Published in final edited form as:

Org Lett. 2013 February 15; 15(4): 868–870. doi:10.1021/ol303573f.

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 (aspidalbidine),² (–)-aspidospermine and (+)-spgazzanine,³ (+)-*N*-methylaspidospermidine, (–)-vindrosine and (–)-vindoline,⁴ and their extension to the total synthesis of vinblastine⁵ 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 late stage modification of a route developed to access (+)-fendleridine² now permits a divergent¹¹ 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

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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.

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 NaCNBH₃ 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 methylthiocarbonate **5** (NaH, CS₂, 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 (Bu₄NF, THF, 98%) in **6** and conversion of the primary alcohol **8** to the methylthiocarbonate **9** (86%) set the stage for the key bond formation. Treatment of **9** (0.1 M) with SmI₂ 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 co-workers have shown that the scope of such SmI₂-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 (C₆H₆, 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 SmI₂-mediated reaction, represents the less stable of the two C3 diastereomers ($\Delta E = 1.7$ kcal/mol), indicating that it is the result of kinetic versus thermodynamic protonation of the enolate derived from a subsequent SmI₂ reduction of the radical addition intermediate. Completion of the concise total synthesis simply involved treatment of **10** with Lawesson's reagent¹⁷ to provide the thiolactam **11** (90%) which upon treatment with Raney-Ni (EtOH, 25 °C, 3 h, 95%) underwent both desulfurization and *N*-debenzylation to provide kopsinine (**1**), spectroscopically (¹H and ¹³C 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 SmI₂-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the financial support of the National Institutes of Health (CA042056) and the Skaggs Institute for Chemical Biology. A.L.W. is a Skaggs Fellow and recipient of a NSF graduate fellowship (2009–2012).

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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.

Scheme 2.

Scheme 3.