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Progress toward the Total Synthesis of Bacchopetiolone: Application of a Tandem Aromatic Oxidation/Diels–Alder Reaction

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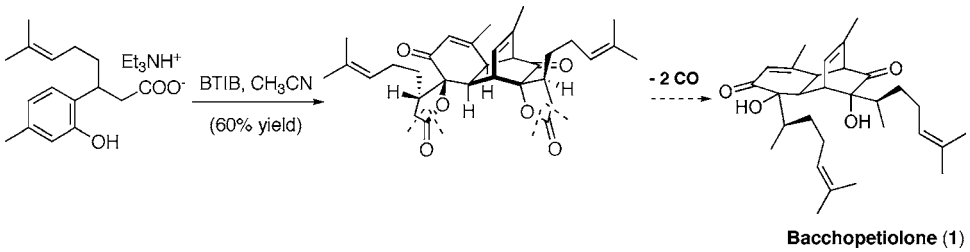
ABSTRACT



A stereoselective synthesis of the bacchopetiolone (1) carbocyclic core using a tandem phenolic oxidation/Diels–Alder reaction is described.

Bacchopetiolone (**1**) is a dimeric sesquiterpene that was isolated from a Chilean shrub, *Baccaris petiolata*, and reported by Niemeyer and co-workers in 1991.[1] Although no total synthesis has been reported, the biogenesis of **1** has been proposed to proceed through a [4+2] cycloaddition of the bisabolene derivative **2** (Scheme 1). In considering the proposed biosynthesis of **1**, we recognized that synthesis, in the form of a biomimetic synthetic strategy, could provide some insight into the dimerization leading to **1**. To this end, we envisioned that a tandem phenolic oxidation/Diels−Alder reaction of **4** would give rise to **3**, an advanced intermediate which is only two CO units removed from the natural product.

The feasibility of this strategy was supported by recent studies in our laboratories on the tandem phenolic oxidation/Diels−Alder reactions of aryl propionic acids.[2] Of particular relevance from these studies is the reactivity observed for 3-(2-hydroxyphenyl)-propionic acid **5** (Scheme 2) which, upon exposure to bis(trifluoroacetoxy)-iodobenzene (BTIB), produces a polycycle (**6**) that possesses the same relative stereochemistry as that found in **1**. This stereochemical outcome indicates that the initially formed spirolactone undergoes dimerization via approach of the two oxygen-bearing faces[3] in an endo transition state.[4]

In addition to **5**, we explored the reactivity of 3-(2-hydroxyphenyl) butyric acid (**7**), wherein stereogenicity resides at the benzylic position. Importantly, this substrate undergoes diastereoselective spirolactonization to furnish **9** which, in the presence of MVK, engages in a stereoelectronically controlled [4+2] reaction (cf., **5** to **6**) to furnish **8** as a single diastereomer.

On the basis of the previously observed reactivity of **5** and **7**, we speculated that exposure of an appropriately substituted 3-(2-hydroxyphenyl)-propionic acid (e.g., **4**) to

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(1) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, *30*, 1597−1601.

(2) Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493−496.

(3) Hou, H. F.; Peddinti, R. K.; Liao, C. C. *Org. Lett.* **2002**, *4*, 2477−2480.

(4) Gao, S. Y.; Ko, S.; Lin, Y. L.; Peddinti, R. K.; Liao, C. C. *Tetrahedron* **2001**, *57*, 297−308.

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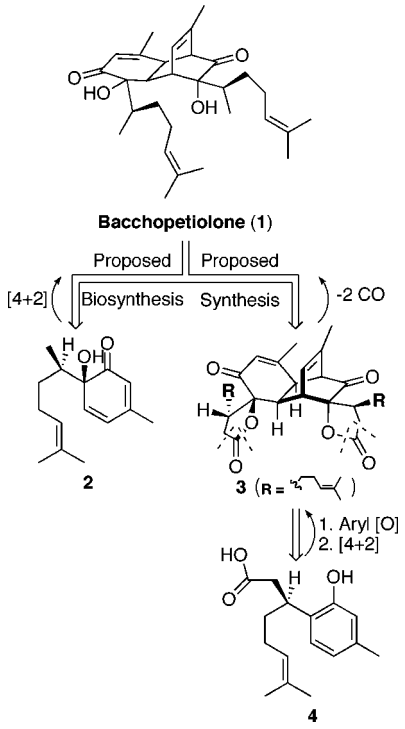
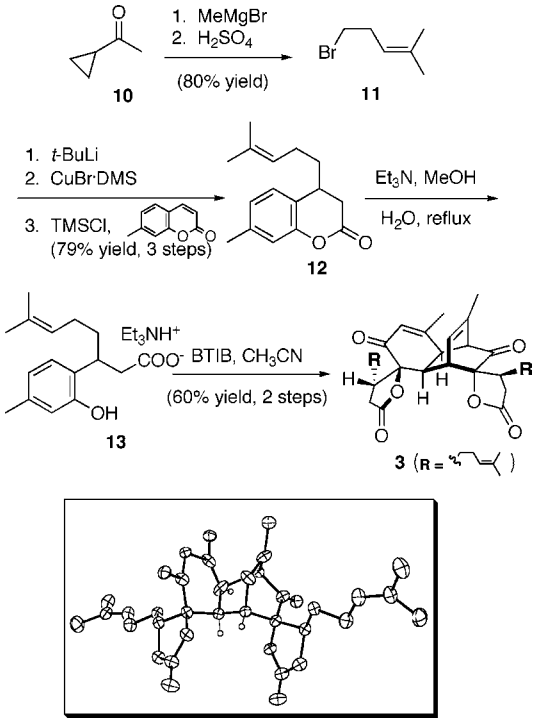
Scheme 1



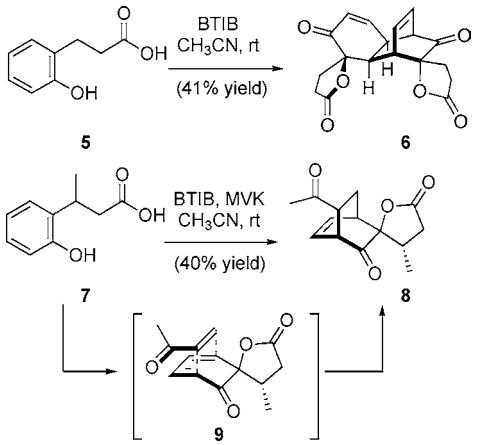
Scheme 3



BTIB would result in the stereoselective formation of **3** (Scheme 1).

To explore this hypothesis, we initiated a synthetic effort that began with large scale production of bromide **11** from cyclopropylmethyl ketone (**10**).[5] Subsequent exposure of **11** to lithium−halogen exchange followed by copper-mediated

Scheme 2

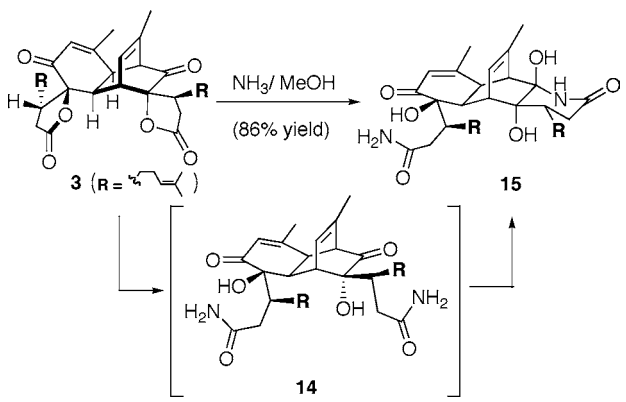


conjugate addition to 7-methylcoumarin provided the alkylated dihydrocoumarin (**12**, Scheme 3) in 79% isolated yield.

Hydrolysis of the lactone **12** and in situ conversion to the triethylamine salt (**13**) set the stage for the key phenolic oxidation. To our delight, we found that treatment of **13** with BTIB resulted in smooth aromatic oxidation followed by Diels−Alder cycloaddition to provide dimer **3** as a single diastereomer in 60% yield.[6] This short reaction sequence allowed access to several grams of dimer **3**, and single X-ray analysis provided structural proof that **3** possesses the relative stereochemistry found in bacchopetiolone (Scheme 3, inset).

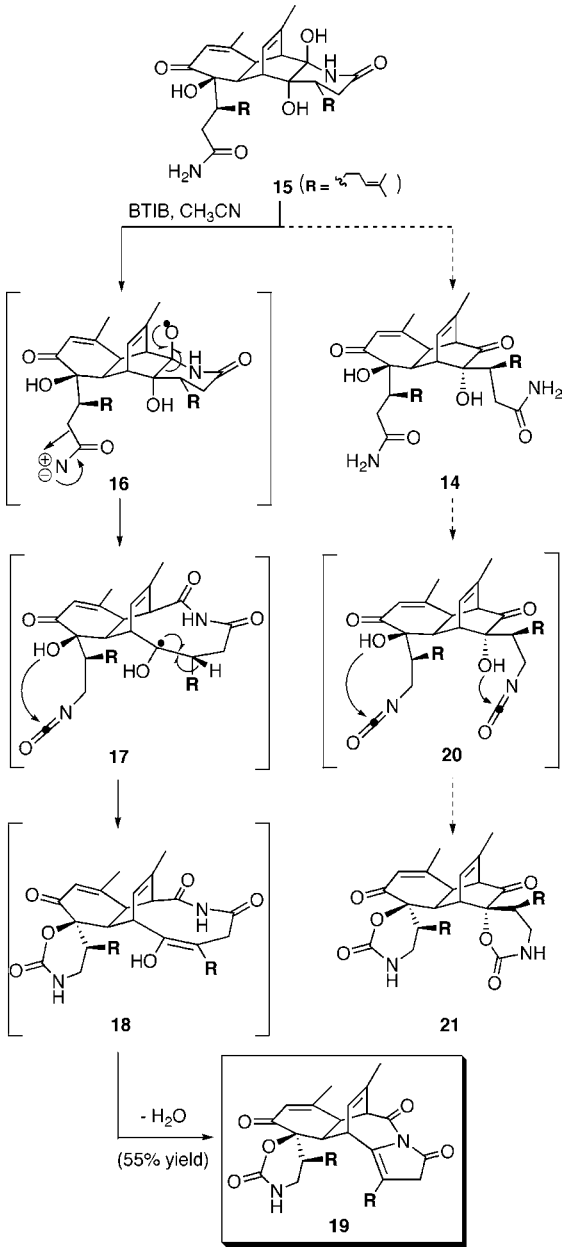
Having assembled the polycyclic skeleton of bacchopetiolone, we turned our attention to the bis-decarbonylation required for converting **3** to **1**. Although there are a number of conceivable approaches, preliminary investigations focused on transformations of the corresponding bisamide (**14**). The latter was readily available from **3** via treatment with

Scheme 4



(5) Biernacki, W.; Gdula, A. *Synthesis* **1979**, *1*, 37−38.

Scheme 5



ammonia; subsequent addition of one amide moiety into the nearby ketone delivered cyclic carbinolamide **15** (Scheme 4).[7]

We hoped that the cyclic hemiaminal formation would be reversible, allowing for a potential Hofmann rearrangement on both amide functional groups of **14** (Scheme 5). To this end, we explored the use of BTIB in anhydrous acetonitrile as a means of generating nitrene species and rearranging them to bisisocyanate **20**.[8] As illustrated in Scheme 5, we had anticipated the terminal product to be **21**, a compound arising from intramolecular trapping of the tertiary alcohols.[9]

Although exposure of **15** to BTIB efficiently produced nitrene **16**, it also generated an alkoxy radical. The subsequent reactivity was bifurcated and furnished the undesired ring expansion product **19**, confirmed by single X-ray analysis (Figure 1).[10]

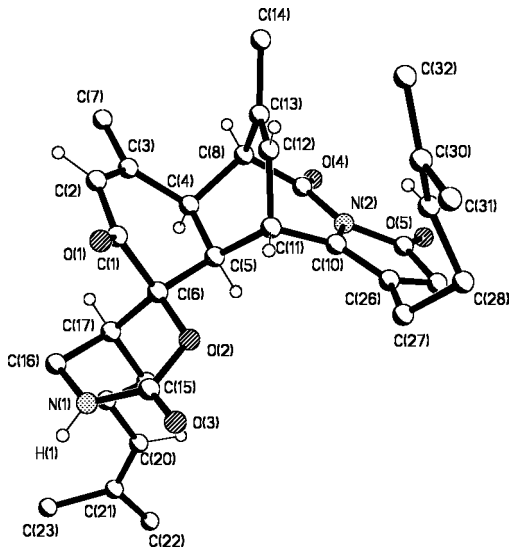


Figure 1. Structural representation of **19**.

As illustrated, this product (**19**) is believed to arise from **16** via the desired rearrangement and intramolecular trapping to the cyclic urethane on the left side; concomitantly and in contrast, the right portion of **16** undergoes ring expansion to a [2.2.3]bicycle, presumably via radical β-fragmentation. Suárez et al. have reported similar β-fragmentation of bicyclo[3.3.0]-carbinolamidyl radicals generated by irradiation with visible light in the presence of hypervalent organoiodine.[11,12] In contrast to Suárez's substrates, the fragmentation of **16** delivered a tertiary C-radical that presumably loses a hydrogen atom to generate enol **18**.

(6) It is important to note that this homochiral dimerization involves two stereoselective steps, lactone formation and a Diels−Alder reaction. On the basis of simple ground-state energy calculations (e.g., MM2 and MNDO), the product selectivity observed in each step cannot be attributed solely to product stability. The energetic features underpinning what appear to be kinetic selectivities have yet to be fully delineated and require investigation beyond the scope of the current manuscript.

(7) The yield of this reaction is based on isolation of a mixture of mono-opened lactones and resubjecting them to the reaction conditions to isolate **15** in 86% combined yield.

(8) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272−4276.

(9) Completion of the synthesis from intermediate **21** would require hydrolysis of the urethane followed by deamination. For leading references regarding the latter, see: Barton, D. H. R.; Bringmann, G.; Lamotte, G.; Motherwell, R. S. H.; Motherwell, W. B. *Tetrahedron Lett.* **1979**, 2291.

(10) Bravais lattice and space group assignments were unambiguous. Solution and refinement in the space group *P*-1 yielded promising initial results; however subsequent refinements were ineffective, and geometric parameters deviated significantly from the expected values. The light atom structure possessed low diffraction intensity ($I/\sigma = 8.54$) despite multiple data sets from several recrystallizations. The molecule is plagued with positional disorder in the C(27−32) side chain, and all attempts to effectively model alternative sites for these atoms were unsuccessful. Without a successful model, the structure refinement can only afford reliable atom connectivity.

(11) Hernández, R.; Melián, D.; Prangé, T.; Suárez, E. *Heterocycles* **1995**, *41*, 439−454.

(12) Hernández, R.; Suárez, E. *J. Org. Chem.* **1994**, *59*, 2766−2772.

Tautomerization to the corresponding ketone and condensation with the imide nitrogen furnish enamine **19**.

In conclusion, we have developed a highly efficient phenolic oxidation/Diels−Alder sequence that furnishes the desired tricyclic skeleton of bacchopetiolone with complete control of the relative stereochemistry. Although as yet unsuccessful in delivering **1**, decarbonylation attempts have illustrated the potential utility of BTIB-mediated oxidations in delivering ring expansion products (e.g., **19** in Scheme 5). Current efforts are focusing both on alternatives for completing the synthesis of **1** and on Suárez fragmentation modifications.

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Supporting Information Available: Materials and methods, experimental procedures, and ^{1}H and ^{13}C NMR and IR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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