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A Formal Synthesis of (−)-Englerin A by Relay Ring Closing Metathesis and Transannular Etherification

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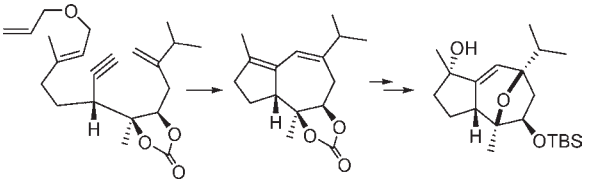
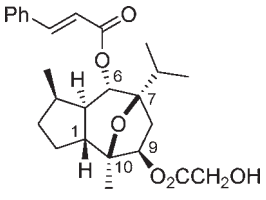
ABSTRACT



A bicyclization approach to englerin A has culminated in a formal asymmetric total synthesis. Key transformations in the 10-step sequence are a regiospecific epoxide opening and a relay ene-yne-ene metathesis that converts linear substrates specifically to $\Delta^{4,6}$-guaiadiene-9,10 diol derivatives. Regiospecific functionalization of the diene moiety installs the oxygen bridge required for the englerin tricyclic core.

(−)-Englerin A (**1**, Figure 1) is a natural product from *Phyllathus engleri*, a plant common in East Africa.[1] It displays selective and potent inhibition of the growth of renal cancer cell lines in the NCI-60 screen.

The compact and intriguing structure of this new lead has inspired several total syntheses.[2] The strategies conceived for the total synthesis of (−)-englerin A have provided analogs, and these have contributed to the development of a preliminary structure−activity relationship (SAR).[3] In light of the unique activity profile of (−)-englerin A, one can anticipate optimization of its pharmacological properties by the exploitation of mechanism of action studies and also by more extensive medicinal chemistry. In this context, each total synthesis is valuable in that it establishes proof-of-principle for a synthetic route to the tricyclic framework and also provides opportunities for variations on the scaffold itself.



1 (−)-englerin A

Figure 1. Structure of englerin A.

Our analysis of the structure of the englerin core (Scheme 1) led us to consider the hydroazulene **3** as the product of an ene-yne-ene metathesis-based bicyclization.[4] In this approach, bicyclic **3** would arise from tandem ring closure initiated by the ruthenium carbene **4**. Site-specific generation of this reactive intermediate required that our

(1) Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57.

(2) For completed syntheses and approaches, see the following reviews: (a) Chain, W. J. *Synlett* **2011**, 2605. (b) Pouwer, R. H.; Richard, J.-A.; Tseng, C.-C.; Chen, D. Y.-K. *Chem.—Asian J.* **2012**, *7*, 22. and (c) Lu, Y.; Yao, H.-Q.; Sun, B.-F. *Chin. J. Org. Chem.* **2012**, *32*, 1. Also, see: (d) Wang, C.-L.; Sun, B.-F.; Chen, S.-G.; Ding, R.; Lin, G.-Q.; Xu, J.-Y.; Shang, Y.-J. *Synlett* **2012**, *23*, 263.

(3) (a) Akee, R. K.; Ransom, T.; Ratnayake, R.; McMahon, J. B.; Beutler, J. A. *J. Nat. Prod.* **2012**, *75*, 459. (b) Ushakov, D. B.; Navickas, V.; Strobele, M.; Maichle-Mossmer, C.; Sasse, F.; Maier, M. E. *Org. Lett.* **2011**, *13*, 2090. (c) Chan, K. P.; Chen, D. Y.-K. *ChemMedChem* **2011**, *6*, 420. (d) Xu, J.; Caro-Diaz, E. J. E.; Batova, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Chem.—Asian J* **2012**, *7*, 1052. (e) Radtke, L.; Willot, M.; Sun, H.; Ziegler, S.; Sauerland, S.; Strohmann, C.; Frohlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3998.

(4) Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269.

(5) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

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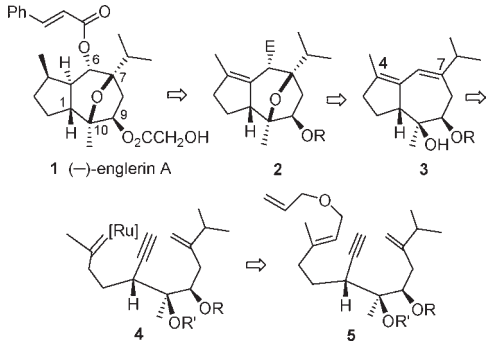
strategy be developed to include a relay metathesis step.[5] Thus, we designed substrate **5**. A metathesis cascade, specifically and conveniently initiated at the monosubstituted olefin of allyl ether **5**, was envisioned to proceed by way of ruthenium carbene **4** to give the desired **3**.

Scheme 1. Retrosynthetic Analysis



In order to complete a synthesis based on hydroazulene **3** with efficiency, we would have to differentiate the two double bonds so as to further the synthetic scheme. We postulated that reversible addition of a soft electrophile to diene **3** would be accompanied by transannular etherification across the seven-membered ring, leaving the cyclopentene olefin untouched (**3** → **2**). Indeed, examination of the two unstrained conformations available to an intermediate bridged cation **6** (Figure 2) led us to believe that the hydroxyl nucleophile would effect ring opening by attack at C-7 (conformation 2) as it cannot adopt a position that would allow backside attack at C-6.

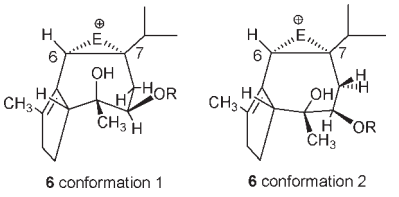
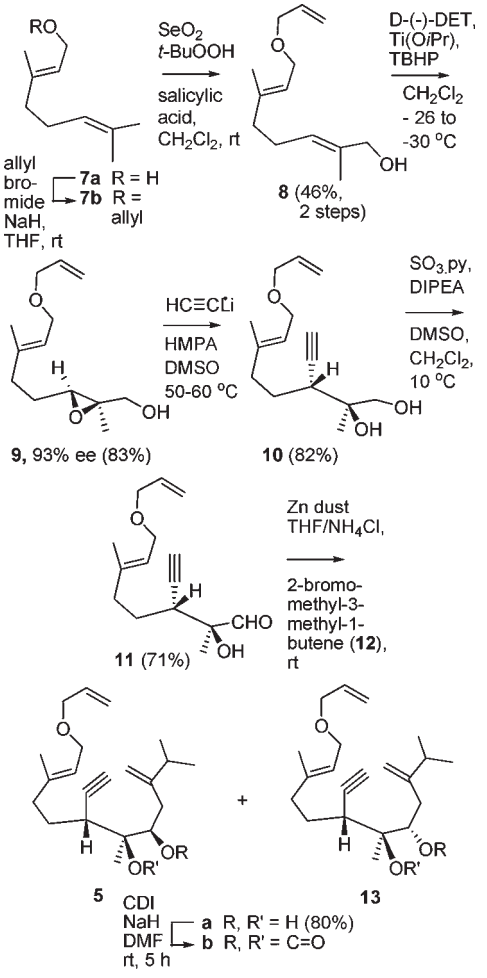


Figure 2. Two conformations available to bridged cation **6**.

Our strategy was attractive because it appeared that the relay ring closing metathesis (RRCM) substrate **5** would be readily available from geraniol (**7a**). Opening the ring of a 2,3-disubstituted epoxy alcohol at the 3-position (see **9** → **10**) seemed likely to provide access to the desired functionality pattern for substrate **5**. Implementation of a scheme based on these original concepts has now progressed to a formal total synthesis of (−)-englerin A.

Geraniol (**7a**) was converted to a mixture of diol derivatives **5b** and **13b** in seven steps (Scheme 2). *O*-Allylation followed by catalytic SeO_2 oxidation[6] gave a useful yield of the (*E*)-allylic alcohol **8**. Then Sharpless epoxidation[7] introduced chirality[8] and provided an opportunity to incorporate the required alkyne substituent with the desired stereochemistry at the latent C-1 (see **9**).

Scheme 2. Synthesis of RRCM Substrate **5**



We were surprised that we were unable to find an unbiased example of an acetylide opening of a 2-alkyl 2,3-epoxy alcohol or a derivative of such an alcohol.[9,10] Consequently we tested conditions reported to effect ring opening of 3-substituted 2,3-epoxy alcohols and their derivatives. Of these, the most successful was treatment of the epoxide opening with the Li-acetylide ethylene

(6) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5525. (b) Gaich, T.; Mulzer, J. *Org. Lett.* **2010**, *12*, 272.

(7) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Org. Chem.* **2009**, *74*, 230. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487.

(8) The enantiomeric excess of the Sharpless product was calculated from the ^{1}H NMR spectra of its Mosher esters; see the Supporting Information.

(9) See, however, the regiospecific ring opening of vinyl substituted examples: Narjes, F.; Schaumann, E. *Liebigs Ann. Chem* **1993**, 841.

(10) In addition, one might note the successful addition of acetylide to the 3-position of 2-substituted 2,3-epoxy esters: Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941.

(11) Parker, K. A.; Chang, W. *Org. Lett.* **2005**, *7*, 1785. Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521.

diamine complex in HMPA/DMSO.[11] This protocol provided diol **10** in 82% yield.

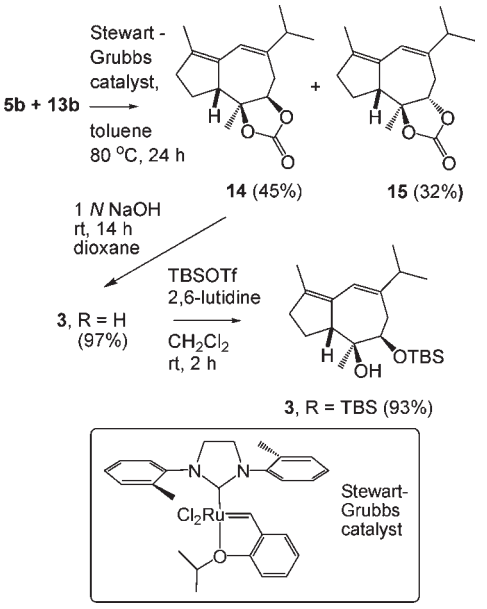
Parikh–Doering oxidation[12] gave aldehyde **11** which was subjected to a Barbier addition[13] with the reagent from 2-bromomethyl-3-methyl-1-butene (**12**).[14] This produced a mixture of the desired diol **5a** and its C-9 epimer, diol **13a**. With the goal of obtaining derivatives that would allow us to assign unambiguously the relative stereochemistries of the two diastereomers and to test metathesis conditions, we prepared the cyclic carbonates **5b** and **13b** by treating the diol mixture with carbonyl diimidazole (CDI).

Relay ring closing metathesis (RRCM) of the carbonate mixture (**5b** + **13b**) with the Stewart–Grubbs catalyst[15] gave a mixture of stereoisomers **14** and **15** (Scheme 3). This reaction is impressive in several respects: (1) only the guaiadiene ring system is generated; no decalin derivative was detected,[16] (2) the formation of the cyclopentene ring illustrates the capability of relay-initiated enyne metathesis to produce tetrasubstituted olefins, and (3) both carbonate stereoisomers **5b** and **13b** undergo bicyclization, giving **14** and the more conformationally rigid **15**, indicating the power of the Stewart–Grubbs catalyst.

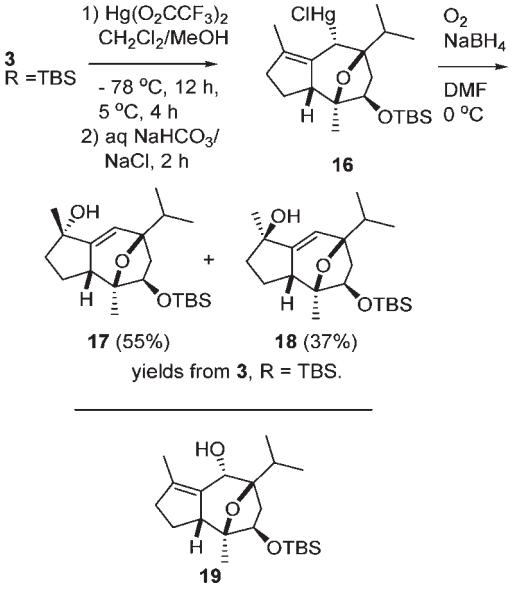
The major compound, isolated by chromatography in 45% yield, was assigned structure **14** on the basis of nuclear Overhauser effects (see the Supporting Information). Hydrolytic removal of the carbonate group gave diol **3** (R = H) and selective silylation of the secondary alcohol gave cyclization substrate **3** (R = TBS) in 90% yield for the two steps.

After some experimentation, we found conditions for introduction of the oxygen bridge. Our hope of effecting transannular opening of a $\Delta^{6,7}$ epoxide was disappointed when treatment of diene **3** (R = TBS) with mCPBA provided a product in which the olefinic proton was retained. Attempts to connect the oxygen bridge by haloetherification were uniformly unsuccessful, leading in most cases to the recovery of starting material. Oxymercuration with $Hg(O_2CCF_3)_2$ followed by addition of $NaCl/NaHCO_3$ solution[17] gave the alkyl mercurial **16** from regio- and stereospecific addition to the $\Delta^{6,7}$ olefin[18] (Scheme 4). Therefore, product formation was consistent with the proposed concerted addition portrayed in Figure 2.

Scheme 3. RRCM and Preparation of Transannular Etherification Substrate



Scheme 4. Oxymercuration/Oxidative Demercuration of Hydroazulene **3**



Oxidative demercuration[19] with $NaBH_4$ and O_2 in DMF provided a mixture of stereoisomeric tertiary alcohols **17** and **18** in which the functionality pattern of the allylic system has been reversed. Separation of the two diastereomers resulted in isolation of a 55% yield of the α-alcohol

(12) Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(13) Petrier, C.; Einhorn, J.; Luche, J. L. *Tetraheron Lett* **1985**, *26*, 1449.

(14) The known bromide **12** was prepared from the corresponding alcohol (see the Supporting Information) by the method of Barton, D. H.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. C* **1971**, 1968.

(15) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.

(16) This result may be compared with the nonspecific, nonrelay eneyne-ene metathesis of a similar, highly substituted system in which reaction, carried out under ethylene, is presumably initiated at the acetylene; see: Knueppel, S.; Rogachev, V. O.; Metz, P. *Eur. J. Org. Chem.* **2010**, 6145.

(17) (a) Broka, C. A.; Lim, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876. See also: (b) Kang, S. H.; Kim, M.; Kang, S. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 6177.

(18) One should note that this result is not inconsistent with regiochemistry observed in the oxymercuration of simple conjugated dienes; see: Barluenga, J.; Perez-Prieto, J.; Asensio, G. J. *Chem. Soc., Perkin Trans. 1* **1984**, 629.

(19) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

17 and 37% yield of the β-isomer **18**. Although the ionic transannular oxymercuration reaction was specific in the desired sense, oxidative demercuration through the radical intermediate resulted in oxygenation at C-4 rather than at C-6.

Although we would have preferred to obtain the known $\Delta^{4,5}$ C-6 alcohol **19**[20] directly, alcohol **17** has been converted to (−)-englerin A in seven steps (by way of alcohol **19**).[20] Therefore, access to alcohol **17** completes a formal synthesis of (−)-englerin A (**1**).

The synthesis of alcohol **17** illustrates the efficient opening of the epoxide ring of a β-substituted α-epoxy alcohol under the lithium acetylide conditions and the relay ene-yne-ene metathesis method for the preparation of a bicyclic diene that is disubstituted on both ends and that contains a tetrasubstituted olefin. Furthermore, the conversion of diene **3** to the mercurial **16** provides proof-of-concept for the soft electrophile-initiated regio- and stereoselective transannular etherification of $\Delta^{4,5}$, $\Delta^{6,7}$ guaiadienes. Approaches to compounds in the englerin series remain under investigation in our laboratories.

(20) This alcohol is a known compound, prepared from alcohol **17** in two steps and 60% yield as described in Molawi, K.; Delpont, N; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517.

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Supporting Information Available. Experimental procedures with analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.