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Synthesis of (−)-Conduramine A1, (−)-Conduramine A2 and (−)-Conduramine E2 in Six Steps from Cyclohexa-1,4-diene

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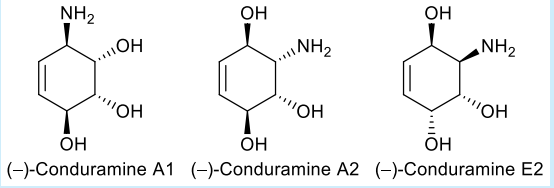
Supporting Information

ABSTRACT: A method to enable the synthesis of conduramines and their *N*-substituted derivatives (enantiopure or racemic form) in six steps (five steps for *N*-substituted derivatives) from cyclohexa-1,4-diene is reported. Key features of this reaction sequence include a preparation of benzene oxide that is amenable to multigram scale, and its efficient ring-opening upon treatment with a primary amine. Epoxidation of the resultant amino alcohols (40% aq HBF_4 then *m*-CPBA) is accompanied by hydrolytic ring-opening in situ to give the corresponding *N*-substituted conduramine derivatives directly. These may undergo subsequent *N*-deprotection to give the parent conduramines, as demonstrated by the preparation of enantiopure (−)-conduramine A1, (−)-conduramine A2, and (−)-conduramine E2 (the latter two for the first time). The selectivity of the epoxidation reaction is proposed to be the result of competitive ammonium-directed and hydroxyl-directed epoxidation processes, followed by either direct (S_N2-type) or conjugate (S_N2'-type) ring-openings of the intermediate epoxides.



Conduramines are derivatives of conduritols (cyclohexa-5-ene-1,2,3,4-tetraols) **1** in which one of the hydroxyl functionalities has been replaced by an amino functionality.[1] They have attracted interest due to their often potent biological activity as selective glycosidase inhibitors, a class of enzymes which are involved with the progression of a number of diseases.[1] The residue of conduramine F1, for example, is found as a substructural unit within acarbose (glucobay) **2**, a drug used for the treatment of type 2 diabetes mellitus.[2] This property of the conduramines has resulted in a significant amount of investigation being lavished on them. Interestingly, it has been found that derivatives of conduramines often possess enhanced biological activity over that of the parents; for example, (−)-conduramine B1 **3** itself has been shown to lack any inhibitory activity against a range of glycosidases, while the corresponding *N*-benzyl derivative **4** was found to display selective activity.[3] To further the interest in these compounds, a number of natural products containing the conduramine core are also known, including the *Amaryllidaceae* alkaloids narciclasine **5**[4] and lycoricidine **6**,[5] both of which contain the residue of conduramine A1 as a substructural unit and possess desirable biological activity (Figure 1).

The only source of these biologically interesting amino polyols is by means of laboratory synthesis, as none of the conduramine family themselves are naturally occurring.[1] Unsurprisingly, therefore, several routes to these compounds and their derivatives have been reported, although these are often rather lengthy and give rise to only one or two conduramine products.[1,6] Given our previous experience concerning the synthesis of dihydroconduramines,[7−9] we proposed that epoxidation (treatment with H^+ then *m*-CPBA) of allylic amino alcohols **7**, derived from the ring-opening of benzene oxide, would give the corresponding ring-opened products **8** and **9**, i.e., conduramines (R = H) or their *N*-protected derivatives (R ≠ H) directly. This approach to these compounds would be attractive in that it may allow the

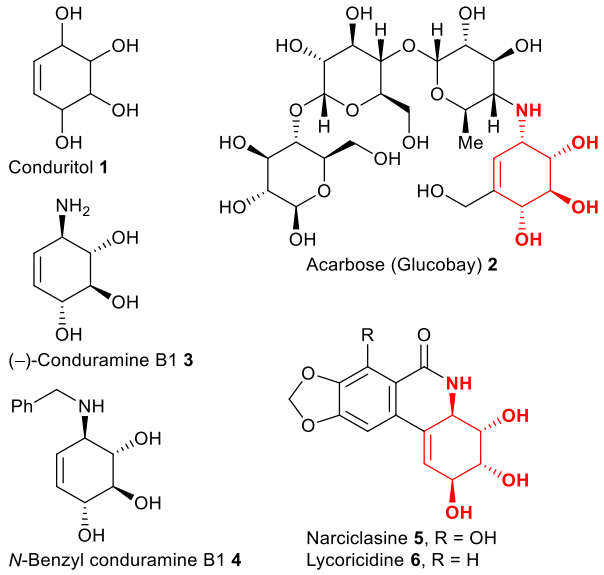


Figure 1. Structures of conduritol **1**, acarbose (glucobay) **2**, (−)-conduramine B1 **3**, *N*-benzyl conduramine B1 **4**, narciclasine **5**, and lycoricidine **6**.

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preparation of several diastereoisomers of the targets for biological profiling in very short order, and in any case would provide further insight into the relative abilities of the ammonium functionality versus the hydroxyl functionality to direct the epoxidation reaction.[10] Herein, we report our preliminary findings within this area, which culminates in the preparation of the racemic *N*-benzyl derivatives of conduramines A1, A2, and E2, and the enantiopure conduramines (−)-A-1, (−)-A2, and (−)-E2 themselves, in six steps or fewer from cyclohexa-1,4,-diene in each case (Figure 2).

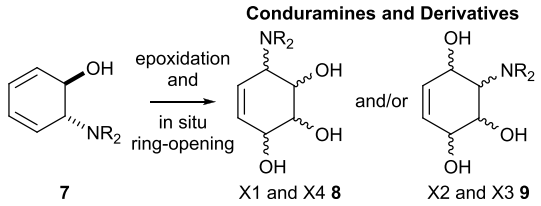
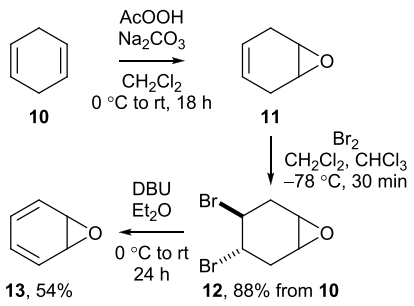


Figure 2. Proposed synthesis of conduramines and their derivatives **8** and **9** from allylic amino alcohols **7**.

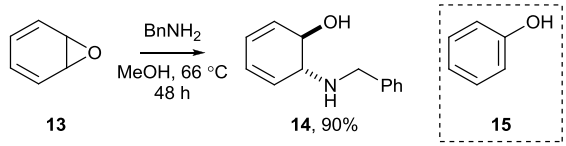
Our first goal was the development of a synthesis of benzene oxide amenable to scale-up, which was achieved by modification of the method first reported by Günther.[11] Treatment of cyclohexa-1,4-diene **10** with AcOOH in CH_2Cl_2 gave cyclohexa-1,4-diene monoepoxide **11** in 66% yield. Treatment of **11** with Br_2 in a mixture of CH_2Cl_2 and $CHCl_3$ delivered dibromide **12** in 91% yield (60% overall yield from **10**). When these two steps were telescoped, diluting the initial reaction mixture with $CHCl_3$ and adding Br_2 to the same reaction flask (i.e., obviating the isolation and purification of **11**), dibromide **12** was isolated in 88% overall yield from **10**, on a multigram scale. Final treatment of **12** with DBU in Et_2O gave benzene oxide **13** in 54% yield; this was generated, isolated, and immediately used, as required (Scheme 1).

Scheme 1. Large Scale Preparation of Benzene Oxide 13



Benzene oxide **13** remains an under-utilized building block in synthesis and its ring-opening, for example, has been surprisingly little explored.[12] We chose the ring-opening of **13** using benzylamine as a model system. Problems encountered were lack of reactivity, or promotion of an undesired rearrangement pathway giving phenol **15**. However, after optimization (variation of solvent, time, temperature, and the presence of Lewis acids) it was found that treatment of **13** with benzylamine in MeOH at 66 °C gave allylic amino alcohol **14** almost exclusively, and as a single diastereoisomer (>95:5 dr), with only trace amounts (<5%) of phenol **15** being formed, and upon purification **14** was isolated in 90% yield. The relative configuration within **14** could be confidently assigned as *trans*, due to the diagnostically large value of the ^{1}H NMR ^3J coupling constant (^3J = 12.1 Hz) between the protons attached to the two stereogenic centers (Scheme 2).

Scheme 2. Preparation of Allylic Amino Alcohol 14



Treatment of **14** with 40% aq HBF_4 and then *m*-CPBA gave a 21:36:31:12 mixture of four compounds, subsequently identified as *N*-benzyl conduramine A1 (**18**), *N*-benzyl conduramine A2 (**19**), *N*-benzyl conduramine E2 (**20**), and *N*-benzyl conduramine F2 (**21**), respectively. Purification by preparatory t.l.c. gave **18** in 8% yield, **19** in 23% yield, **20** in 18% yield, and an impure sample of **21** in ∼5% yield, as single diastereoisomers (>95:5 dr) in each case (Scheme 3). The gross structures of **18**−**21** were assigned by analyses of the typical range of 1D and 2D NMR spectra, while their relative configurations were subsequently established following treatment of each of **18**−**21** with H_2 in the presence of $Pd(OH)_2/C$, which effected tandem hydrogenation of the olefin functionality and hydrogenolytic removal of the *N*-benzyl group to give the corresponding dihydroconduramines A1 (**22**), A2 (**23**),[8] E2 (**24**),[9] and F2 (**25**);[9,13] the samples of **23**−**25** gave ^{1}H and ^{13}C NMR spectra that matched those previously reported[8,9] (thus confirming their identities, and hence the identities of **19**−**21**), while diagnostic values of the ^{1}H NMR ^3J coupling constants observed for **22** allowed its relative configuration (and hence that of **18**) to be confidently assigned. The observation of the four products **18**−**21** is consistent with monoepoxidation of the diene functionality within **14** being followed by a hydrolytic ring-opening reaction. In order to gain some insight into the precise details of the mechanism, the reaction was repeated using $HBF_4{\cdot}OEt_2$ in $H_2{}^{18}O$ (≥98% ^{18}O) in place of 40% aq HBF_4, which resulted in formation of the same four compounds in the same ratio (within experimental error), labeled with a single ^{18}O atom (92% incorporation of an ^{18}O label in each case, as judged by mass spectrometric analysis). The nature of the fragmentation of these compounds rendered mass spectrometry unsuitable as a tool to locate the position of the ^{18}O label, and therefore analysis of ^{16}O/^{18}O isotope-induced chemical shifts[14] in the ^{13}C NMR spectrum was employed to unambiguously locate the ^{18}O atom within each of these samples of **18**−**21**: >95% incorporation of the ^{18}O label was observed at C(1) in all cases, with all other positions showing negligible (<5%) incorporation of the label (Scheme 3). On the basis of these results, the following mechanistic hypothesis is proposed. As one of the olefins bears an allylic hydroxyl functionality and the other an allylic *N*-benzylamino functionality, both of which are known to be able to direct the olefinic epoxidation reaction to the proximal (*syn*) face in a six-membered-ring-system (presumably by formation of a hydrogen bond in the transition state),[15] the rate of background (nondirected epoxidation) was expected to be so low as to be a negligible contributor to the selectivity observed in the epoxidation step. Thus, out of the four possible regio- and diastereoisomeric products resulting from monoepoxidation of **14**, it is expected that only **16** (resulting from direction by the hydroxyl group) and **17**

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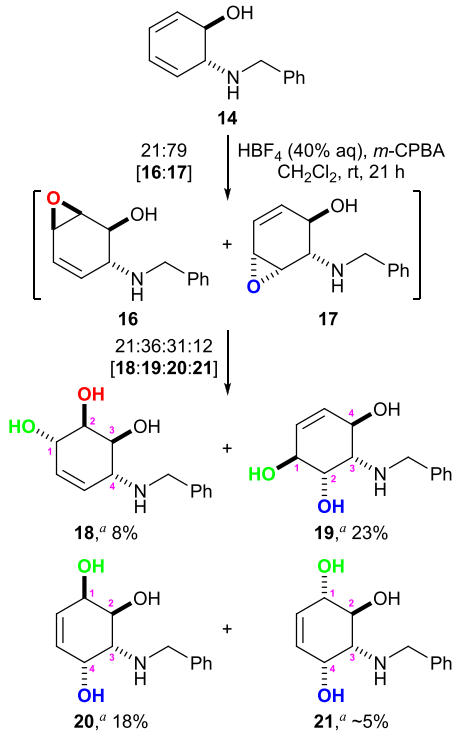
Scheme 3. Preparation of Racemic *N*-Benzyl Conduramines A1 (18), A2 (19), E2 (20), and F2 (21)

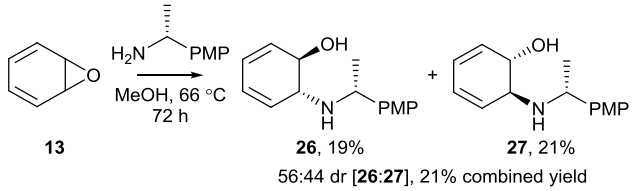


[a]The positions of the ^{18}O labels when run with $H_2{}^{18}O$ (see text) are shown in green; the proposed positions of the oxygen atoms derived from *m*-CPBA are shown in either red (for **16** and derivatives) or blue (for **17** and derivatives) for clarity. IUPAC numbering of **18**–**21** is also shown.

(resulting from direction by the *N*-benzylammonium group) are formed as intermediates in this reaction. Regioselective ring-opening of **16** in an S_N2-type fashion (with inversion of configuration) gives **18**, and an analogous process for **17** gives **19**. Competitive S_N2'-type ring-opening of epoxide **17** would result in the formation of **20** and **21**. Although both S_N1'- and S_N2'-types of hydrolytic ring-opening of **17** could give rise to **20** and **21** as a mixture of epimers,[16] it is proposed that the latter (i.e., S_N2'-type process) is more likely in operation, as we have observed no evidence of a predilection toward the formation of a cation intermediate in any of the examples of this reaction that we have previously studied.[17] Importantly, the lack of incorporation of the ^{18}O label at C(4) within **20** indicated that S_N2'-type hydrolytic ring-opening of epoxide **16** was a negligible contributor to the production of **20** in this reaction. Assuming this mechanistic rationale, the ratio of the intermediate epoxides **16** and **17** in this reaction is therefore represented by the ratio **18**:(**19**+**20**+**21**), i.e., approximately 1:4, which is a measure of the relative directing abilities of the two functionalities in this specific instance (Scheme 3). The superior ability of the *N*-benzylamino substituent versus the hydroxyl substituent to direct the epoxidation reaction (i.e., promote a faster reaction) is consistent with our previous observations in a related system.[10]

With a route to racemic conduramine derivatives in hand, a route to enantiopure materials was investigated. Ring-opening of benzene oxide **13** upon treatment with enantiopure (*R*)-*α*-methyl-*p*-methoxybenzylamine gave a mixture of two compounds, **26** and **27**, in an approximate 50:50 ratio—thus showing no propensity for desymmetrization under these conditions, as expected.[18] These compounds were separated chromatographically to give **26** in 19% yield and **27** in 21% yield, along with a mixed fraction in 21% combined yield (Scheme 4). The relative configuration within **27** was unambiguously assigned by single crystal X-ray diffraction analysis,[19] with the absolute configuration following from the known (*R*)-configuration of the *α*-stereocenter (Figure 3). The dihedral angle between the two protons on the two stereogenic centers in the solid state was 175°, and as before, the large value of the ^1H NMR ^3J coupling constant (^3J = 12.9 Hz) between these protons was consistent with an analogous conformation being favored in solution and also indicative of the *trans* relative configuration. On this basis, **26** was assigned as the alternative *trans* diastereoisomer that would result from ring-opening of the *meso*-epoxide **13** by the enantiopure nucleophile; the large value of the ^1H NMR ^3J coupling constant (^3J = 11.5 Hz) between the protons on the two stereogenic centers was supportive of this assignment.[20]

Scheme 4. Preparation of Allylic Amino Alcohols 26 and 27



PMP = *para*-methoxyphenyl.

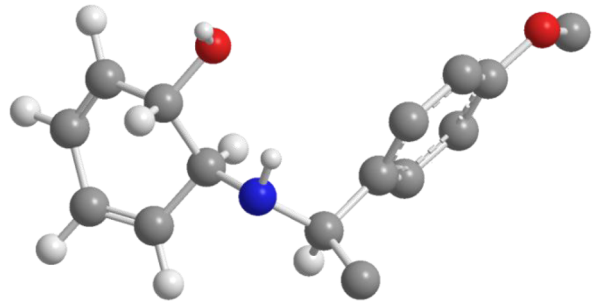


Figure 3. X-ray crystal structure of **27** (selected H atoms have been omitted for clarity).

Allylic amino alcohol **26** was arbitrarily selected for elaboration to the corresponding conduramines (as **26** and **27** may be considered as pseudoenantiomeric for this purpose). Treatment of **26** with 40% aq HBF_4 and then *m*-CPBA gave a 17:37:32:14 mixture of four compounds, identified as *N*-*α*-methyl-*p*-methoxybenzyl conduramine A1 (**30**), *N*-*α*-methyl-*p*-methoxybenzyl conduramine A2 (**31**), *N*-*α*-methyl-*p*-methoxybenzyl conduramine E2 (**32**), and *N*-*α*-methyl-*p*-methoxybenzyl conduramine F2 (**33**), respectively. Purification by preparatory t.l.c. gave **30** in 8% yield, **31** in 21% yield, **32** in 15% yield, and an impure sample of **33** in ~5% yield, as single diastereoisomers (>95:5 dr) in each case. As before, the gross structures of **30**–**33** were assigned by analyses of the typical range of 1D and 2D NMR spectra and the relative configurations within **31**–**33** were then assigned on the basis of the similarities between their ^1H NMR ^3J coupling constants and those of the corresponding products **19**–**21** derived from amino alcohol **14**.[13] The absolute

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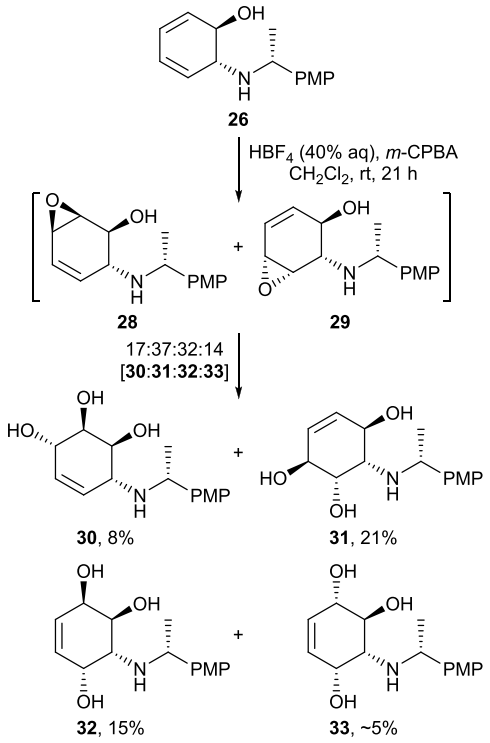
configurations then followed from the known absolute configurations of the stereocenters derived from the *trans*-amino alcohol **26**. The relative configuration within **30**, meanwhile, was subsequently assigned (vide infra). As the ratio of **30**−**33** is the same (within experimental error) as the ratio of the corresponding products **18**−**21** generated when **14** was subjected to the same reaction conditions, analogous mechanisms to rationalize the formation of each of **30**−**33** from amino alcohol **26** may be surmised (Scheme 5).

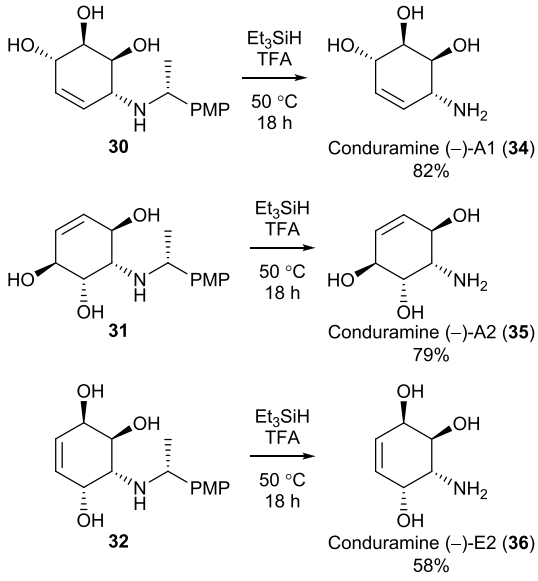
Scheme 5. Preparation of Enantiopure *N*-α-Methyl-*p*-methoxybenzyl Conduramines A1 (30), A2 (31), E2 (32), and F2 (33)



Finally, treatment of **30**−**32** with Et_3SiH in the presence of TFA effected removal of the α-methyl-*p*-methoxybenzyl fragment to give (−)-conduramine A1 (**34**), (−)-conduramine A2 (**35**), and (−)-conduramine E2 (**36**), in 82%, 79%, and 58% yield, respectively, and in >95:5 dr in each case. The former, (−)-conduramine A1 (**34**), has been previously described[21] (as has its antipode),[22] and thus the relative and absolute configurations of **30** were secured. The latter two, (−)-conduramine A2 (**35**) and (−)-conduramine E2 (**36**), have not been previously described (Scheme 6).

In conclusion, the synthesis of a range of conduramines and their *N*-protected derivatives has been achieved in very short order from cyclohexa-1,4-diene. The key steps of the process involve formation of benzene oxide and its ring-opening with a primary amine. Epoxidation (HBF_4 then *m*-CPBA) of the resultant allylic amino alcohols is controlled by hydrogen-bonding to either the allylic hydroxyl functionality or the in situ formed allylic *N*-benzylammonium moiety, with the latter being superior over the former in its ability to promote epoxidation of the proximal olefin. Hydrolytic ring-opening of the resultant epoxide intermediates occurs in situ, via either a direct (S_N2-type) process or a conjugate (S_N2'-type) process, giving a mixture of the corresponding amino triol products.

Scheme 6. Preparation of Enantiopure Conduramines (−)-A1 (34), (−)-A2 (35), and (−)-E2 (36)



Despite the modest diastereoselectivity of the epoxidation reactions and multiple hydrolytic ring-opening reactions resulting in the production of mixtures of isomeric products, the low step-count results in overall yields which are comparable to or better than those of other multistep processes, as well as allowing rapid production of unknown conduramines and derivatives for biological profiling—these derivatives may display biological activity superior to that of the parent compounds. In the case of an *N*-α-methyl-*p*-methoxybenzyl protecting group, the corresponding enantiopure conduramines may be accessed upon deprotection. Further investigations, including investigation of the diastereoselectivity of the epoxidation reaction itself, are currently ongoing in our laboratory and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02914.

Experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1940566 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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