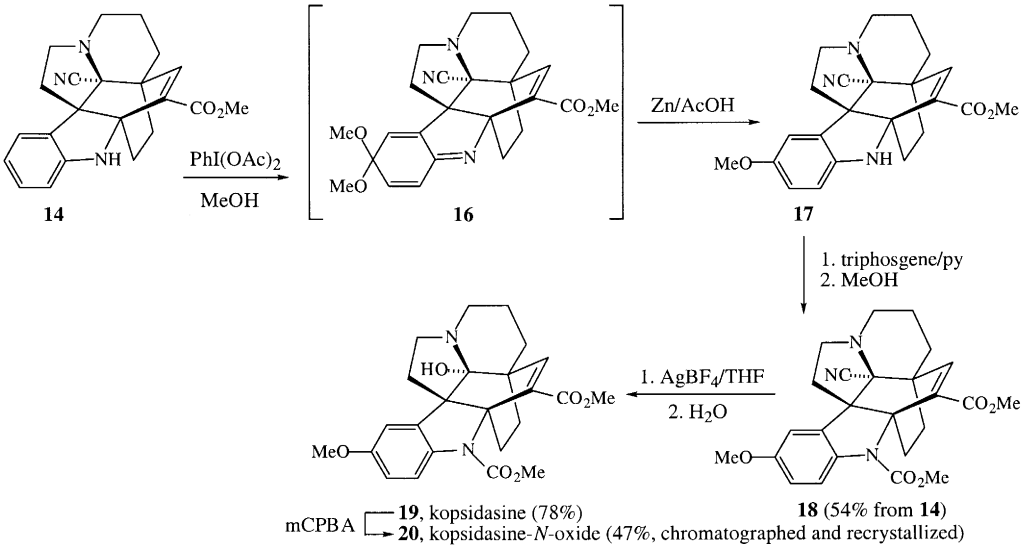


Fig. 1. Chem 3D representation of **6** from the X-ray coordinates

Kopsidasine **19** and kopsidasine-*N*-oxide **20** were isolated from *Kopsia dasyrachis* Ridl. and their structures elucidated by NMR and chemical correlation.[13] It seemed reasonable to attempt to convert **14** into these compounds, and thus provide unequivocal evidence for their structures.

Treatment of **14** with $Pb(OAc)_4$ or Frémys salt following literature protocols for the hydroxylation of tryptamines and tryptophans[14] did not proceed satisfactorily, whereas exposure of **14** to $PhI(OAc)_2$/MeOH cleanly gave **16**, which was directly reduced with Zn/AcOH to **17** (Scheme 3).[15] Conversion of **17** into **18** proceeded as before, and when **18** was treated with $AgBF_4$/THF followed by

aqueous $NaHCO_3$ it was converted into (±)-kopsidasine **19**. While the spectral data for **19** compared well with the literature,[13] an authentic sample of **19** was not available, whereas a sample of the derived *N*-oxide **20** exists.[16] Consequently, **19** was converted into **20** by treatment with *m*-chloroperoxybenzoic acid (*m*CPBA). Comparison of synthetic **20** with natural **20** by TLC (multiple elutions) and $^1H/^{13}C$ NMR confirmed their identity, and an X-ray crystal structure of **20** (Fig. 2) unequivocally demonstrated the structure of **20**.



Scheme 3.

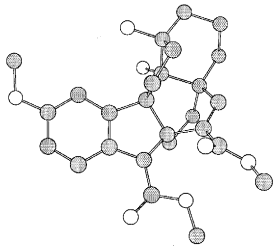


Fig. 2. Chem 3D representation of **20** from the X-ray coordinates

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16. Dr. Manfred Hesse (University of Zurich) is thanked for an authentic sample of **20**.