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Total Synthesis of (±)-Nardoaristolone B and Its Analogues

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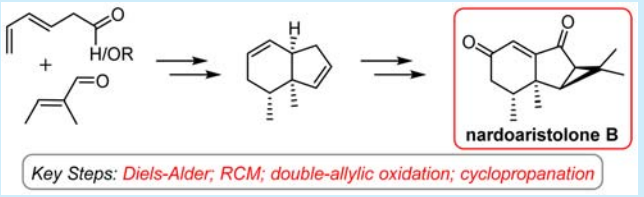
Supporting Information

ABSTRACT: The first total synthesis of nardoaristolone B, a nor-sesquiterpenoid with an unusual fused ring system and having protective effects on the injury of neonatal rat cardiomyocytes, has been accomplished. Stereoselective synthesis of its novel analogues inlcuding *exo*-cyclopropyl ring fusion is also part of this disclosure. In addition, an alternate and more efficient one-step method to make a 3/5/6 tricyclic ring system using the Robinson annulation method has been developed toward the generation of a library of compounds around this skeleton.



Very recently, the nardoaristolone B (**1**) natural product was isolated from the underground parts of *Nardostachy chinensis* plants[1] which have been used as sedative and analgesic agents in traditional Chinese medicine for centuries (Figure 1).[2] The structure elucidation of **1** was carried out using various

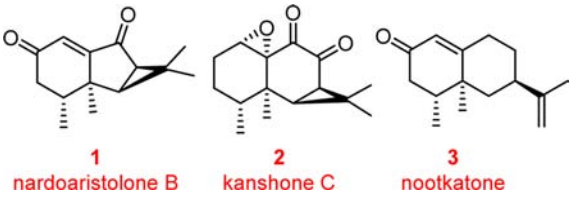
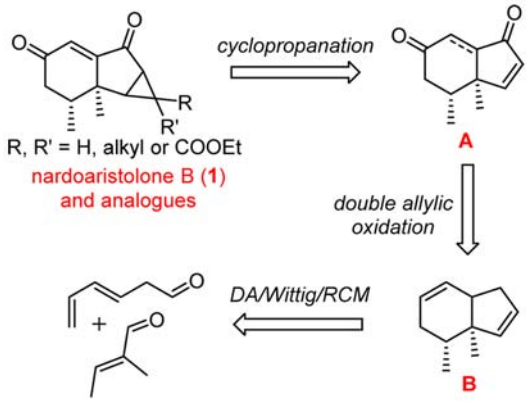


Figure 1. Structures of natural products.

spectral and X-ray diffraction methods, and it is believed to be biogenetically derived from kanshone C (**2**).[1] The nardoaristolone B has shown protective effects on the injury of neonatal rat cardiomyocytes in a dose-dependent manner.[1] In view of its potential biological activity and a rare skeleton with a 3/5/6 tricyclic fused ring system, nardoaristolone B (**1**) attracted our attention and this program was initiated. It is also worth highlighting that the structure of **1** is close to that of nootkatone (**3**), an interesting natural product with effective insect repellent/insecticidal activity[3] and AMPK (Adenosine Monophosphate Kinase) activity.[4] As the structural features are similar to that of nootkatone **3**, compound **1** and its analogues are expected to show a range of biological activities.[5] The synthesis of the nardoaristolone B and its close analogues are described here.

The retrosynthetic analysis is shown in Scheme 1. Nardoaristolone B (**1**) and its analogues could be prepared using stereoselective cyclopropanation of dienone **A**. The dienone **A** could be prepared from diene **B** through double allylic oxidation. The requisite hydrindane scaffold **B** could be constructed from tiglic aldehyde, and the appropriate diene, through a sequence of Diels–Alder (DA), Wittig, and ring-closing metathesis (RCM) reactions.

Scheme 1. Retrosynthetic Analysis



The synthesis began with a borontrifluoride-mediated Diels–Alder reaction between the diene **4**[6] and tiglic aldehyde to provide the Diels–Alder adduct,[7,8] which was immediately subjected to one carbon Wittig reaction to give the desired diene **6** in poor yield (8%–10%) but with very high diastereoselectivity (>9:1). The observed low yield could probably be due to inter/intramolecular condensation of both starting aldehydes. After a few trials, the same transformation was achieved in ∼41% overall yield by replacing the diene **4** with more stable diene **5**[9] and by the addition of two more steps (DIBAL-H reduction and Wittig reaction). The DA reaction of **5** also produced high diastereoselectivity (>9:1) as in the case of **4**. The Lewis acid mediated intermolecular Diels–Alder reaction produces the *endo*-adduct having both arms on the same side. The diastereo- and regioselectivity can be explained on the basis of secondary orbital interactions and atomic coefficient preferences, respectively.[10] The diene **6** was subjected to ring-closing metathesis (RCM) using the Grubbs'

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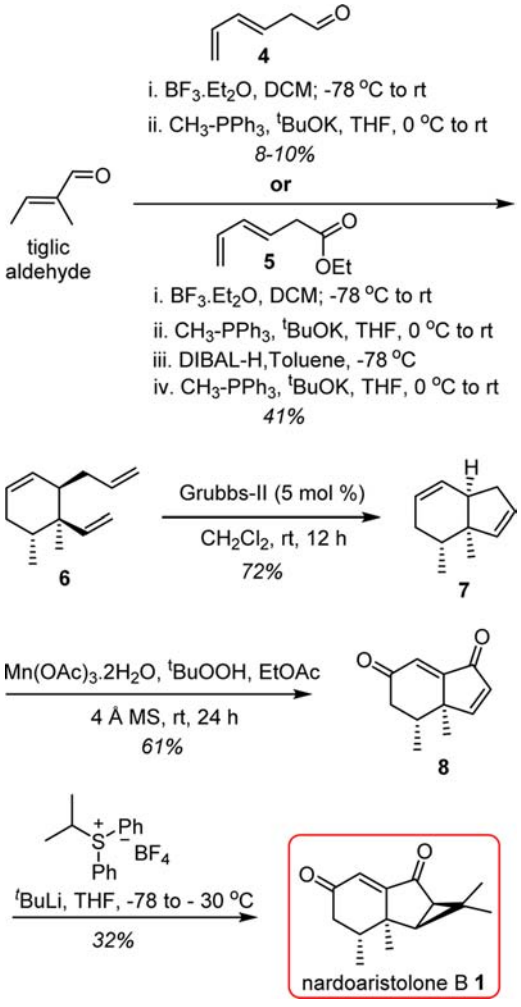
second-generation catalyst to obtain the *cis*-fused hydrindane **7** in 72% yield.[11] To prepare the desired ene-dione moiety present in **8** from **7**, a few different reagents/catalysts were explored through double-allylic oxidation. The combination of $Mn(OAc)_3{\cdot}2H_2O$–^{t}BuOOH[12] gave the best result to obtain compound **8** in 61% recycled yield.[13] After a few attempts, *gem* dimethyl cyclopropanation[14] was achieved by the treatment of diphenylisopropyl sulfonium tetrafluoroborate[15] with ^{t}BuLi in THF at −78 °C to −30 °C to give the target compound nardoaristolone B (**1**) in 32% yield (Scheme 2).[16] All the

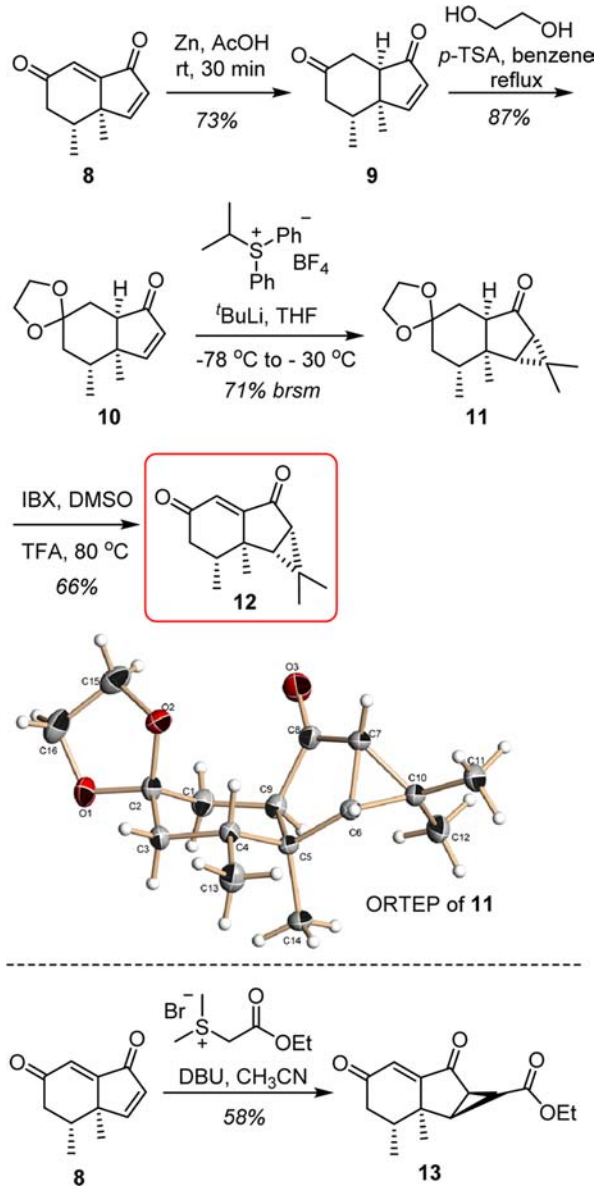
Scheme 2. Total Synthesis of Nardoaristolone B



spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS) were found to be identical to those reported in the isolation paper.[1] Thus, we have accomplished the first and protecting group-free total synthesis of (±)-nardoaristolone B (**1**) in just a few steps.

After the successful synthesis of nardoaristolone B, efforts were diverted to synthesize various close analogues of **1** which may help in developing a medicinal chemistry program around this novel scaffold. Toward this effort, compound **8** was treated with zinc dust in acetic acid[17] to yield *cis*-hydrindane compound **9** (73% yield) in a highly chemoselective and stereoselective manner. The isolated ketone moiety present in **9** was selectively protected as a ketal (ethylene glycol/cat. *p*-TSA, reflux conditions) to give **10**. The *gem* dimethyl cyclopropanation was achieved under similar conditions as described for compound **1** to afford the compound **11** with an *exo*-cyclopropyl ring. The assigned *exo*-stereochemistry of the cyclopropane ring was confirmed unambiguously by its single crystal X-ray analysis. Treatment of compound **11** with IBX/DMSO at 80 °C resulted in the desired compound **12** in 66% yield (Scheme 3). The assigned structure was further confirmed

Scheme 3. Synthesis of Nardoaristolone B Analogues



by additional 2D NMR spectroscopic data, and the details are provided in the Supporting Information. It is noteworthy to mention that one-pot ketone deprotection followed by oxidation to give enone was not documented in the literature.[18] The opposite stereoselectivities observed during cyclopropanation in compounds **8** and **10** could be explained simply by using the shape of these compounds as shown in Figure 2. The nearly planar structure in compound **8** will favor the reagent sulfur ylide to approach from the *endo* side (opposite side of methyl groups), and the convex-shape of compound **10** will favor the approach from the *exo* side (same side of methyl groups). It is possible to generate cyclopropyl diversity using the intermediates dienone **8** and enone **10** with various cyclopropanating reagents. It was demonstrated with one such

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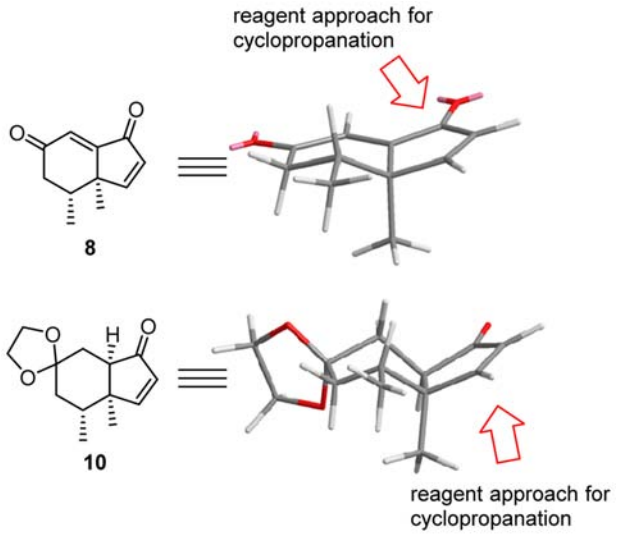


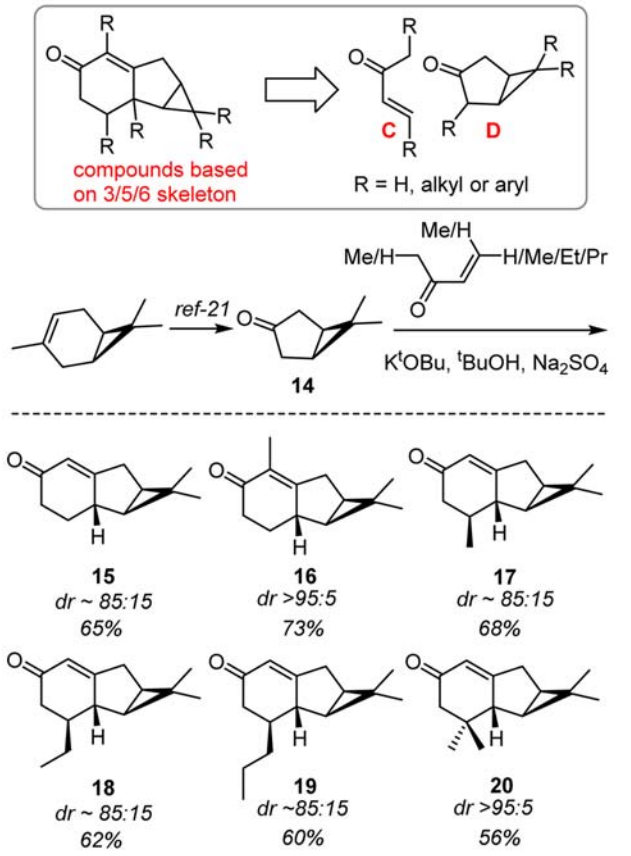
Figure 2. Plausible explanation for the observed stereoselectivity during cyclopropanation (structures are minimized using Chem3D).

reaction using carboethoxymethyl-dimethyl sulfonium bromide ($Me_2S^+CH_2CO_2Et\ Br^-$)[19] in the presence of DBU to afford compound **13** in 58% yield.

As the 3/5/6 tricyclic fused ring system is an unusual skeleton,[20] developing multiple and simple methods to access these compounds will be useful, in particular, for synthesizing a library of molecules in medicinal chemistry programs. For this purpose, we have envisioned the synthesis of a 3/5/6 tricyclic fused system using a simple approach starting from appropriately substituted enones **C** and cyclic ketones **D** as shown in Scheme 4. To demonstrate the planned strategy, the symmetric ketone **14**[21] prepared from 3-carene was treated with various acyclic enones in the presence of 10 mol % of potassium *tert*-butoxide in *tert*-butanol[22] to furnish the desired enones (**15**–**20**) with a 3/5/6 tricyclic fused system in just one step. The complete experimental details are provided in the Supporting Information. The observed diastereomeric ratios and the obtained yields are compiled in Scheme 4. The high stereoselectivity of the newly generated chiral centers can be explained by the rigid convex shape of the starting ketone **14**. All the products **15**–**20** were fully characterized, and the assigned stereochemistry was supported by 2D NMR experiments on two compounds **16** and **18** (Figure 3).[23] The use of appropriate starting materials and experimental conditions can produce a vast library of compounds based on the 3/5/6 tricyclic scaffold including enantiopure ones.

In conclusion, we have accomplished the first stereoselective synthesis of (±)-nardoaristolone B using a very short and protecting-group-free sequence. We have synthesized a few novel analogues of nardoaristolone B including an *exo*-cyclopropyl containing compound. The Diels–Alder/Wittig/RCM reaction sequence, double allylic oxidation, and stereoselective cyclopropanations are the highlights of our synthesis. In addition, we have designed and demonstrated another simple strategy using Robinson annulation to access a library of molecules with the 3/5/6 tricyclic fused ring system, which are close analogues of the target nardoaristolone B.

Scheme 4. Alternate Strategy To Access Compounds Based on the 3/5/6 Skeleton



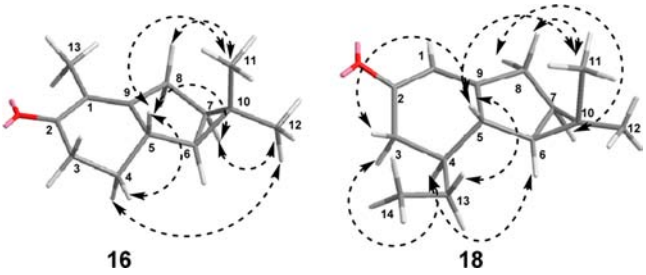


Figure 3. Observed NOE correlations of **16** and **18**.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, NMR spectra, 2D-NMR analysis, detailed experimental procedures, and CIF file of X-ray crystal structure (CCDC #1009596). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) The ratio of diastereomers was determined using ^{1}H NMR of the crude material. Additional details of 2D NMR analysis are available in the Supporting Information.