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Total Synthesis of 7′,8′-Dihydroaigialospirol

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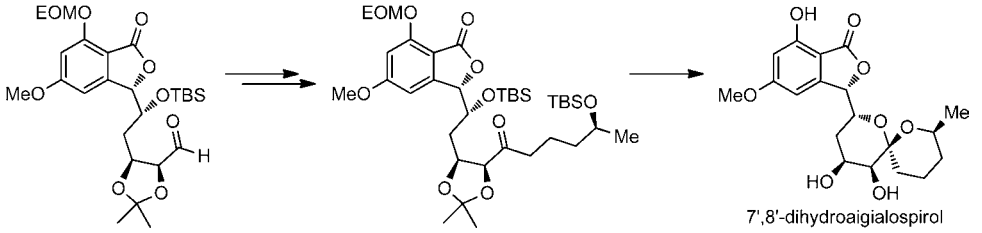
ABSTRACT



A highly convergent total synthesis of 7′,8′-dihydroaigialospirol is described. Key steps of the synthesis include a Nozaki–Hiyama–Kishi (NHK) coupling of an iodoalkyne with an advanced phthalide-aldehyde and a remarkable one-pot acid-mediated global deprotection/spiroacetalization.

The aigialomycins A–E (**1**–**5**; Figure 1) belong to the resorcylic acid lactone family of natural products that were isolated from the mangrove fungus *Aigialus parvus BCC 5311*.[1] These 14-membered resorcylic macrolides differ only in the oxidation pattern around the macrocyclic ring and/or the configuration of the olefin at C1′–C2′. The most potent member of the family, aigialomycin D (**4**), exhibits antimalarial[1] (IC_{50}: 6.6 μg/mL against *P. falciparum*), antitumor[1] (IC_{50}: 3.0 μg/mL for KB cells and 1.8 μg/mL for Vero cells), and kinase inhibitory activity[2,3] (IC_{50}: 6 μM for CDK1/5, 21 μM for CDK2, and 14 μM for GSK). Consequently, **4** has attracted considerable interest from the synthetic community, resulting in eight total syntheses.[2,4] Additional aigialomycin derivatives (**6**–**10**), obtained by extended fermentation of *Aigialus parvus*, have since been reported.[5] Associated bioactivity of these novel metabolites has not been reported.

As part of our ongoing synthetic program to probe the pharmacological properties of spiroacetal-containing natural products (especially aromatic spiroacetals),[6,7] our attention focused on the total synthesis of the spiroacetal-containing members of the post-PKS modified aigialomycin derivatives (**8**–**10**). To date, only one total synthesis of these phthalide-spiroacetals has been reported by the Hsung group,[8] wherein aigialospirol (**8**) was furnished using a cyclic acetal-tethered ring-closing metathesis with a late stage epimerization of the spiroacetal center under acidic conditions. Based on this observation, we postulated that an acid-catalyzed spirocyclization would be an effective strategy to achieve the direct formation of these

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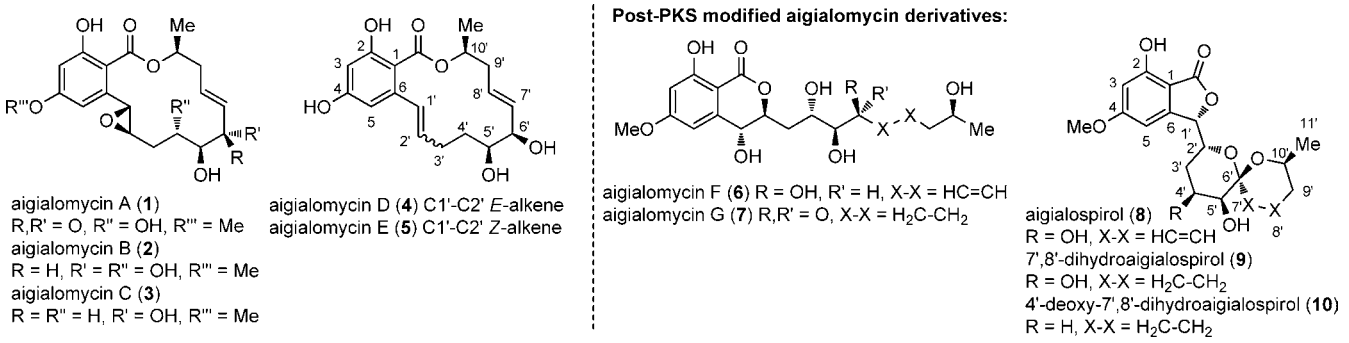


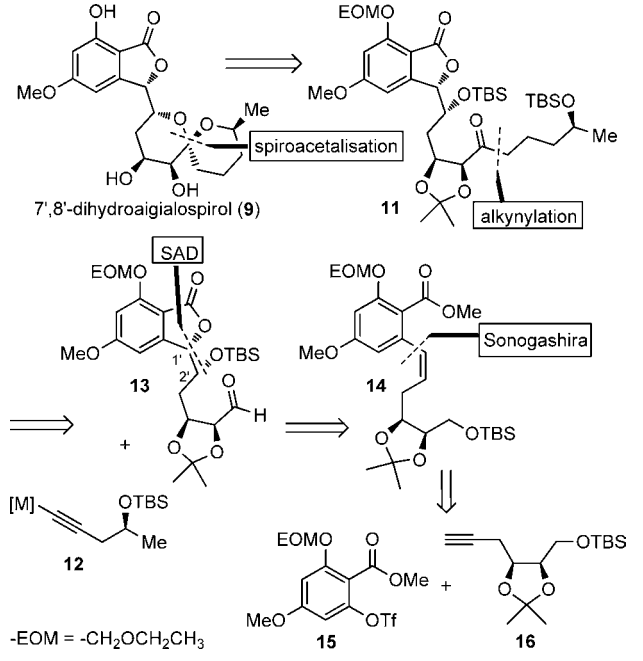
Figure 1. Structure of aigialomycins A–G (**1**–**7**) and the aigialospirol derivatives (**8**–**10**).

spiroacetals. We therefore report our total synthesis of 7′,8′-dihydroaigialospirol (**9**) based on the union of a functionalized alkyne to a preformed phthalide-aldehyde to construct the key spirocyclization precursor.

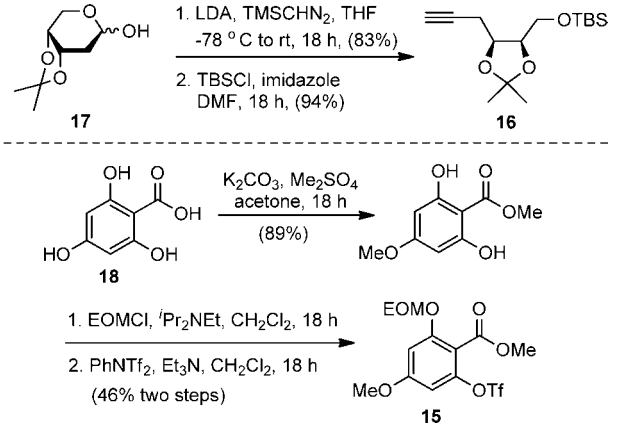
Retrosynthetically, ketone **11** constitutes a suitable spirocyclization precursor for the synthesis of 7′,8′-dihydroaigialospirol **9** (Scheme 1). This key intermediate was envisioned to be accessible by the addition of a suitable organometallic reagent (**12**) to phthalide-aldehyde **13** followed by reduction of the alkyne moiety. The stereocenters at C1′ and C2′ can be installed *via* a Sharpless asymmetric dihydroxylation (SAD) of olefin **14**. While *cis*-disubstituted alkenes are generally poor substrates for the SAD model, moderate to good diastereocontrol has been observed for acyclic, benzylic substrates using *O*-indolinylcarbamoyl (IND) based chiral ligands.[9] Alkene **14**, in turn, could be constructed by Sonogashira cross-coupling of triflate **15** with alkyne **16**, followed by semihydrogenation of the resultant disubstituted alkyne.

Our synthesis thus began with the preparation of the Sonogashira coupling partners **15** and **16** as illustrated in Scheme 2. Alkyne **16** was assembled from known acetonide-protected D-2-deoxyribose[10] **17** whereby the inherent *syn*-diol functionality is converted to C4′ and C5′ of 7′,8′-dihydroaigialospirol (**9**). Thus, subjection of lactol **17** to Colvin rearrangement[11] followed by silyl protection of the homologated alkyne afforded **16** in 78% over two steps. Triflate **15** on the other hand was readily prepared from commercially available 2,4,6-trihydroxybenzoic acid (**18**) by sequential methylation, EOM protection, and triflation.

Scheme 1. Retrosynthesis of 7′,8′-Dihydroaigialospirol (**9**)



Scheme 2. Synthesis of Alkyne **16** and Triflate **15**



Sonogashira reaction of **15** with **16** and subsequent semihydrogenation of the internal triple bond over Lindlar's catalyst proceeded smoothly to afford alkene **14**. Sharpless

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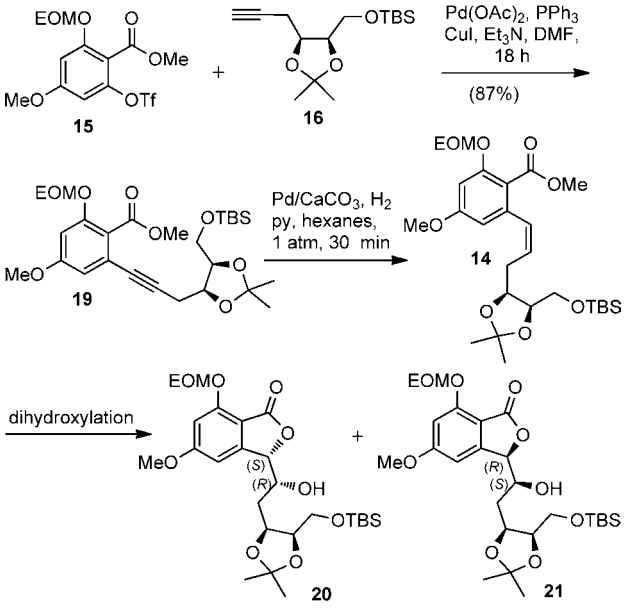
asymmetric dihydroxylation of *cis*-alkene **14** using DHQ-IND (entry 1, Table 1) proceeded with concomitant lactonization to give a separable mixture of diastereomeric phthalides **20** and **21** (76% yield, dr **20:21** 1:2.3). Using the Sharpless mnemonic,[9] the major phthalide was predicted to possess the desired 1′*S*,2′*R* stereochemistry (**20**). Surprisingly, assignment of the C2′ stereocenter by Mosher ester analysis[12] established that the SAD resulted in the formation of the undesired isomer **21**. Similarly, use of DHQD-IND (entry 2) unexpectedly provided the desired phthalide diastereoisomer (**20**) but with lower stereoselectivity (dr **20:21** 1.3:1). To ensure the samples and ligands were not inadvertently mixed up, these experiments were repeated several times, but similar findings were obtained.

Table 1. Dihydroxylation of *cis*-Olefin **14**

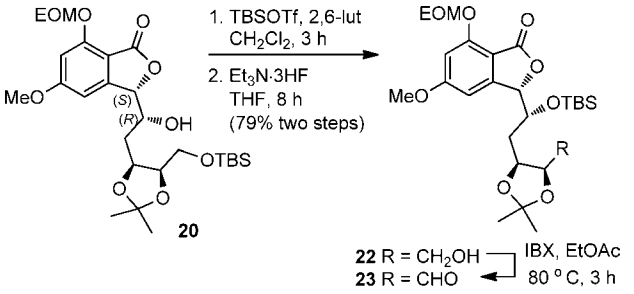


entry	reaction conditions	yield (%)[a]	**20:21**
1	OsO_4, DHQ-IND, K_3FeCN_6, K_2CO_3, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O, 0 °C to rt, 30 h	76	1:2.3
2	OsO_4, DHQD-IND, K_3FeCN_6, K_2CO_3, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O, 0 °C to rt, 30 h	78	1.3:1
3	OsO_4, $(DHQ)_2PHAL$, K_3FeCN_6, K_2CO_3, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O, 0 °C to rt, 30 h	80	1:1
4	OsO_4, $(DHQ)_2PYR$, K_3FeCN_6, K_2CO_3, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O, 0 °C to rt, 30 h	72	1:1
5	OsO_4, $(DHQ)_2AQN$, K_3FeCN_6, K_2CO_3, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O, 0 °C to rt, 30 h	70	1.1:1
6	OsO_4, NMO, acetone/H_2O, 18 h	67	1:1
7	OsO_4, TMEDA, CH_2Cl_2, −78 °C, 2 h	62	1:1

[a] Combined yield (over two steps, from **19**) of chromatographically separable phthalides **20** and **21**.

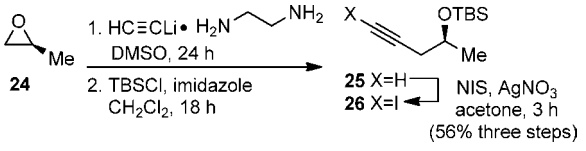
To our disappointment, no improvement was observed with phthalazine- (PHAL), pyrimidine- (PYR), or anthraquinone- (AQN) based DHQ ligands (entries 3−5). Investigation of the inherent diastereoselectivity of the chiral *cis*-olefin (**14**) using stoichiometric OsO_4 and NMO (entry 6) or TMEDA[13] (entry 7) was also unrewarding. The origin of the unexpected reversal of the SAD selectivity remains unclear.[14] However, the presence of the chiral acetonide group may have been a contributing factor. While the level of stereocontrol was disappointing, formation of the diastereomeric phthalide (**21**) does enable access to analogues for a future medicinal chemistry program.

Scheme 3. Synthesis of Aldehyde **23**



Moving forward, the desired alcohol **20** was protected as the silyl ether (Scheme 3). Chemoselective cleavage of the primary TBS ether and IBX oxidation[15] delivered aldehyde **23**. No purification of the product was required beyond simple filtration.

Scheme 4. Synthesis of Alkynes **25** and **26**



The required organometallic reagent **12** for the key alkynylation of aldehyde **23** was envisioned to be derived from alkyne **25** or **26**, both of which are available from (*S*)-propylene oxide **24** (Scheme 4). Thus, ring opening of **24** with the lithium acetylide−ethylenediamine complex proceeded cleanly to afford the corresponding homopropargylic alcohol which was immediately converted to silyl ether **25**. Iodoalkyne **26**, in turn, was synthesized by subjecting **25** to standard iodination conditions (NIS, $AgNO_3$).

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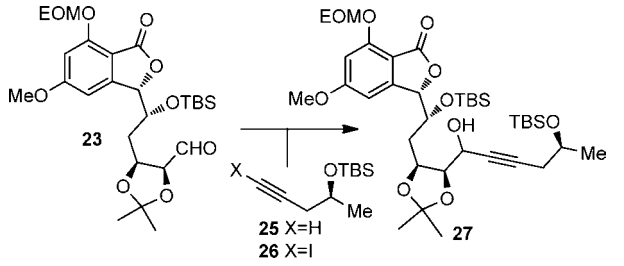
Table 2. Union of Aldehyde **23** with Alkyne **25** or Iodoalkyne **26**



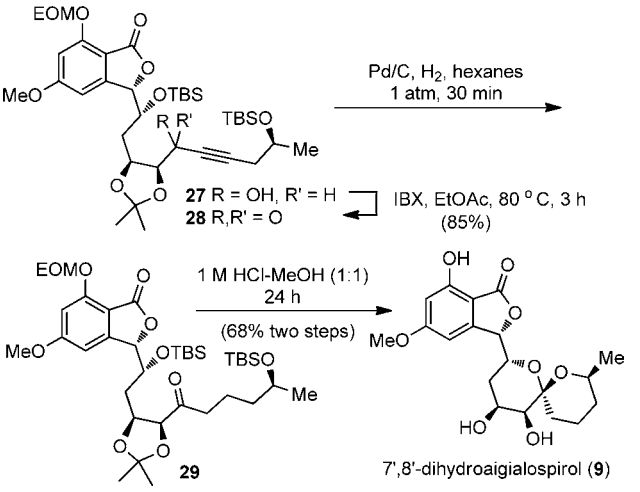
entry	substrate	reaction conditions	yield (%)[a]
1	**25**	^{n}BuLi, THF, −78 °C to rt, 18 h	complex mixture
2	**25**	(+)-*N*-methylephedrine $Zn(OTf)_2$, Et_3N, toluene, 2 h	complex mixture
3	**26**	Et_2Zn, PPh_3, CH_2Cl_2, 24 h	recovered **23**
4	**26**	In, CH_2Cl_2, 50 °C, 5 h	decomposition
5	**26**	$CrCl_2$, $NiCl_2$, DMF, 18 h	13
6	**26**	$CrCl_2$, $NiCl_2$, THF, 18 h	recovered **23**
7	**26**	$CrCl_2$, $NiCl_2$, DMF, 50 °C, 18 h	36
8	**26**	$CrCl_2$, $NiCl_2$, DMSO/THF, 50 °C, 18 h	33
9	**26**	$CrCl_2$, $NiCl_2$, DMF/THF, 50 °C, 18 h	49

[a] Isolated yield over two steps, from **22**.

Initial attempts to use the lithium or zinc[16] acetylide derivative of **25** and **26** to effect coupling with aldehyde **23** (entries 1−3, Table 2) to produce alcohol **27** only afforded complex mixtures or unreacted aldehyde **23**. Indium-mediated[17] coupling (entry 4) resulted predominantly in decomposition. These complications were thought to arise from the presence of the phthalide moiety, and the possibility of nucleophilic addition to the phthalide carbonyl group could not be ruled out. Successful coupling of iodoalkyne **26** with aldehyde **23** was finally accomplished using Nozaki−Hiyama−Kishi (NHK)[18] conditions in DMF (entry 5), affording **27** as a single diastereoisomer.[19] After extensive experimentation, it was found that the yield of the NHK reaction was extremely sensitive to the sequence of addition of the reagents, the activity of the metal salts,[20] and the reaction temperature and medium. Use of THF as solvent (entry 6) resulted in no reaction, while conducting the NHK reaction in DMF at 50 °C (entry 7) afforded a higher yield of **27** (36%). Pleasingly, a significant improvement in yield (49%) was observed when the reaction was carried out in a mixture of DMF−THF at 50 °C (entry 9).

With alcohol **27** in hand, the endgame of the synthesis of 7′,8′-dihydroaigialospirol **9** commenced with IBX oxidation of **27** to ketone **28** (Scheme 5). Subsequent hydrogenation of the alkyne moiety provided **29** uneventfully. At this point, the one-pot deprotection/spiroacetalization sequence was investigated. This process required the cleavage of three orthogonal protecting groups to reveal five hydroxyl groups that would selectively undergo spiroacetalization without accompanying elimination processes. Gratifyingly, exposure of **29** to methanolic HCl effected the desired transformation to furnish 7′,8′-dihydroaigialospirol (**9**) as a single stereoisomer (68% yield over two steps). The spectroscopic data for synthetic **9** {mp 75−78 °C, $[\alpha]_D$ +17.3 (*c* 0.13, $CHCl_3$)} was in excellent agreement with those reported for the natural product {mp 80−83 °C, $[\alpha]_D$ +14.0 (*c* 0.10, $CHCl_3$)}.[5b]

Scheme 5. Synthesis of 7′,8′-Dihydroaigialospirol (**9**)



In summary, the synthesis of 7′,8′-dihydroaigialospirol **9** has been achieved in 13 steps from D-2-deoxyribose. Initial attempts to install the stereochemistry at the C1′ and C2′ positions *via* SAD using the recommended DHQ-IND ligand unexpectedly led to the wrong diastereoisomer in a mismatched reaction. Use of DHQD-IND, on the other hand, reversed the substrate bias to favor the desired 1′*S*,2′*R*-isomer, *albeit* with reduced diastereoselectivity. Other features of the synthesis include the use of a late stage NHK protocol to forge a C−C bond between phthalide-aldehyde **23** and iodoalkyne **26** and the use of an acid-catalyzed concomitant global deprotection/spiroacetalization to construct the heterocyclic core. Studies toward the total synthesis of aigialospirol (**8**) and 4′-deoxy-7′,8′-dihydroaigialospirol (**10**) and analogues thereof continue in our laboratory.

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

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(18) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(19) The stereochemistry of the secondary alcohol is inconsequential as the stereocenter is oxidized in the next step.

(20) $CrCl_2$ and $NiCl_2$ were activated by heating to 200 °C for 4 h under high vacuum prior to use.

The authors declare no competing financial interest.