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Syntheses of Optically Pure Conduramines via the Strategy of Hetero Diels−Alder Reaction of Masked *o*-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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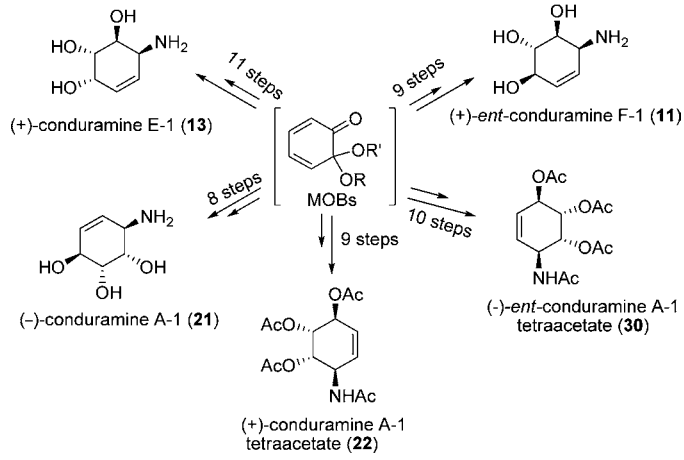
ABSTRACT



Highly stereoselective hetero Diels−Alder reactions of masked *o*-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 (+)-lycoricidine,[2] (+)-narciclasine,[3] (−)-lycorine,[4] and azasugars[5] (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 (±)-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-workers[10] 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 dihydroxydiene[10] and chiral building blocks, such as L-quebrachitol,[9] D-glucose,[11] and their derivatives.[16,17]

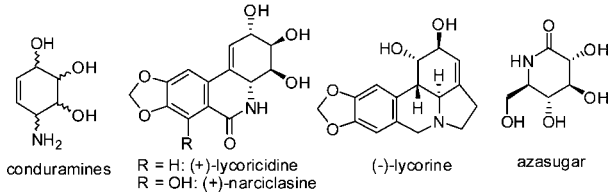

Figure 1. Conduramines and various types of interesting natural products containing conduramine frameworks.

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 (±)-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 dienophiles[24] 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 Bu_4NIO_4. 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 A_1 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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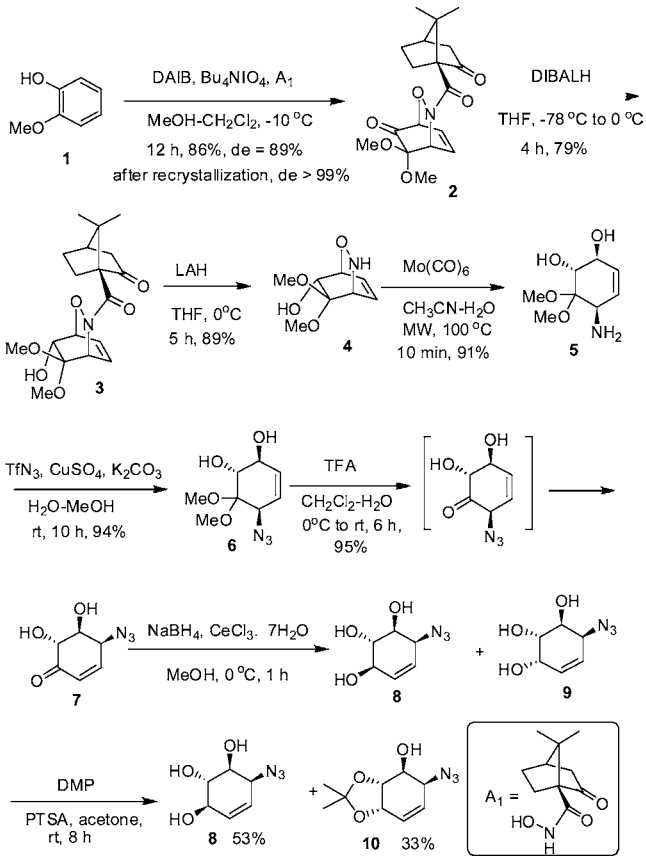
Scheme 1. Syntheses of Allylic Azide **6**, Enone **7**, and Precursors of (+)-*ent*-Conduramine F-1 **8** and (+)-Conduramine E-1 **10**



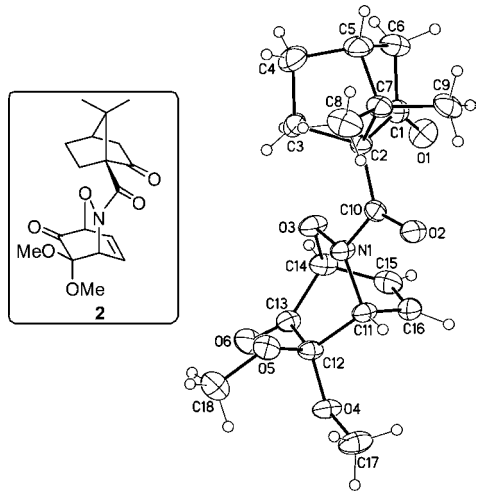


Figure 2. ORTEP diagram of Diels−Alder adduct **2**.

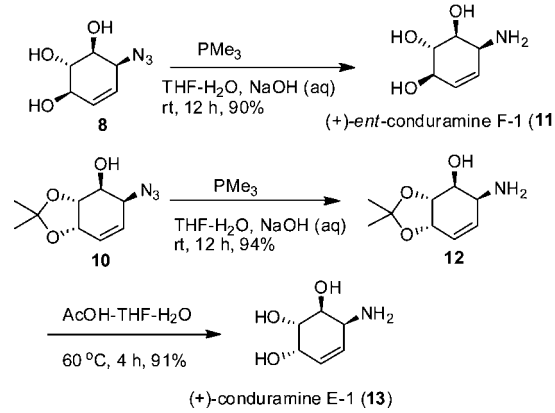
absolute configuration of **2** was confirmed by single-crystal X-ray diffraction (Figure 2 for ORTEP diagram and CCDC # 751811).

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 ketopinic acid which was then converted to A_1 for reuse.[25] Reductive cleavage of the nitrogen−oxygen bond of oxazine **4** in the presence of $Mo(CO)_6$ 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 rearrangement[28] 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 A_2, 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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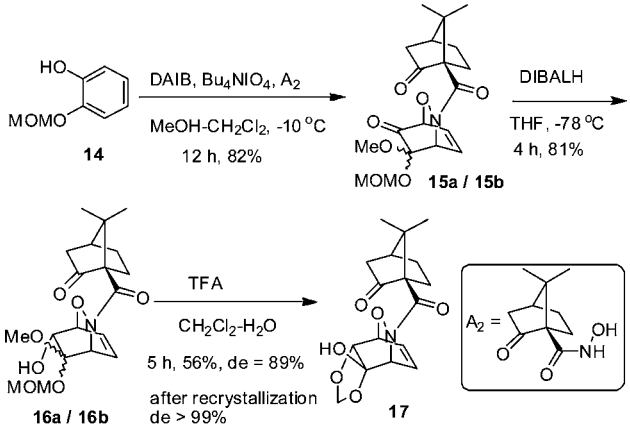
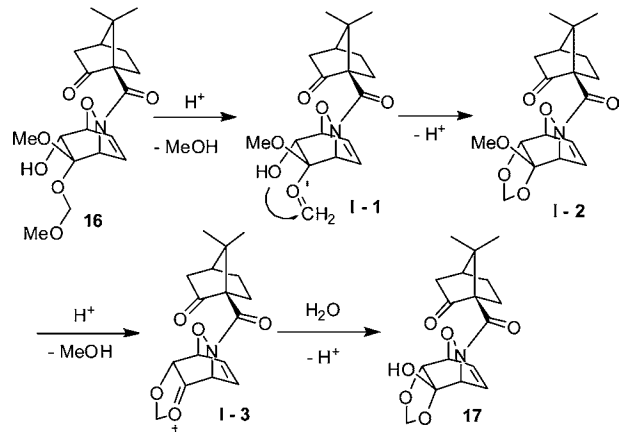
group to give **16a** and **16b** in 81% yield. The mixture of **16a** and **16b** was hydrolyzed to hemiketal **17** in the presence of TFA in 56% yield and 89% de, which was enhanced to >99% after recrystallization (Scheme 3). The tentative mechanism for the conversion of **16** to **17** is represented in Scheme 4.

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

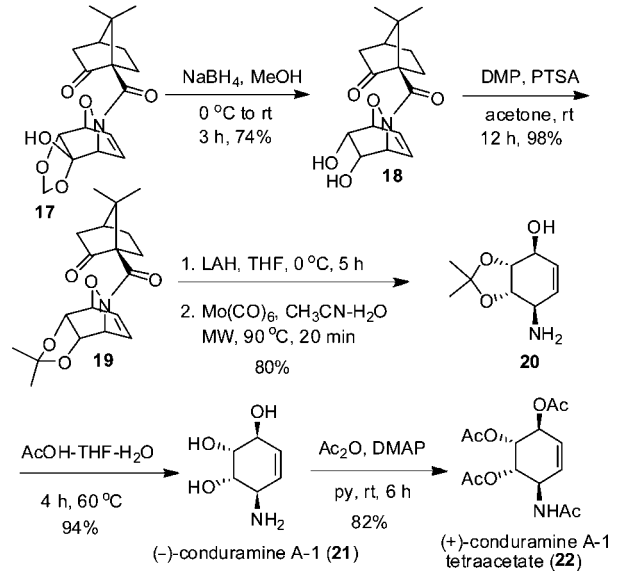


Scheme 4. Proposed Mechanism for Intermediate **17**



After several attempts at reduction with various reducing reagents, such as DIBALH, L-selectride, and $NaBH_4$, the best results were obtained when hemiketal **17** was treated with $NaBH_4$ 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, acetonide **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 A_1 (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, ^{13}C 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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