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An Enantioselective Total Synthesis of (+)-Aigialospirol

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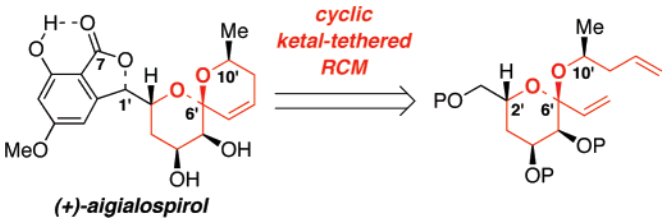
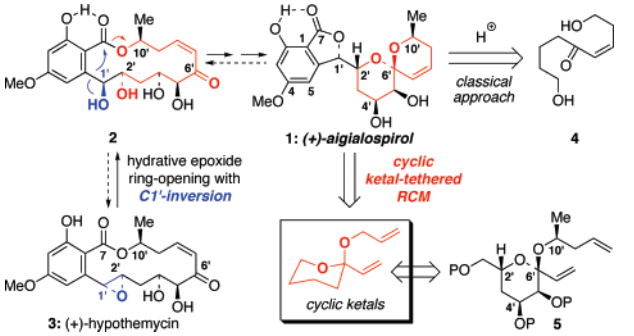
ABSTRACT



A concise and enantioselective total synthesis of (+)-aigialospirol is described here, featuring the first complex natural product synthesis that employs a cyclic ketal-tethered ring-closing metathesis strategy and an unexpected stereoselective epimerization of a benzylic hydroxyl group. The 15-step synthetic sequence illustrates the proof-of-concept that such an approach can be competitive with the classical spiroketal formation in the natural product synthesis.

Recently, Isaka[1] reported the isolation of (+)-aigialospirol (**1**), which was obtained after an extended fermentation of the marine fungus *Aigialus parvus* BCC 5311 that was found in the mangrove Ascomycete. Although useful biological activities of **1** remain unknown, natural products of marine fungi origins in general represent medicinally significant structural scaffolds.[2] More significantly, **1** is thought to be biosynthetically related to the known resorcylic macrolactone hypothemycin (**3**),[3−6] which was also found from the same fungus, and **3** possesses potent antimalarial[7] and anticancer[8] properties. Specifically, (+)-aigialospirol **1** is postulated to be from hypothemycin (**3**) through macrolactone **2** via (a) translactonization and (b) spiroketal formation. The macrolactone **2** was derived from a hydrative opening of the epoxide in **3** with inversion of stereochemistry at C1′ (Scheme 1). Transformations in a reverse direction from **1** to **3** are not known.

Scheme 1. Aigialospirol and Hypothemycin



Our recent interest[9] in developing cyclic ketal-tethered methods for constructing spiroketals[10,11] led us to (+)-aigialospirol (**1**). We recognized that **1** represents a unique opportunity to demonstrate the expediency of a cyclic ketal-tethered ring-closing metathesis (RCM)[12] as a strategy in the total synthesis of spiroketal-containing natural products and

(1) Vongvilai, P.; Isaka, M.; Kittakoop, P. Prasert Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457.
(2) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1.
(3) (a) Nair, M. S. R.; Carey, S. T. *Tetrahedron Lett.* **1980**, *21*, 2011. (b) Nair, M. S. R.; Carey, S. T.; James, J. C. *Tetrahedron* **1981**, *37*, 2445.
(4) Revised structure of hypothemycin: Agatsuma, T.; Takahashi, A.; Kabuto, C.; Nozoe, S. *Chem. Pharm. Bull.* **1993**, *41*, 373.
(5) For a leading review on syntheses of hypothemycin and related resorcylic macrolides, see: Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22.

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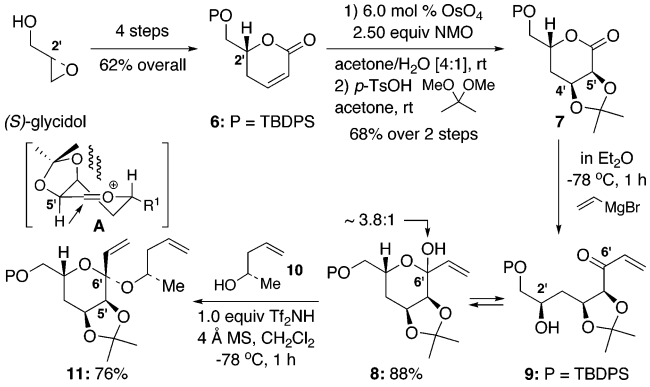
that it can challenge the classical approach using keto diols (see **4**) in the spiroketal synthesis. We report here the first total synthesis of (+)-aigialospirol featuring a cyclic ketal-tethered RCM in constructing the spiroketal core and a facile epimerization of the benzylic hydroxyl group.

Our synthesis commenced with (*S*)-glycidol as the chiron source for the C2′ stereocenter and prepared the known dihydro-α-pyrone **6**[13,14] in 62% yield over four steps (Scheme 2). Dihydroxylation[15] of **6** followed by acetonide formation

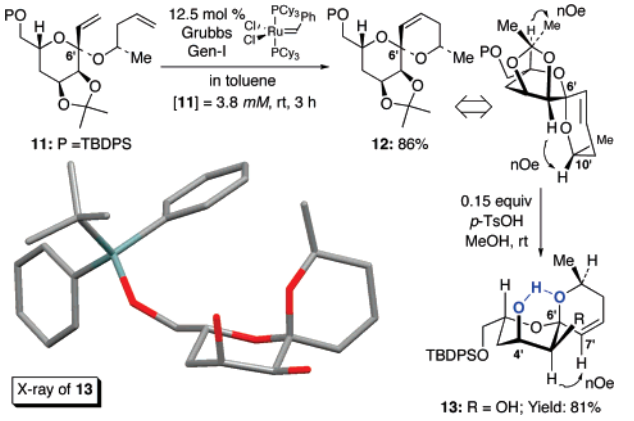
Scheme 2. Synthesis of Key Cyclic Ketal



gave δ-lactone **7**, and addition of vinyl Grignard to **7** gave an equilibrating mixture of lactol **8** and vinyl ketone **9** in 88% yield overall. After being exposed to 1.00 equiv of Tf_2NH at −78 °C for 1 h,[16,17] the key formation of cyclic ketal **11** was accomplished in 76% yield from the lactol−ketone mixture and the chiral homoallylic alcohol **10**.[13] While the C6′ stereochemistry was confirmed at a later stage, cyclic ketal **11** was isolated as a single diastereomer. It is noteworthy that the overall sequence leading to the key RCM precursor **11** is short.

With cyclic ketal **11** in hand, the ring-closing metathesis proceeded smoothly to give spiroketal **12** in 86% yield employing 12.5 mol % of Grubb's first generation catalyst (Scheme 3).[12] However, at this stage, NOE experiments using

Scheme 3. Cyclic Ketal-Tethered RCM and C6′ Epimerization



12 confirmed our earlier fear when examining NOEs of **11**,[13] which only hinted that the stereochemistry at the C6′ spiroketal center could be wrong. The assignment of **12** implies that the alcohol **10** had added to the oxocarbenium ion **A** (see Scheme 2) in an equatorial manner *anti* to the C5′ oxygen. Fortuitously, when we removed the acetonide group under acidic conditions, we found that the spiroketal center had completely epimerized to the desired C6′ stereocenter as evident by both NOE and X-ray structure of diol **13**.

B3LYP/6-31G* calculations revealed that the acetonide-protected spiroketal **12** is actually 0.68 kcal mol^{-1} more stable than its corresponding C6′ epimer, whereas ΔE is 2.13 kcal mol^{-1} in favor of **13** over its C6′ epimer. Such an enhanced stability is likely a result of hydrogen bonding between C4′-OH and spiroketal oxygen, which was seen in the X-ray structure and the minimized molecular model of **13**.

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(13) See Supporting Information.

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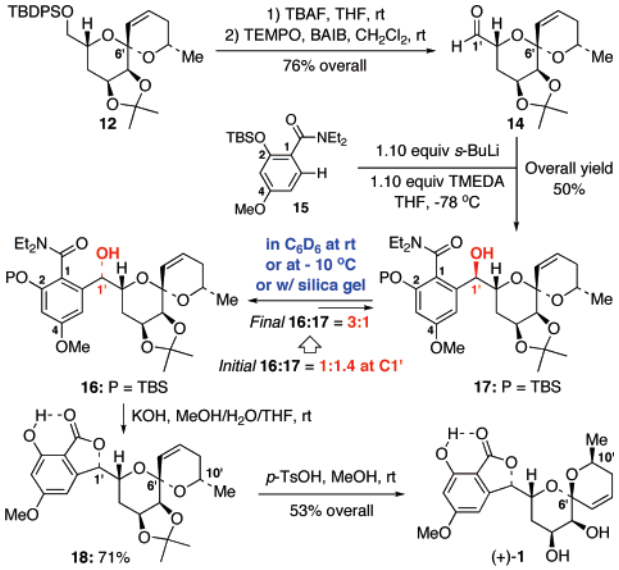
To complete our total synthesis, we elected to utilize spiroketal **12** instead of **13** and pursue the epimerization of C6′ spiroketal center at the very end. As shown in Scheme 4, desilylation and oxidation of **12** gave aldehyde **14**.

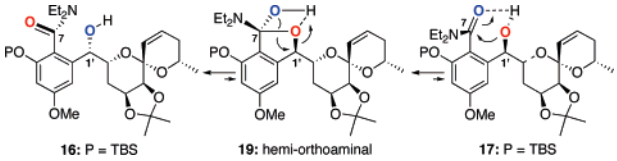
Scheme 4. Total Synthesis of (+)-Aigialospirol (**1**)



Subsequent addition of the aryl lithium intermediate, generated via a Snieckus' directed ortho-metalation[18] of amide **15**,[6a] afforded a readily separable mixture of alcohols **16** and **17** with an isomeric ratio 1:1.4. Given that we were uncertain which was the desired C1′ epimer, we pursued the lactone formation employing both alcohols **16** and **17**. Intriguingly, we found that both **16** and **17** led to the same lactone **18** (with loss of the TBS group). Lactone **18** was taken to (+)-aigialospirol after removal of the acetonide group concomitant with C6′ epimerization. Our synthetic sample completely matches the reported spectroscopic data for (+)-aigialospirol.[1]

While this concludes the total synthesis effort, we were intrigued by the lactonization/epimerization. A careful examination revealed that alcohol **16** gave lactone **18**, while alcohol **17** readily epimerized to **16** under the same lactonization conditions, which is basic. In fact, pure **17** epimerizes to **16** in C_6D_6 at rt when being frozen in C_6D_6 at −10 °C or under a prolonged exposure to silica gel. Given that there is no apparent energetic difference between **16** and **17** from our preliminary calculations, one possible pathway is shown in Scheme 5.

Scheme 5. A Possible Mode for the C1′ Epimerization



This pathway features a C1′ scrambling that is intramolecular in nature and involves the hemi-orthoaminal intermediate **19** that would allow for "swapping (or a turnstile-like mechanism)" of the original C7 amido carbonyl oxygen atom with the C1′ hydroxy oxygen atom (red). It is likely that the formation of **19** is more readily from **17** with a β-C1′-OH. This model is consistent with the observation that C1′ epimerization occurs under basic, acidic, or neutral conditions. It is noteworthy that this epimerization involves the same C1′ stereocenter that is critical in the biosynthetic relation between hypothemycin and aigialospirol. We are currently probing the origin of this intriguing epimerization.

We have described here an enantioselective total synthesis of (+)-aigialospirol featuring a cyclic ketal-tethered ring-closing metathesis strategy and an unexpected stereoselective epimerization of a benzylic hydroxy group. This 15-step synthetic sequence from (*S*)-glycidol firmly demonstrates that cyclic ketal-tethered RCM can be competitive with the classical spiroketal synthesis.

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Supporting Information Available: Experimental details, characterization data, X-ray structural analysis, and NMR spectral for all new compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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