

Enantioselective Total Synthesis of (+)- and (–)-Nigellamine A₂

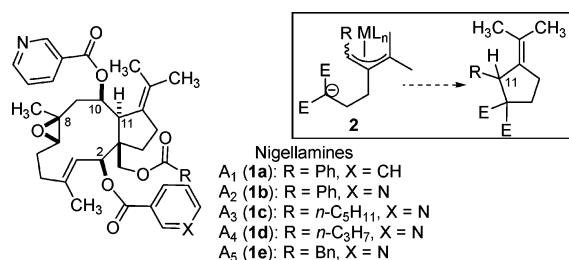
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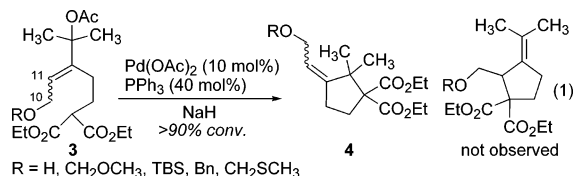
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Dolabellane diterpenes have been isolated from marine and terrestrial sources and are produced by animals, plants, and fungi. That their broad distribution reflects the privileged status of the dolabellane ring system is supported by the correspondingly impressive array of biological activities associated with these natural products and by the fact that both enantiomeric forms occur in nature.² The ubiquity of these natural products combined with their structural complexity has stimulated substantial activity in the synthetic community.^{2,3}

Scheme 1



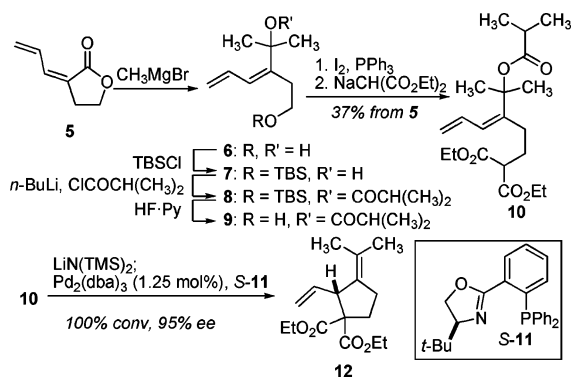
Yoshikawa and co-workers recently disclosed the two- and three-dimensional structures of a series of alkaloids possessing the dolabellane 5,11-trans-fused bicyclic ring system (1a–e). Isolated from *Nigella sativa* (black cumin), these nigellamine alkaloids are associated with potent lipid metabolism-promoting activity.⁴ In considering a total synthesis of the nigellamines, we recognized that an intramolecular addition of a substituted malonate onto a metal-coordinated allyl moiety (2) might generate the isopropylidene cyclopentane core appended with functionality to install the 11-membered ring (Scheme 1). The successful implementation of this strategy would require the formation of a tetrasubstituted M(π -allyl) from the corresponding allyl acetate followed by a regio- and enantioselective anti-Baldwin cyclization—a series of events with little literature precedent.⁵



In initial attempts to execute the plan outlined above, we focused on substrates incorporating C₁₀ oxygenation (nigellamine numbering). To this end, a series of allylic acetates 3 was cyclized in the presence of a palladium catalyst (eq 1). While we had anticipated malonate addition to the less-hindered C₁₁ terminus of the presumptive Pd(π -allyl) intermediate (2, M = Pd), in fact attack occurred at the more substituted carbon to return the undesired isomer 4 as the sole cyclization product. Reasoning that this regiochemical outcome was dictated by electronics rather than sterics,⁶ we sought

to replace the electron-withdrawing alkoxy group with an electron-donating surrogate. Accordingly, allylic ester 10 was prepared as outlined in Scheme 2. Performing the sequence without chromatographic purification of any intermediates facilitated the preparation of multigram quantities. Exposure of the lithium enolate of 10 to a Pd(phosphinooxazoline) complex⁷ resulted in the production of diene 12 in 95% ee as the only reaction product.

Scheme 2

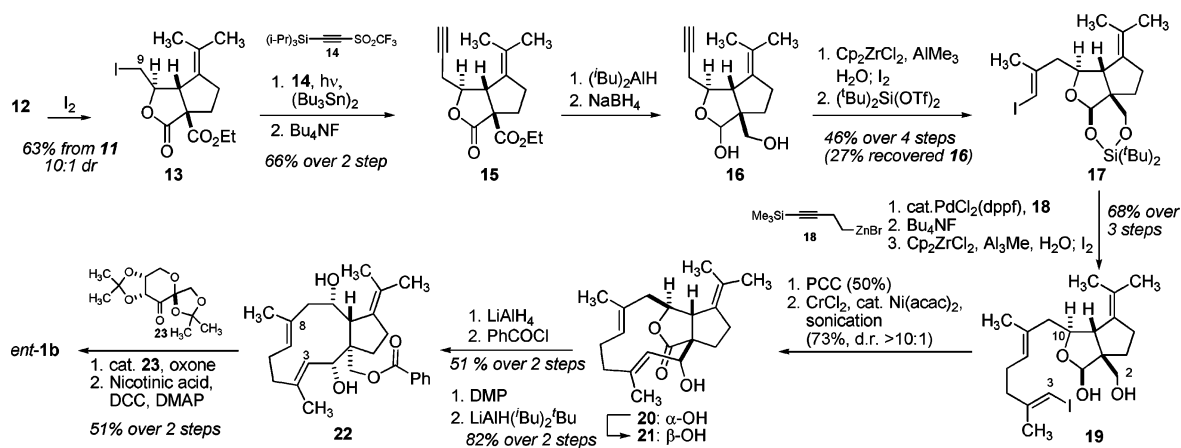


Iodolactonization of diene 12 differentiated the two carbonyls and installed the C₁₀ hydroxyl with good diastereoselectivity (Scheme 3). X-ray crystallographic analysis of the minor diastereomer (C₁₀-*epi*-13) established the stereochemical outcome of the Pd-catalyzed cyclization and, by extension, the absolute stereochemistry of synthetic 1b.⁸ Nucleophilic substitution of the primary iodide in 13 proved untenable, and failure met all attempts to convert the iodolactone to a terminal epoxide. Eventually, a high yielding functionalization of C₉ was found in Fuchs' radical alkylation reaction using triflone 14.⁹

Desilylation and reduction yielded terminal alkyne 16, a substrate for Negishi methylodination.¹⁰ Under anhydrous conditions, Cp₂ZrCl₂ did not mediate addition of Me₃Al to the terminal alkyne. Instead, addition to the lactol occurred, resulting in a mixture of methyl-tetrahydrofuran diastereomers. Remarkably, the reagent derived from a 1:1:3 mixture of water, Cp₂ZrCl₂, and Me₃Al effected methylaluminum without competing addition to the lactol. In situ iodination and subsequent silylation afforded vinyl iodide 17 in good yield. While the rate acceleration offered by water in the methylaluminum was described by Wipf,¹¹ the modulation of chemoselectivity has not been documented previously.

The remaining carbon atoms of the nigellamine skeleton were installed through cross-coupling with alkyl zinc reagent 18 and a second methylaluminum/iodination sequence. The 11-membered ring was subsequently formed by means of a Cr-mediated cyclization involving the C₃ vinyl iodide and a C₂ aldehyde.¹² The high yield and complete diastereoselectivity of the Nozaki–Hiyama–Kishi (NHK) cyclization are notable, even more so given the hindered nature of the aldehyde component and the formation of a

Scheme 3



trans-fused ring system. The conformational bias imposed by embedding the C₁₀ stereocenter in a rigid lactone likely minimizes the entropic penalty associated with macrocyclization. Unfortunately, circumstantial evidence convinced us that the newly formed C₂ hydroxyl (**20**) possessed the incorrect relative stereochemistry, a conclusion born out by subsequent transformations. In particular, Dess–Martin oxidation provided an intermediate enone. Reduction with the reagent derived from 1:1 mixture of *t*Bu₂AlH and *t*BuLi produced an allylic alcohol displaying spectroscopic data consistent with the desired C₂ stereochemistry (**21**).¹³ In contrast, reduction with NaBH₄/CeCl₃, CBS catalyst, and Li(O*t*Bu)₃AlH returned the original diastereomer (**20**) while the Selectrides favored 1,4 addition.

Reductive opening of the lactone and selective acylation of the primary alcohol led to a substrate for epoxidation (**22**). Concerned about competition among the three reactive olefins, we reasoned that the C₂ alcohol might deactivate the C₃–C₄ olefin while the ketone catalyst **23** might be unreactive toward tetrasubstituted olefins.¹⁴ In fact, preliminary studies showed rapid oxidation of all three olefins with reagents such as *m*CPBA. Using the Shi catalyst and oxone, however, oxidation proceeded regio- and stereoselectively to produce the desired epoxide as the major product. Only a single report has detailed the epoxidation of a macrocyclic olefin using ketone catalyst **23**,¹⁵ and we were therefore interested in deciphering substrate versus catalyst control. In this regard, substrate conformation appears to dictate facial preference as both **23** and *ent*-**23** generated the same product as a single diastereomer. Interestingly, the enantiomeric catalysts displayed slight differences in olefin preference. Epoxidations employing ketone **23** yielded a 7:1 ratio of monoepoxides, favoring epoxidation of the C₇–C₈ olefin over the C₃–C₄ olefin. In contrast, otherwise identical epoxidations, save for the use of *ent*-**23**, resulted in a 2:1 ratio of the same epoxides.

Finally, acylation of the two secondary alcohols with nicotinic acid provided *ent*-nigellamine A₂. The synthetic material was fully consistent with the natural product by ¹H NMR, ¹³C NMR, and MS analysis. The optical rotation ([α]_D²⁰ = +19.6, *c* = 0.5 CHCl₃) was opposite in sign and similar in magnitude to that reported for the natural product ([α]_D²⁷ = –24.2, *c* = 1.00 CHCl₃),¹⁶ confirming the stereochemical assignment made by the Yoshikawa group.

Natural nigellamine A₂ was produced from *ent*-**12** following a sequence analogous to that outlined in Scheme 3.^{8,17} Minor modifications of this synthesis should provide other members of the nigellamine family. Having access to numerous congeners of both enantiomeric series should facilitate detailed biological studies.

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Supporting Information Available: Complete experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) CD (MeOH) showed a positive Cotton effect at 261 nm. Natural **1b** shows a negative Cotton effect at 256 nm.
- (17) Diene **10** was cyclized in the presence of a catalyst incorporating ligand (*R*)-**11**.

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