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Biomimetic Syntheses of the Neurotrophic Natural Products Caryolanemagnolol and Clovanemagnolol

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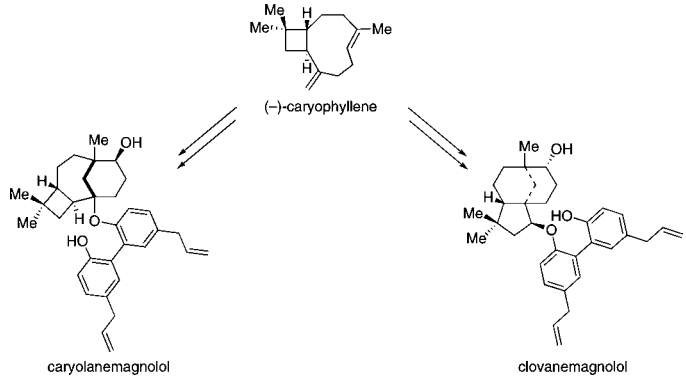
ABSTRACT



Separate short and modular syntheses of the isomeric natural products caryolanemagnolol and clovanemagnolol have been achieved starting from commercially available (−)-caryophyllene. The postulated biosynthetic pathways guided the syntheses of the neuroregenerative small molecules allowing their assembly in as few as two steps.

The discovery and study of small molecules capable of inducing biological function hold significant potential in the development of treatments for degenerative diseases that currently lack therapeutic options. In this line of inquiry, the sesquiterpene-neolignans caryolanemagnolol (**1**) and clovanemagnolol (**2**) were isolated from the bark of *Magnolina obovata* in a screen for compounds with potential neuroregenerative properties.[1,2] Treatment of primary neuronal cell cultures, derived from fetal rat cerebral hemisphere, with caryolanemagnolol led to neurite outgrowth, relative to controls, with pronounced growth at 0.1 mM. In addition, treatment of cultured neurons with caryolanemagnolol at the same concentration resulted in choline acetyltransferase (ChAT) activity being augmented by 163% relative to control cultures, leading to an increased biosynthesis of the neurotransmitter acetylcholine. Similarly, an isomeric natural product clovanemagnolol was shown to have the same neurotrophic activity at 10-fold higher concentrations.[1a,b] The understanding of how these small molecules cause a gain of biological function has potential in the discovery of new avenues for the treatment of

(1) (a) Fukuyama, Y.; Otoshi, Y.; Kodama, M. *Tetrahedron Lett.* **1990**, *31*, 4477. (b) Fukuyama, Y.; Otoshi, Y.; Miyoshi, K.; Nakamura, K.; Kodama, M.; Nagasawa, M.; Hasegawa, T.; Okazaki, H.; Sugawara, M. *Tetrahedron* **1992**, *48*, 377.

(2) (a) Heymann, H.; Tezuka, Y.; Kikuchi, T.; Supriyatna, S. *Chem. Pharm. Bull.* **1994**, *42*, 138. (b) Heymann, H.; Tezuka, Y.; Kikuchi, T.; Supriyatna, S. *Chem. Pharm. Bull.* **1994**, *42*, 941. (c) Matsuda, H.; Kageura, T.; Oda, M.; Morikawa, T.; Sakamoto, Y.; Yoshikawa, M. *Chem. Pharm. Bull.* **2001**, *49*, 716. (d) Wang, J.-D.; Zhang, W.; Li, Z. Y.; Xiang, W.-S.; Guo, Y.-W.; Krohn, K. *Phytochemistry* **2007**, *68*, 2426. (e) Zhu, Y.; Zhao, Y.; Huang, G.-D.; Wu, W.-S. *Helv. Chim. Acta* **2008**, *91*, 1894.

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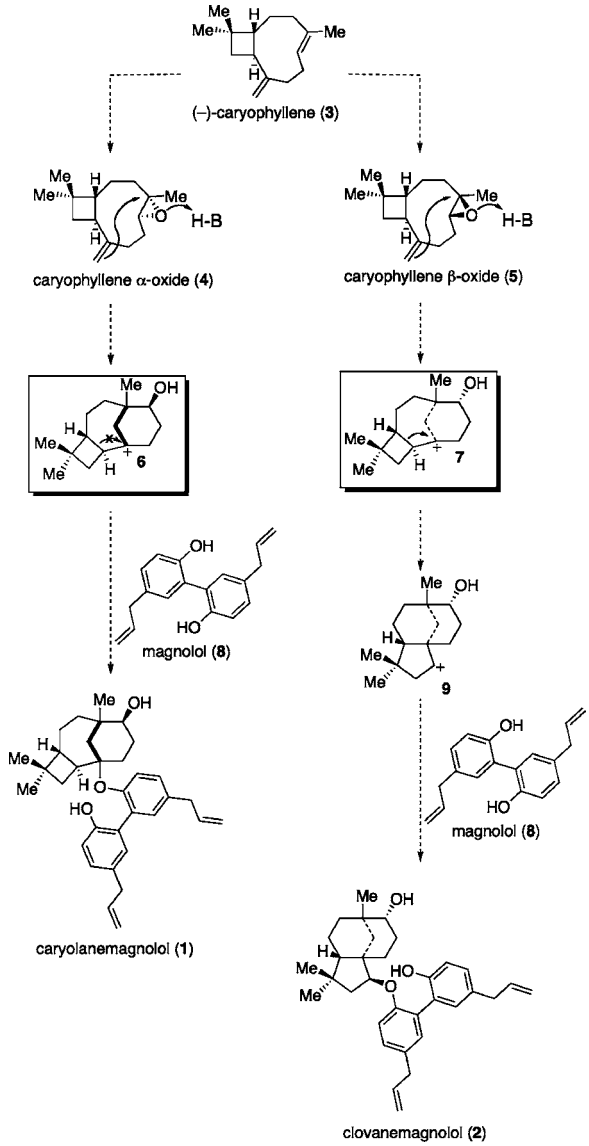
degenerative diseases associated with neuronal atrophy and/or diminished acetylcholine levels. Examples include Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and myasthenia gravis.

In addition to their related biological activities, caryolanemagnolol and clovanemagnolol likely arise in nature from the same starting material, (−)-caryophyllene (**3**). As put forth by Fukuyama and co-workers, the oxidation of (−)-caryophyllene (**3**), a bicyclic sesquiterpene found in many plant species including *Magnolia obovata*, provides either caryophyllene α-oxide (**4**) or caryophyllene *β*-oxide (**5**).[1,2a,3] Brønsted acid activation of either of the epoxides followed by intramolecular attack of the exocyclic alkene generates diastereomeric bridgehead carbocations **6** and **7** (Scheme 1).

Scheme 1. Proposed Biosyntheses of Caryolanemagnolol (**1**) and Clovanemagnolol (**2**)



In the caryolanemagnolol series, the trapping of bridgehead cation **6** by magnolol (**8**) directly generates the natural product. Cation **6** is expected to possess added stability as elimination reactions would form a strained anti-Bredt alkene and the transannular cyclobutyl carbon−carbon bond cannot migrate due to poor orbital overlap with the cation.[4] However, in the clovanemagnolol biosynthetic sequence, the cation of **7** is aligned with the transannular bond, enabling a ring expansion/ring contraction to form the cationic tricycle **9**. The secondary cation of **9** is subsequently trapped by magnolol (**8**) forming clovanemagnolol. In the structural elucidation of caryophyllene, Barton and co-workers were the first to describe these caryophyllene rearrangement reactions, which generated clovane and caryolane-based structures.[5] The postulated cascade reactions are predicted to facilitate the assembly of the polycyclic compounds. While the reported syntheses are not aimed at proving or disproving the plant-based pathways, the proposals provided inspiration for the synthetic routes.

Following from the proposed biosynthetic pathway, our synthesis of caryolanemagnolol was initiated using (−)-*β*-caryophyllene. As a starting material (−)-*β*-caryophyllene is ideal as it is available on large scale due to its use in the flavoring and fragrance industry and its high concentration in several essential oils including clove oil. The selective conversion of (−)-caryophyllene (**3**) to the α-epoxide **4** proved challenging due to the inherent stereochemical bias of the bicyclic system. Epoxidation of (−)-caryophyllene using *m*-CPBA provides a mixture of epoxides in a ratio of 1:5 favoring the *β*-epoxide **5** (Figure 1).[6] Attempts to change

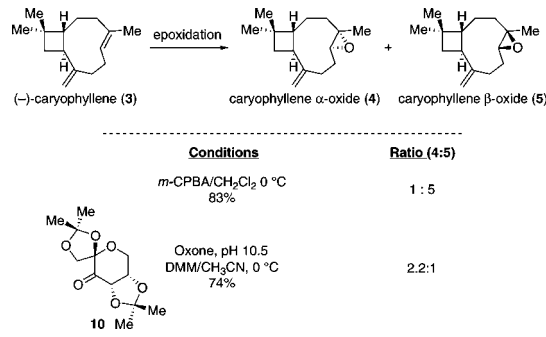


Figure 1. Diastereoselective epoxidation of (−)-*β*-caryophyllene.

the diastereoselectivity of the epoxidation reaction using halohydrin formation followed by base failed to generate either epoxide, instead generating allylic halides through an ene-type process.[7] Fortunately, the Shi catalyst **10**, which was prepared from l-sorbose in six steps, provided epoxide

(3) (a) Fujita, M.; Itokawa, H.; Sashida, Y. *Yakugaku Zasshi* **1973**, *93*, 415. (b) Sashida, Y.; Itokawa, H.; Akita, Y.; Fujita, M. *Yakugaku Zasshi* **1976**, *96*, 218.

(4) Bredt, J.; Thouet, H.; Schmitz, J. *Liebigs Ann. Chem.* **1924**, *437*, 1.

(5) (a) Aebi, A.; Barton, D. H. R.; Lindsey, A. S. *J. Chem. Soc.* **1953**, 3124. (b) Aebi, A.; Barton, D. H. R.; Burgstahler, A. W.; Lindsey, A. S. *J. Chem. Soc.* **1954**, 4659.

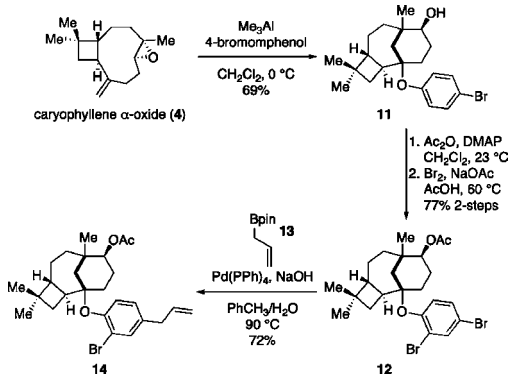
(6) Barrero, A. F.; Molina, J.; Oltra, J. E.; Altarejos, J.; Barragan, A.; Lars, A.; Segura, M. *Tetrahedron* **1995**, *51*, 3813.

(7) This reactivity likely arises from the lack of an appropriate approach for the water to open the corresponding bromonium species.

4 as the major product (2.2:1 ratio of α to *β*, 86% yield) overriding the substrate's diastereoselective preference.[8]

After significant experimentation with Brønsted and Lewis acids it was determined that the rearrangement of the α-epoxide **4** was optimally achieved using the in situ derived aluminum phenoxide generated through the combination of 4-bromophenol and trimethyl aluminum (3:1) in dichloromethane at 0 °C.[9] This reagent, when combined with **4**, provides the carbocyclic core of caryolanemagnolol in a single operation, yielding bromide **11** in 69% yield (Scheme 2). To verify the structural assignment the X-ray crystal

Scheme 2. Synthesis of Bromide **14**

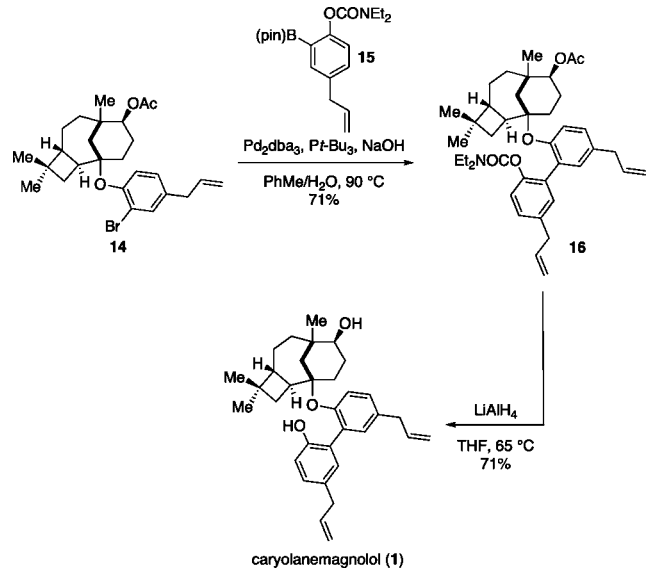


structure of the 3,5-dinitrobenzoyl ester of **11** was obtained.[10]

Due to the inability of 2,4-dibromophenol to effectively participate in the rearrangement reaction, the bromination of **11** was required for subsequent palladium bond-forming reactions. Preliminary attempts at halogenation of the aryl group occurred with competitive oxidation of the secondary alcohol, forming the corresponding ketone of **11**. As a result, protection of the secondary alcohol of **11** was required. An acetate was appended under standard conditions followed by installation of a second bromide using bromine and sodium acetate at elevated temperature (60 °C) to generate the dibromide **12** in 77% yield over two steps (Scheme 2). With the bromine atoms installed, sequential Suzuki reactions were used to form the allyl appendage and the biaryl bond.[11] In the majority of allylation reactions examined, Suzuki cross coupling led to diallylation of **12**. Using pinacol allylboronate **13**, tetrakis(triphenylphosphine)palladium catalysis, and close monitoring of the reaction, however, compound **14** could be isolated in 72% yield.

A second Suzuki reaction between bromide **14** and pinacol ester **15** (prepared in three steps from 4-allylanisole, Supporting Information) using conditions developed by Fu and co-workers formed the required biaryl bond, generating **16** in 71% yield (Scheme 3).[12] Simultaneous removal of the

Scheme 3. Completion of the Synthesis of Caryolanemagnolol



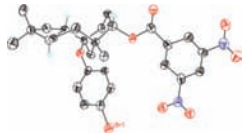
acetate and carbamoyl groups was achieved with lithium aluminum hydride providing caryolanemagnolol in 71% yield. While the synthetic material matched the spectra for the isolated caryolanemagnolol it should be noted that the original isolation report incorrectly stated the chemical shifts.[13]

The synthesis of clovanemagnolol was achieved over six steps similar to those used for the synthesis of caryolanemagnolol (Scheme 4). Unfortunately, the aluminum phenoxide reagent used in the caryolanemagnolol sequence failed to convert epoxide **5** to the carbocyclic clovane core structure. Therefore, starting from the recrystallized, commercial caryophyllene *β*-oxide (**5**) the rearrangement was achieved using diphenyl phosphate and 4-bromophenol providing the clovane core in 35% yield. Of the Brønsted and Lewis acids examined diphenyl phosphate proved optimal. Regrettably, as a result of a competing elimination reaction providing clovene, the rearrangement was less efficient than the reaction forming the caryolane core.[5,14] Conversion of bromide **17** to clovanemagnolol was achieved using the same set of transformations used in the caryolanemagnolol synthesis. The spectral properties of natural and synthetic clovanemagnolol fully match.[1,13]

(8) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, S. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

(9) (a) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1417. (b) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747.

(10) X-ray crystal structure of the 3,5-dinitrobenzoyl ester of **11**:

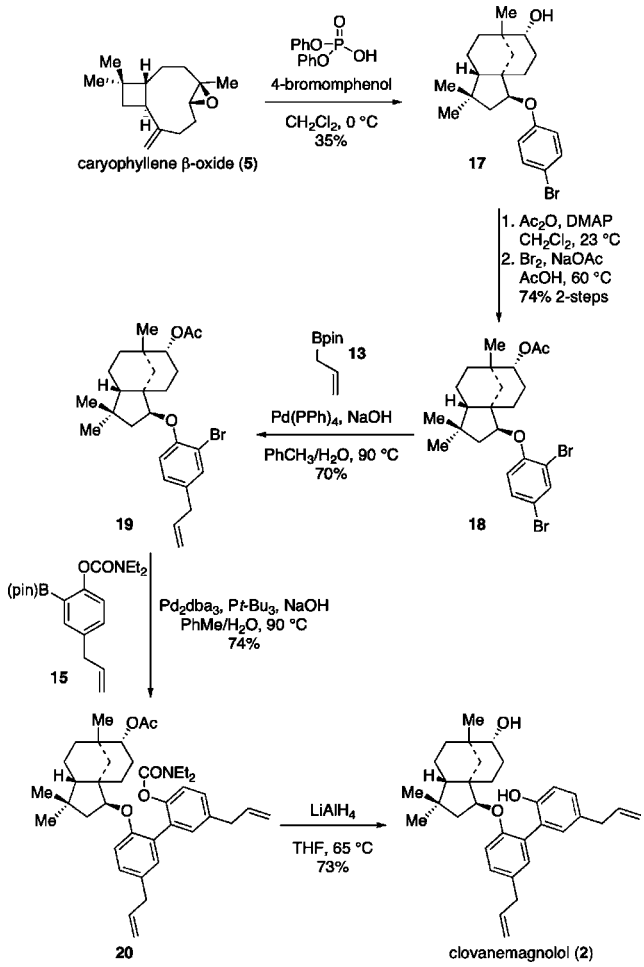


(11) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Sambasivarao, K.; Manoranjan, B.; Vrajesh, S. *Synlett* **2005**, 1877.

(12) (a) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

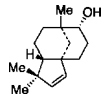
(13) Please see the Supporting Information for spectral comparisons of isolated caryolanemagnolol and clovanemagnolol to synthetic material. In addition, optical rotations of synthetic material were larger than those reported for the isolated compounds.

Scheme 4. Synthesis of Clovanemagnolol

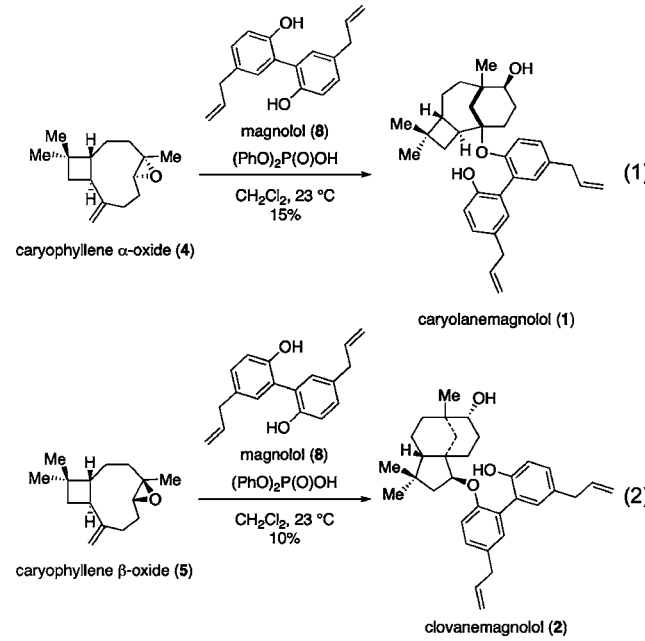


In an abbreviated approach the single step conversion of epoxides **4** and **5** to caryolanemagnolol and clovanemagnolol, respectively, was achieved using diphenyl phosphate and magnolol. Rearrangement of epoxide **4** with diphenyl phosphate and magnolol led to the formation of caryolanemagnolol in 15% yield (eq 1 below), comparing well with the multistep synthesis (19% overall from epoxide **4**).

(14) Structure of clovene:



Similarly, the acid mediated rearrangement of epoxide **5** provided clovanemagnolol in 10% yield using the same conditions (eq 2 below).[15] Starting from the corresponding epoxides these single-step transformations provided rapid access to the natural products, albeit in lower yields.



With access to caryolanemagnolol, clovanemagnolol, and synthetic intermediates we are currently investigating the effects of the small molecules on primary neuronal cultures. Through the examination of mRNA expression levels we will determine if specific, desirable gene products are upregulated upon treatment with compound(s).

Acknowledgment. We are grateful for financial support by the Welch Foundation, Texas Institute for Drug and Diagnostic Development, and The University of Texas at Austin. We also thank Prof. Fukuyam (Faculty of Pharmaceutical Sciences of Tokushima Bunri University) for the spectral data for **1** and **2** and helpful discussions.

Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a related transformation of caryophyllene α-oxide and magnolol using sulfuric acid, see ref 1a.