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First Total Synthesis of a Natural Product Containing a Chiral, β-Diketone: Synthesis and Stereochemical Reassignment of Siphonarienedione and Siphonarienolone

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Abstract: The first total syntheses of siphonarienolone and siphonarienedione are described. The development of a stereoselective synthesis of β-diketones facilitated the synthesis of the latter compound. The synthesis of the structures proposed for the natural products afforded compounds whose spectral data did not match those of the natural products. However, the synthesis of compounds isomeric to the proposed structures at C_4 and C_5 afforded compounds identical to the natural products, thereby reassigning the stereochemistry of the natural products.

Introduction

β-Dicarbonyl compounds are commonly associated with the acidity and configurational instability of the α-carbon between the carbonyls. A number of natural products contain β-diketones bearing chiral α-carbons, and a number of these molecules have yielded to stereoselective semi-synthesis from other natural products.[1] However, every target of the syntheses mentioned above contained the α-carbon in a ring system, and syntheses of these compounds relied on thermodynamic, ring-based control to set the configuration of the α-carbon. The stereoselective synthesis of acyclic β-diketones with stereogenic α-carbons requires kinetic control of the stereochemistry and, therefore, poses a more significant challenge. The fact that none of the several natural products containing chiral, acyclic β-diketones have yielded to total synthesis illustrates this challenge.[2] Further, only two sets of studies describe the stereoselective synthesis of such moieties in any context.[3,4] We have rectified this deficiency by developing a method broadly applicable to the synthesis of chiral, acyclic β-diketone natural products, and we have demonstrated the method in the first total synthesis of such a compound.

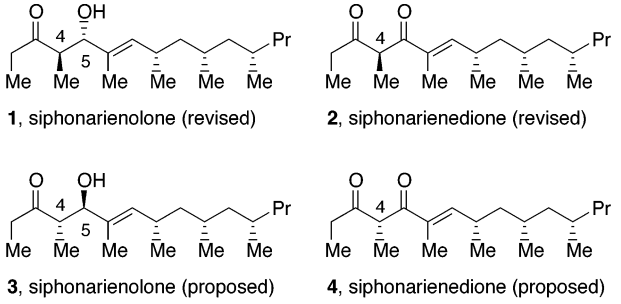

Figure 1. Siphonarienes.

In connection with our synthetic efforts toward the siphonarienes, we became interested in the synthesis of the β-diketone siphonarienedione and its congener, siphonarienolone (Figure 1). Norté et al. reported the isolation of siphonarienedione, which displays moderate activity against several cancer cell lines, as a single epimer.[2a] However, Salvá and co-workers isolated the compound as a 1.1:1 mixture of the natural isomer and its C_4-epimer.[2b] Norté also tentatively assigned the configuration of C_4 and C_5 in siphonarienolone and of C_4 in siphonarienedione as shown for **3** and **4**. We report here the first total syntheses of the two natural products, and provide a revision of the stereochemical assignment of the key chiral centers of both targets to that shown for **1** and **2**.

We predicated our synthesis of siphonarienedione on the ability to oxidize siphonarienolone without epimerization of the product. Norté had shown that such an oxidation with pyridinium chlorochromate yielded siphonarienedione and its C_4-epimer. However, Hoffmann and co-workers indicated that the oxidation of β-hydroxyketones with the Dess−Martin periodinane (DMP) could proceed without epimerization to yield chiral

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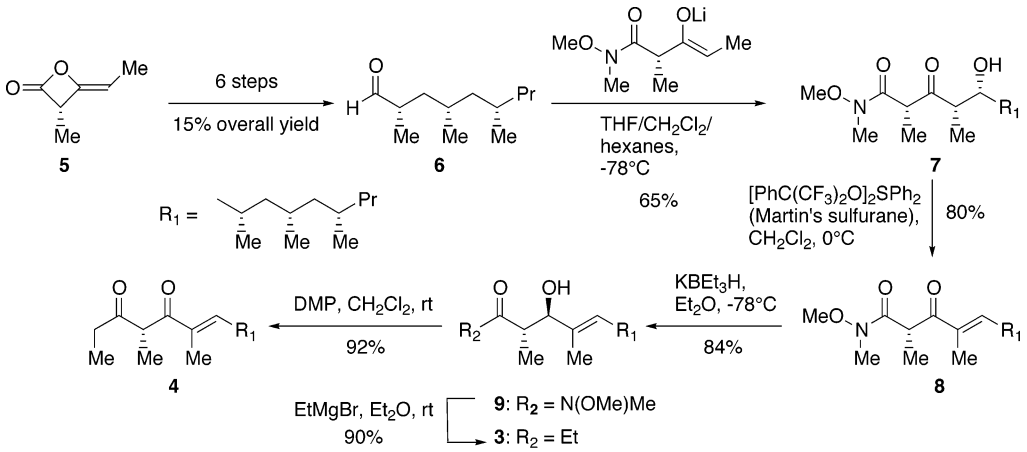
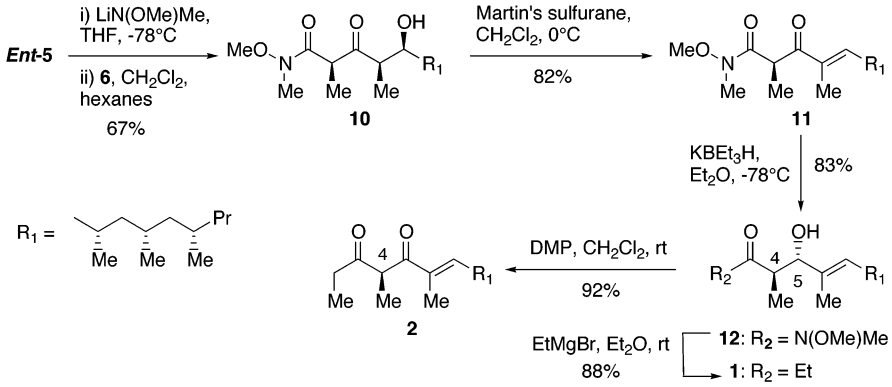
(1) See, for example, the semi-synthesis of cycloepiatalantan: Wu, T. S.; Leu, Y. L.; Chan, Y. Y.; Wu, P. L.; Kuoh, C. S. *Phytochemistry* **1997**, *45*, 1393−1398.
(2) Siphonarienes: (a) Norté, M.; Cataldo, F.; González, A. G.; Rodriguez, M. L.; Ruiz-Perez, C. *Tetrahedron* **1990**, *46*, 1669−1678. (b) Paul, M. C.; Zubi, E.; Ortega, M. J.; Salvá, J. *Tetrahedron* **1997**, *53*, 2303−2308. Niuhinones: (c) Coval, S. J.; Schulte, G. R.; Matsumoto, G. K.; Roll D. M.; Scheuer, P. J. *Tetrahedron Lett.* **1985**, *26*, 5359−5362. Aglajnes: (d) Cimino, G.; Sodano, G.; Spinella, A.; Trivellone, E. *Tetrahedron Lett.* **1985**, *26*, 3389−3392.
(3) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169−9202, and references therein.
(4) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429−6433.

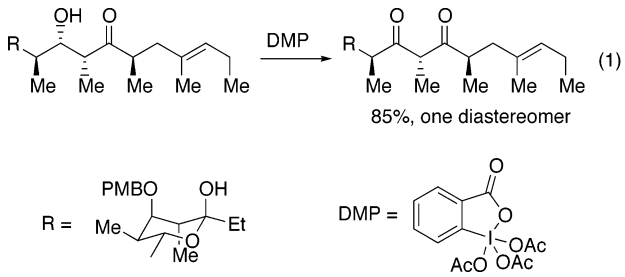
Scheme 1



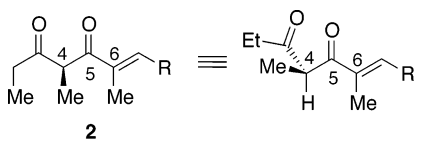
Scheme 2



β-diketone intermediates for the synthesis of the denticulatins (eq 1).[5] Therefore, we selected this reagent to perform the key oxidation.



The conjugation of one of the ketones of siphonarienedione with an alkene would be expected to add to its configurational stability. Restricted rotation about the C_5-C_6-bond of siphonarienedione should fix the rotation about the C_4-C_5-bond via an $A_{1,3}$-interaction (Figure 2). The favored conformation would position σ-C_4-H so that it could not overlap favorably with π^*-C_5-O, thereby lowering the acidity of the C_4-proton. This effect bears many similarities to that described by Evans for β-ketoimides.[6]



2

Figure 2. Conformation of siphonarienedione.

Results and Discussion

We initially synthesized **3** and **4**, the stereoisomers proposed by Norté for siphonarienolone and siphonarienedione (Scheme 1). Our route began with aldehyde **6**, obtained conveniently from methylketene dimer **5**, as we described earlier.[7] Aldol coupling of **6** with the lithium enolate derived from **5** afforded *syn*,*syn*-aldol diastereomer **7** with good diastereoselectivity.[8] Elimination with Martin's sulfurane yielded enone **8** with high *E*-stereoselectivity and no evidence of epimerization.[9] Reduction under conditions selective for the anti-diastereomer afforded alcohol **9**.[10] Grignard addition then produced hydroxyketone **3**. The oxidation of **3** with DMP produced **4** as a single epimer, stable to chromatography and storage in neat form at −10 °C.

Comparison of the spectra of **3** and **4** with those of siphonarienolone and siphonarienedione revealed that the reported stereochemical assignments of the natural products were in error. Although the spectra of **4** did not match those given

(5) Andersen, M. W.; Hildebrandt, B.; Dahmann, G.; Hoffmann, R. W. *Chem. Ber.* **1991**, *124*, 2127−2139.
(6) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154−1156.
(7) Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500−7504.
(8) Calter, M. A.; Guo, X.; Liao, W.; Struss, J. A.*Org. Lett.* **2001**, *3*, 1499−1501.
(9) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443.
(10) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643−4646.

by Norté for siphonarienedione, they did match those of the minor epimer from the mixture reported by Salvá. Therefore, we assumed that siphonarienedione possessed the stereochemistry shown for **2** (Figure 1). On the basis of biosynthetic considerations, we further assumed that siphonarienolone possessed the same configuration as siphonarienedione at C_4. We then tentatively assigned the *S*-stereochemistry to C_5, as the coupling constant between the protons on C_5 and C_4 of natural siphonarienolone (9.2 Hz) indicated an anti-relationship between these centers.[11] This analysis led to the assignment of the stereochemistry of siphonarienolone as shown for **1**.

The synthesis of **1** and **2** closely paralleled that of **3** and **4** (Scheme 2). The aldol reaction of **6** with the enolate derived from the enantiomer of **5** yielded adduct **10**. Conversion of **10** into **1** by way of β-ketoamide **11** and β-hydroxyamide **12** proceed by a sequence similar to that employed for the conversion of **7** into **3**. The spectra of **1** and **2**, produced by oxidation of **1**, exactly matched those reported by Norté for the natural products, confirming our tentative stereochemical assignments. Diketone **2** displayed similar configurational stability to that demonstrated by **4**.

In an effort to facilitate the configurational assignment of similar β-diketones, we acquired the CD spectrum of synthetic **2**. This spectrum possessed a strong, negative Cotton effect peak at 278 nm and a weaker positive one centered at 328 nm.

(11) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294−4299.

Summary

We have completed the first syntheses of siphonarienedione and siphonarienolone. The synthesis of siphonarienedione constitutes the first stereoselective synthesis of a β-diketone contained in an acyclic natural product. The methodology developed during this synthesis allowed us to prepare either stereoisomer of the β-diketone moiety, thereby allowing unambiguous reassignment of the stereochemistry of the natural product. The methodology developed should also be applicable to the synthesis of other classes of β-diketone-containing natural products.

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Supporting Information Available: Synthetic procedures and analytical data for compounds **1**−**4**, and **7**−**12**. Also included are the CD spectra for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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