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Total Synthesis of Kopsinine

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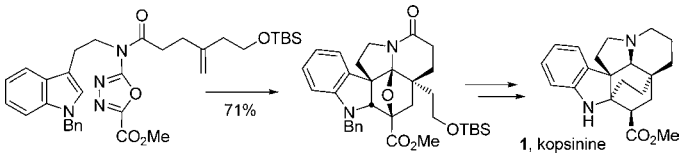
ABSTRACT



The use of a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of an 1,3,4-oxadiazole in the divergent total synthesis of kopsinine (1), featuring an additional unique SmI_2-promoted transannular cyclization reaction for formation of the bicyclo[2.2.2]octane central to its hexacyclic ring system, is detailed.

In recent efforts that targeted key members of the *Aspidosperma* alkaloids, including minovine,[1] (+)-fendleridine (aspidoalbidine),[2] (−)-aspidospermine and (+)-spegazzinine,[3] (+)-*N*-methylaspidospermidine, (−)-vindorosine and (−)-vindoline,[4] and their extension to the total synthesis of vinblastine[5] and related natural products including vincristine,[6] and key analogues,[7] we developed a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles that provides the pentacyclic core and all the stereochemistry of the natural products in a single step.[8] Herein, we report the extension of these studies to the total synthesis of kopsinine (**1**),[9] a *Kopsia* alkaloid first isolated from *Kopsia Longiflora* Merr. and related to the *Aspidosperma* alkaloids by virtue of an additional bond formed by joining the terminal methyl group (C21) of the C5 ethyl substituent with C2 to provide a bicyclo[2.2.2]octane central to its hexacyclic ring system (Figure 1). To date, this bicyclo[2.2.2]octane central to the *Kopsia* core has been accessed only by key Diels–Alder reactions of unnatural aspidosperma-like pentacyclic dienes (C2–C5) necessarily lacking a C5 substituent.[10] Complementary to these efforts, the total synthesis detailed herein enlists a late stage C2–C21 bond formation in an approach that directly links **1** to the structures of the corresponding *Aspidosperma* alkaloids. The added bonus of the strategy is that

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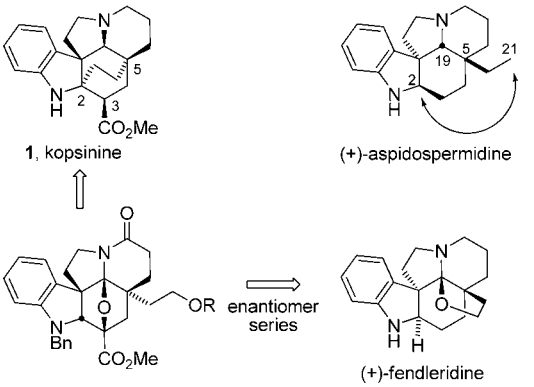
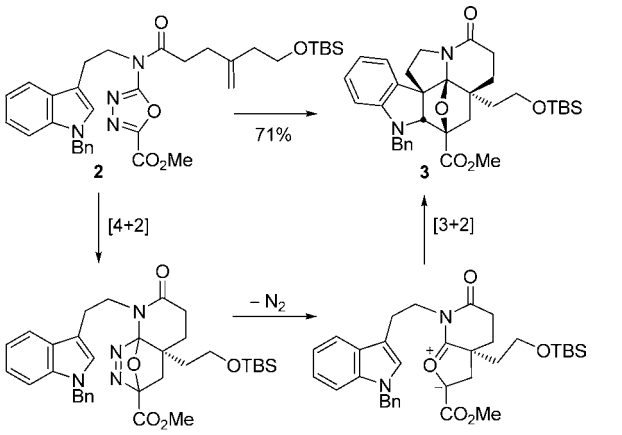


Figure 1. Structure of kopsinine, relationship to *Aspidosperma* alkaloids, and late stage divergent total syntheses of kopsinine and fendleridine.

Scheme 1



late stage modification of a route developed to access (+)-fendleridine[2] now permits a divergent[11] synthesis of kopsinine (**1**) in an approach fundamentally distinct from prior reports.

As detailed in earlier studies, the key intramolecular [4 + 2]/[3 + 2] cycloaddition was accomplished upon warming a solution of **2** at 180 °C in *o*-dichlorobenzene (*o*-DCB) to provide **3** as a single diastereomer in yields as high as 71% (Scheme 1).[2] The cycloaddition cascade is initiated by an intramolecular Diels–Alder reaction of the tethered unactivated dienophile with the central 1,3,4-oxadiazole.[12,13] Loss of N_2 from the initial cycloadduct generates a 1,3-dipole that is uniquely stabilized by the complementary substitution at each of the dipole termini. The ensuing 1,3-dipolar cycloaddition reaction proceeds with a regioselectivity that is dictated by the linking tether, but is reinforced by the intrinsic polarity of the reacting partners, and with a diastereoselectivity that is derived from an indole endo [3 + 2] cycloaddition, in which the dipolarophile is sterically directed to the face opposite the newly formed six-membered ring.[8,14] Four C–C bonds, three rings, five stereocenters, and a pentacyclic skeleton are assembled in a single transformation.

Reductive oxido bridge opening of **3** was accomplished upon treatment with $NaCNBH_3$ in 20% HOAc/*i*-PrOH to provide the alcohol **4** (87%) as a single diastereomer, resulting from convex face hydride reduction of an intermediate *N*-acyliminium ion that is flanked by two quaternary centers (Scheme 2). Conversion of **4** to the methyldithiocarbonate **5** (NaH, CS_2, THF, 0 °C, 1 h followed by MeI, 25 °C, 1 h, 78%) set the stage for a Chugaev elimination.[15] Warming a solution of the xanthate **5** in *o*-dichlorobenzene (*o*-DCB) at 150 °C for 1 h provided a separable 2:1 mixture of **7** and **6** in excellent yield 85%. The observation of a small amount of the rearranged and stable *S*- versus *O*-dithiocarbonate could be avoided by conducting the reaction at a lower temperature in benzene in a sealed vessel at a bath temperature of 130 °C (6 h), affording the elimination products in superb yield (95%). Prior to continuing to address improvements in the regioselectivity of the elimination reaction and with sufficient **6** in hand, studies on the key formation of the C2–C21 bond were conducted. Deprotection of the TBS ether (Bu_4NF, THF, 98%) in **6** and conversion of the primary alcohol **8** to the methyldithiocarbonate **9** (86%) set the stage for the key bond formation. Treatment of **9** (0.1 M) with SmI_2 in 10:1 THF–HMPA (25 °C, 20 min) provided **10** in excellent yield (75%) as a single diastereomer, presumably resulting from a radical-mediated cyclization followed by kinetic protonation of the further reduced conjugate addition ester enolate from the less hindered convex face.[16]

Although not investigated herein, Molander and coworkers have shown that the scope of such SmI_2-mediated conjugate addition reactions is most consistent with radical-mediated versus anionic cyclization.[16] Consistent with this expectation, a $(TMS)_3SiH$-mediated free radical cyclization (C_6H_6, 90 °C, 2 h) of **9** also provided the analogous addition product in good yield (60%), but as a 1:1 mixture of C3 diastereomers. Also consistent with the observations of Molander, the product **10**, obtained as the exclusive diastereomer from the SmI_2-mediated reaction, represents the less stable of the two C3 diastereomers (ΔE = 1.7 kcal/mol), indicating that it is the result of kinetic versus thermodynamic protonation of the enolate derived from a subsequent SmI_2 reduction of the radical addition intermediate. Completion of the concise total synthesis simply involved treatment of **10** with Lawesson's reagent[17] to provide the thiolactam **11** (90%) which upon treatment with Raney-Ni (EtOH, 25 °C, 3 h, 95%) underwent both

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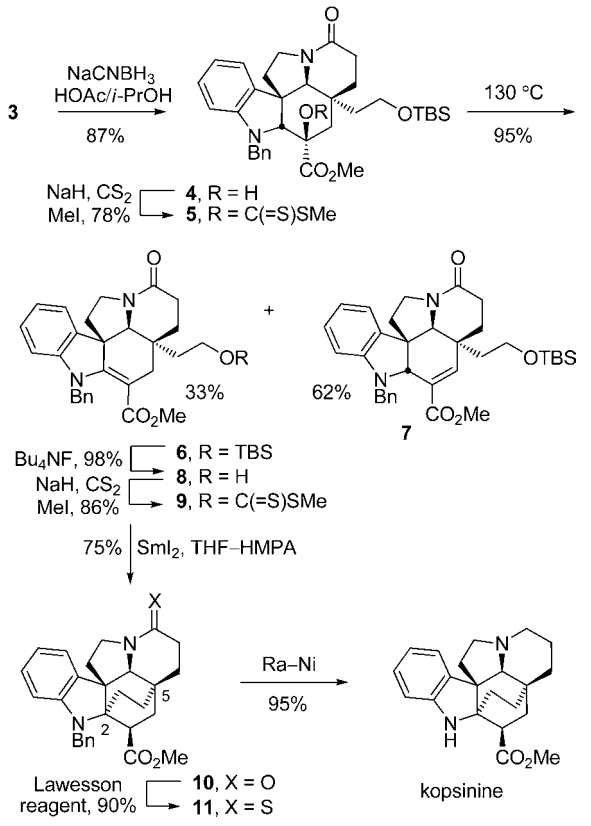
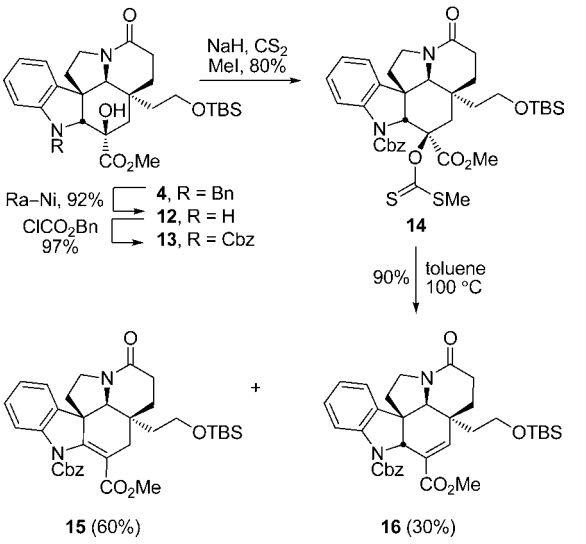
Scheme 2



Scheme 3



desulfurization and *N*-debenzylation to provide kopsinine (**1**), spectroscopically (^{1}H and ^{13}C NMR) identical to authentic material.[10e]

In efforts that improved the regioselectivity of the Chugaev elimination, conversion of **5** to the corresponding indoline Cbz carbamate **13**, followed by methyl dithiocarbonate formation provided **14** (Scheme 3). The intermediate xanthate **14** underwent the thermal elimination reaction under much milder reaction conditions (toluene, 100 °C, 48 h) than **5**, providing a superb yield (90%) of the separable elimination products **15** and **16** in a reversed 2−2.7:1 ratio favoring the $\Delta^{2,3}$ isomer **15** (60%). Clearly the amine carbamate substitution activates C2−H for xanthate syn elimination, now favoring formation of the more substituted and stable olefin. Although not examined, the effective access to **15** provides, in principle, the development of an improved approach to kopsinine.

Herein, we reported the use of a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles in the divergent total synthesis of kopsinine (**1**), featuring an additional unique SmI_2-promoted transannular cyclization reaction for formation of the bicyclo[2.2.2]octane central to its hexacyclic ring system and directly linking it with the pentacyclic *Aspidosperma* alkaloids to which it is related.

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Supporting Information Available. Full experimental details, compound characterizations, and spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.