

Syntheses of Optically Pure Conduramines via the Strategy of Hetero Diels–Alder Reaction of Masked α -Benzoquinones with Homochiral Nitroso Dienophiles

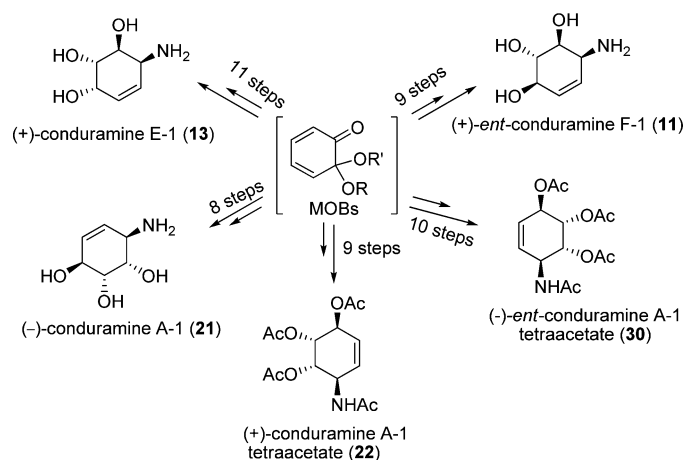
Ping-Hsun Lu,^{†,‡} Ching-Shun Yang,[†] Badugu Devendar,^{†,‡} and Chun-Chen Liao^{*,†,‡}

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan, and
Department of Chemistry, Chung Yuan Christian University, Chungli 32023, Taiwan

ccliao@cycu.edu.tw

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ABSTRACT



Highly stereoselective hetero Diels–Alder reactions of masked α -benzoquinones (MOBs) with homochiral nitroso dienophiles are described along with their application in the syntheses of (+)-*ent*-conduramine F-1, (+)-conduramine E-1, (-)-conduramine A-1, (+)-conduramine A-1 tetraacetate, and (-)-*ent*-conduramine A-1 tetraacetate.

Conduramines are aminocyclohexenetriols formally derived from conduritols, in which one of the hydroxyl groups is exchanged with an amino group. They constitute a continuing and growing class of important compounds with often interesting biological activities. Indeed, some of the conduramines have significant glycosidase inhibitory effects.¹ Some

also serve as important precursors of a wide variety of natural products, such as (+)-lycoridine,² (+)-narciclasine,³ (-)-lycorine,⁴ and azasugars⁵ (Figure 1).

Several research groups^{6–17} have reported fascinating syntheses of racemic^{6–8} and optically pure^{9–12} conduramines

[†] National Tsing Hua University.

[‡] Chung Yuan Christian University.

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and their derivatives. Muchowski and co-workers have developed a synthetic pathway for ($\pm$)-conduramine A-1 from pyrrole.⁸ The first asymmetric synthesis of optically pure (+)-conduramine F-1 was achieved by Paulsen and co-workers,⁹ using homochiral polyols. Later, Hudlicky and co-workers¹⁰ synthesized (+)-conduramine A-1 and (+)-dihydroconduramine A-1 from homochiral cyclohexadienediol and nitrosyl derivatives. Very recently, Studer and co-workers reported an enantioselective nitroso Diels–Alder reaction and its application in the synthesis of (–)-peracetylated conduramine A-1.^{12b} However, the syntheses of chiral conduramines have been limited to methods that use dihydroxydiene¹⁰ and chiral building blocks, such as L-quebrachitol,⁹ D-glucose,¹¹ and their derivatives.^{16,17}

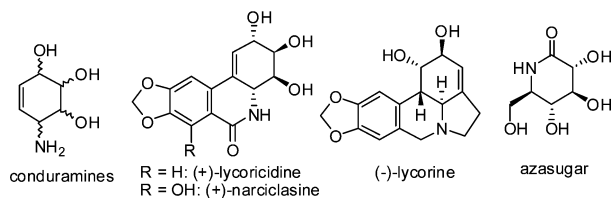


Figure 1. Conduramines and various types of interesting natural products containing conduramine frameworks.

Masked *o*-benzoquinones (MOBs),¹⁸ which are highly reactive cyclohexa-2,4-dienones, can be generated by the oxidation of easily accessible 2-methoxyphenols in methanol with diacetoxyiodobenzene (DAIB) or bis(trifluoroacetoxy)iodobenzene (BTIB). In continuation of our ongoing research program on the Diels–Alder reactions using MOBs,¹⁹ we have recently disclosed the results of hetero Diels–Alder reactions of MOBs with singlet oxygen, which afford a

variety of functionalized cyclopentenones. We have also applied this strategy to the synthesis of ($\pm$)-untenone efficiently.²⁰ We have carried out the first hetero Diels–Alder reactions of MOBs with nitroso dienophiles to access highly functionalized heterocyclic molecules.²¹ We have published intriguing results of highly diastereoselective and asymmetric Diels–Alder reactions of MOBs with homochiral furans, which lead to highly functionalized tricyclic ring systems with four stereogenic centers.²² We have also developed carbohydrate-templated asymmetric Diels–Alder reactions of MOBs for the synthesis of optically active bicyclo[2.2.2]oct-5-en-2-ones.²³ On the basis of this knowledge, our efforts turned toward the development of reactions of MOBs with homochiral nitroso compounds for the syntheses of valuable optically active intermediates for a wide variety of biologically important molecules. We herein report a facile and convenient route for the synthesis of optically pure conduramines starting from MOBs and homochiral nitroso compounds, prepared from (1*S*)-(+)- and (1*R*)-(–)-10-camphorsulfonic acids.

Since MOBs (as a diene^{18,19}) and nitroso dienophiles²⁴ are reactive species, we generated these two species *in situ*. MOBs were obtained from 2-methoxyphenols by oxidation with DAIB in MeOH, and the homochiral nitroso compounds were created from their hydroxylamine precursors with Bu₄NIO₄. Combining the solutions of these two reactive species, generated *in situ* at –10 °C, we produced an optically active nitroso Diels–Alder adduct in a one-pot operation. The chiral auxiliaries were chosen and prepared from (1*S*)-(+)- and (1*R*)-(–)-10-camphorsulfonic acids.²⁵

Accordingly, we synthesized the nitroso Diels–Alder adduct **2**, from 2-methoxyphenol **1** and chiral auxiliary A₁ at –10 °C. It was obtained as the major product of this reaction in 86% yield and 89% de. Upon simple recrystallization, **2** was obtained in high de (>99%) (Scheme 1). The

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Scheme 1. Syntheses of Allylic Azide **6**, Enone **7**, and Precursors of (+)-*ent*-Conduramine F-1 **8** and (+)-Conduramine E-1 **10**

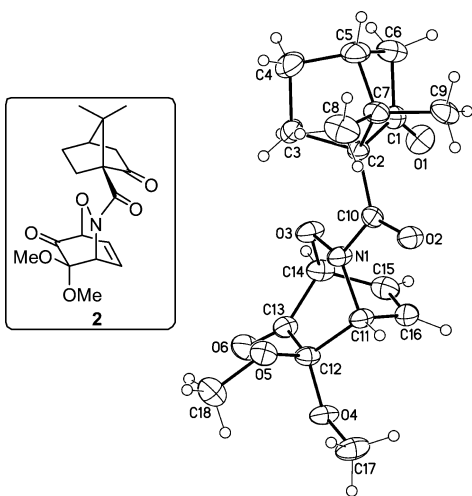
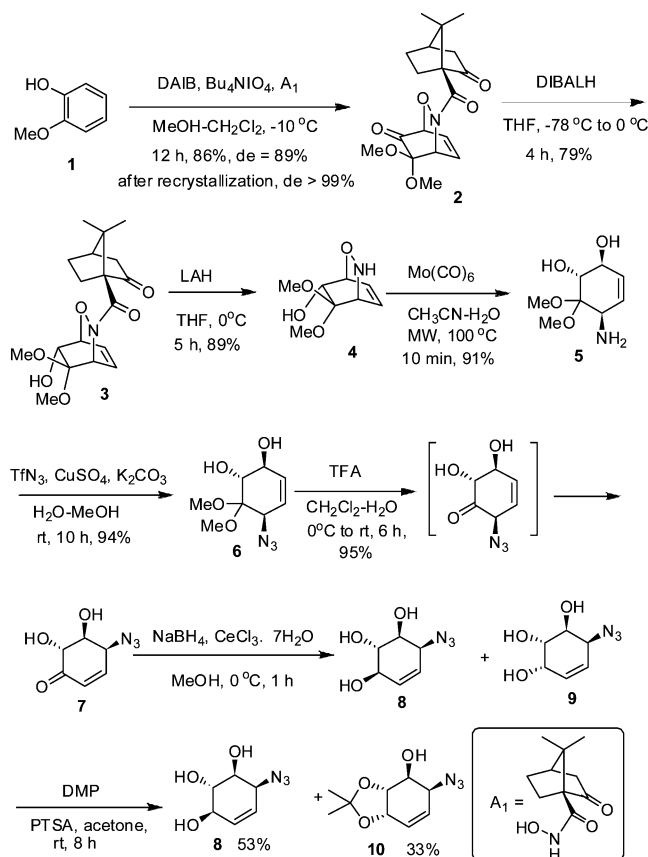


Figure 2. ORTEP diagram of Diels–Alder adduct **2**.

absolute configuration of **2** was confirmed by single-crystal X-ray diffraction (Figure 2 for ORTEP diagram and CCDC # 751811).

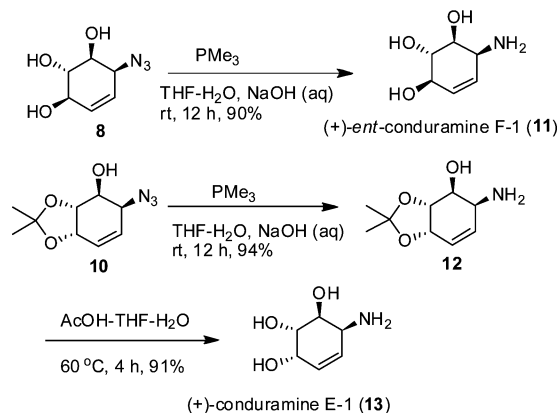
The nitroso Diels–Alder adduct **2** was further treated with DIBALH to obtain the hydroxyl compound **3** in 79% yield

with high stereoselectivity, and the chiral auxiliary was removed by LAH to obtain oxazine **4**; the camphor-based residue was oxidized to ketopinonic acid which was then converted to **A₁** for reuse.²⁵ Reductive cleavage of the nitrogen–oxygen bond of oxazine **4** in the presence of $\text{Mo}(\text{CO})_6$ gave amino alcohol **5**.²⁶

Several attempts were made to convert the ketal of **5** to the ketone without success. Finally, we converted the amine **5** to the azide **6** using TfN_3 and CuSO_4 (Scheme 1).²⁷ Treatment of allylic azide **6** with TFA at room temperature gave enone **7** by hydrolysis of the ketal functional group and [3,3]-sigmatropic rearrangement²⁸ in a one-pot operation. With enone **7** in hand, Luche reduction gave an inseparable mixture of alcohols **8** and **9**.²⁹ The mixture was treated with 2,2-dimethoxypropane (DMP) to protect the *cis*-diol **9** and generate the ketal **10**. The compounds **8** and **10** were isolated in 53% and 33% yields, respectively (Scheme 1).

The alcohol **8** under the Staudinger reaction conditions provided (+)-*ent*-conduramine F-1 (**11**).²⁷ A similar procedure was implemented for the synthesis of compound **12** from the alcohol **10**, and subsequent deprotection of the ketal group in the presence of AcOH produced the (+)-conduramine E-1 **13** (Scheme 2).

Scheme 2. Total Syntheses of (+)-*ent*-Conduramine F-1 **11** and (+)-Conduramine E-1 **13**



After successful delivery of (+)-*ent*-conduramine F-1 **11** and (+)-conduramine E-1 **13**, our interest was directed to the synthesis of (–)-conduramine A-1.

To achieve our target synthesis of (–)-conduramine A-1, we investigated the reaction of the MOB derived from 2-(methoxymethoxy)-phenol **14** with chiral auxiliary **A₂**, prepared from (1*R*)-(–)-10-camphorsulfonic acid. This provide **15a** and **15b** in 82% yield as an inseparable mixture which was further treated with DIBALH to reduce the ketone

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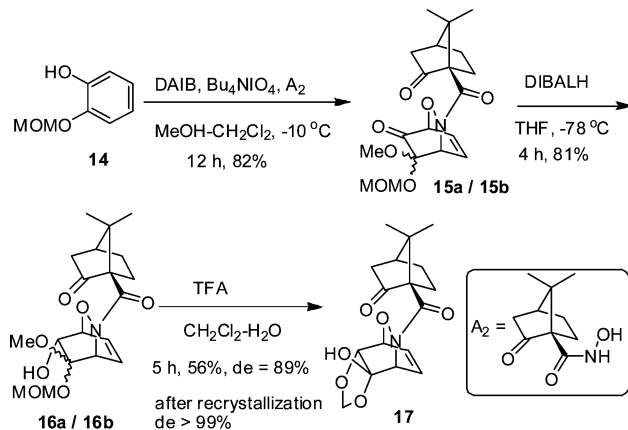
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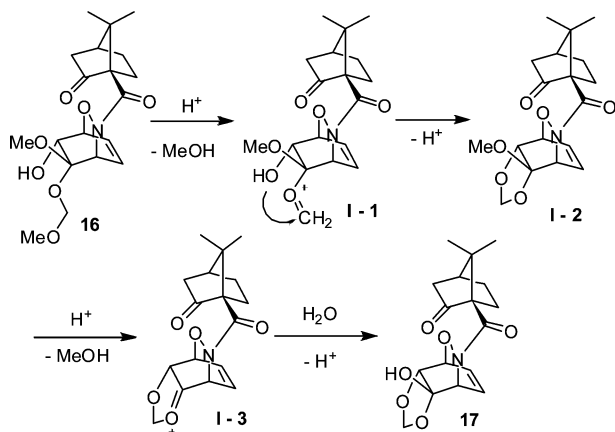
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group to give **16a** and **16b** in 81% yield. The mixture of **16a** and **16b** was hydrolyzed to hemiketal **17** in the presence of TFA in 56% yield and 89% de, which was enhanced to >99% after recrystallization (Scheme 3). The tentative mechanism for the conversion of **16** to **17** is represented in Scheme 4.

Scheme 3. Synthesis of Key Intermediate **17**

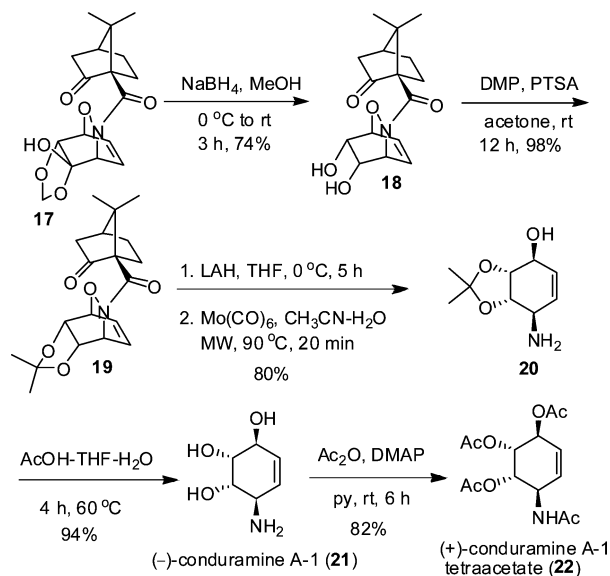


Scheme 4. Proposed Mechanism for Intermediate **17**



After several attempts at reduction with various reducing reagents, such as DIBALH, *L*-selectride, and NaBH₄, the best results were obtained when hemiketal **17** was treated with NaBH₄ in MeOH. This furnished the desired diol compound **18**, which was further treated with DMP to obtain ketal **19**. With the compound **19** in hand, we treated it successively with LAH and Mo(CO)₆ to obtain amino alcohol **20** in 80% overall yield over two steps. Under acidic conditions, acetone **20** was converted into the target (–)-conduramine A-1 **21** in 94% yield after purification by silica gel column chromatography. To compare the specific rotation with reported (+)-conduramine A-1 tetraacetate,⁷ we derivatized our (–)-conduramine A-1 **21** as (+)-conduramine A-1 tetraacetate **22** as depicted in Scheme 5.

Scheme 5. Syntheses of (–)-Conduramine A-1 **21** and (+)-Conduramine A-1 Tetraacetate **22**



We also successfully synthesized (–)-*ent*-conduramine A-1 tetraacetate **30**, from 2-(methoxymethoxy)phenol **14** and the homochiral nitroso compound, generated from chiral auxiliary A₁ (prepared from (1*S*)-(+)-10-camphorsulfonic acid). All the products (**25**–**29**) were well characterized by spectral data analysis (see Supporting Information).

In summary, we have developed the first diastereoselective hetero Diels–Alder reactions of MOBs with homochiral acylnitroso compounds from (1*S*)-(+)- and (1*R*)-(–)-10-camphorsulfonic acids to furnish bicyclo[2.2.2]octenone derivatives in high yields and high diastereoselectivities. We have also successfully applied these derivatives in the syntheses of (+)-*ent*-conduramine F-1 **11**, (+)-conduramine E-1 **13**, (–)-conduramine A-1 **21**, (+)-conduramine A-1 tetraacetate **22**, and (–)-*ent*-conduramine A-1 tetraacetate **30**. The utilization of this methodology for the synthesis of conduramine-based natural products is in progress.

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Supporting Information Available: Experimental details, ¹H, ¹³C NMR, DEPT spectra, and HPLC chromatograms for compounds **2**, **17**, and **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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