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Enantioselective Total Synthesis of (+)- and (−)-Nigellamine A_2

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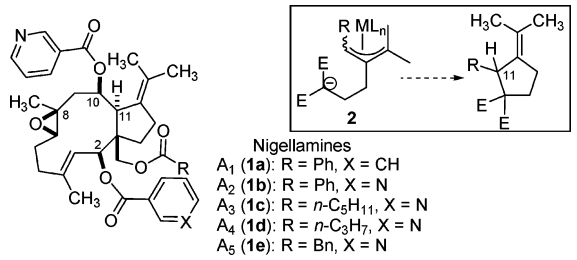
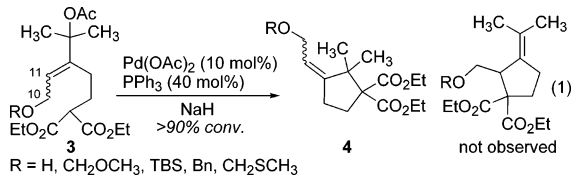
Dolabellane diterpenes have been isolated from marine and terrestrial sources and are produced by animals, plants, and fungi. That their broad distribution reflects the privileged status of the dolabellane ring system is supported by the correspondingly impressive array of biological activities associated 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

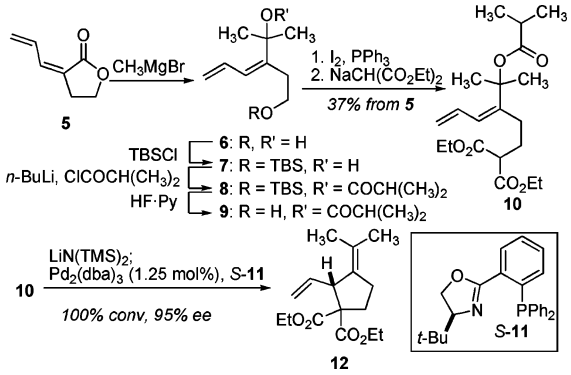


Yoshikawa and co-workers recently disclosed the two- and three-dimensional structures of a series of alkaloids possessing the dolabellane 5,11-trans-fused bicyclic ring system (**1a**−**e**). Isolated from *Nigella sativa* (black cumin), these nigellamine alkaloids are associated with potent lipid metabolism-promoting 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 C_{10} 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 C_{11} 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) complex[7] 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 C_{10} hydroxyl with good diastereoselectivity (Scheme 3). X-ray crystallographic analysis of the minor diastereomer (C_{10}-*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 C_9 was found in Fuchs' radical alkynylation reaction using triflone **14**.[9]

Desilylation and reduction yielded terminal alkyne **16**, a substrate for Negishi methyliodination.[10] Under anhydrous conditions, Cp_2ZrCl_2 did not mediate addition of Me_3Al 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, Cp_2ZrCl_2, and Me_3Al effected methylalumination 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 methylalumination 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 methylalumination/iodination sequence. The 11-membered ring was subsequently formed by means of a Cr-mediated cyclization involving the C_3 vinyl iodide and a C_2 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

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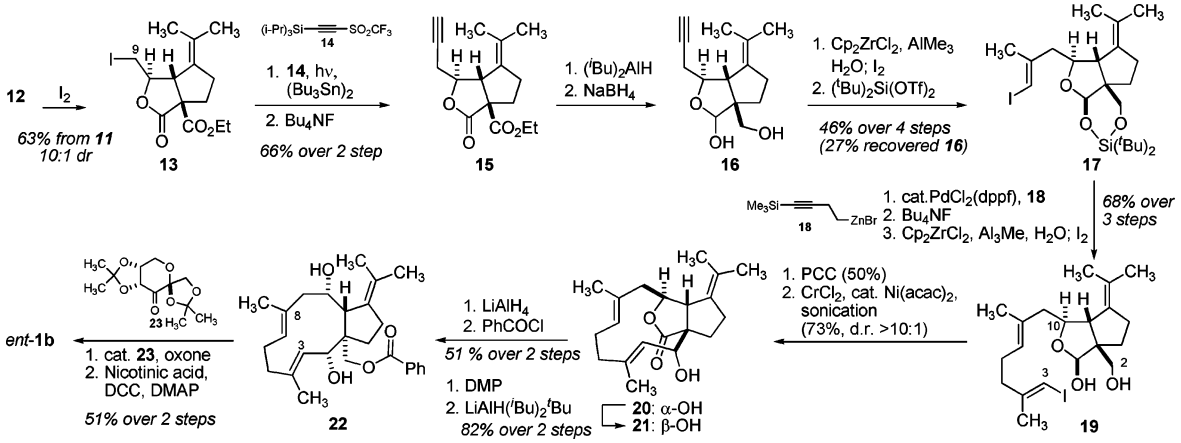
Scheme 3



trans-fused ring system. The conformational bias imposed by embedding the C_{10} stereocenter in a rigid lactone likely minimizes the entropic penalty associated with macrocyclization. Unfortunately, circumstantial evidence convinced us that the newly formed C_2 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 $(^i\text{Bu})_2\text{AlH}$ and $^t\text{BuLi}$ produced an allylic alcohol displaying spectroscopic data consistent with the desired C_2 stereochemistry (**21**).[13] In contrast, reduction with $NaBH_4/CeCl_3$, CBS catalyst, and $\text{Li}(O^t\text{Bu})_3\text{AlH}$ 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 C_2 alcohol might deactivate the C_3-C_4 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 C_7-C_8 olefin over the C_3-C_4 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 A_2. The synthetic material was fully consistent with the natural product by ^{1}H NMR, ^{13}C NMR, and MS analysis. The optical rotation ($[\alpha]^{20}_D = +19.6$, $c = 0.5$ $CHCl_3$) was opposite in sign and similar in magnitude to that reported for the natural product ($[\alpha]^{27}_D = -24.2$, $c = 1.00$ $CHCl_3$),[16] confirming the stereochemical assignment made by the Yoshikawa group.

Natural nigellamine A_2 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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