Natural Product Synthesis

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Asymmetric Total Synthesis of Soraphen A: A Flexible Alkyne Strategy**

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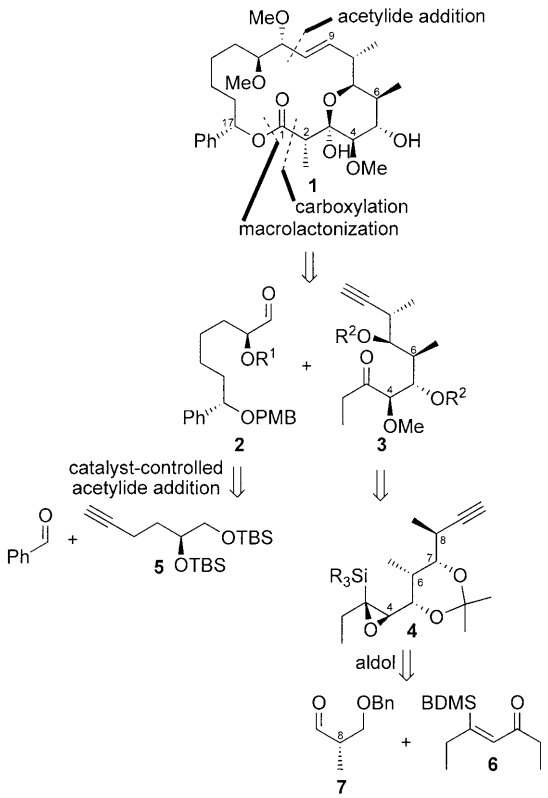
Soraphen A (**1**, Scheme 1) is a complex polyketide natural product whose structre was first disclosed in 1988 after isolation from the soil bacterium *Sorangium cellulosum* by Höfle and co-workers.[1] Importantly, **1** is a potent antifungal agent possessing activity against a broad spectrum of fungi.[2] Furthermore, the antifungal activity of **1** results from a unique mode of action, whereby selective inhibition of the acetyl-CoA carboxylase (ACC) enzyme of the fungus results in cell death by disruption of lipid synthesis in the cell.[3] As a result, **1** has the potential for application in the treatment of obesity, diabetes,[4] and cancer.[5] Structurally, **1** is comprised of an 18-membered macrolactone, which includes ten stereocenters and a highly substituted pyranose ring system. These features make **1** a challenging target for total synthesis. To date, only one completed total synthesis of **1** has been reported by Giese and co-workers.[6] In addition, several groups have reported their efforts towards the synthesis of **1**.[7] Herein we report our asymmetric total synthesis of **1** that relies on the versatility of the alkyne functional group to provide a concise route to **1**.

Alkynes are flexible functional groups because they can be used both as nucleophiles by deprotonation of a terminal alkyne and as electrophiles[8] by activation of the alkyne with a transition metal. Our retrosynthetic plan (Scheme 1) was devised around the concept of using this dual nature of the alkyne moiety to provide a concise synthesis of the target. Accordingly, the C10–C11 bond could arise from a Felkin-selective acetylide addition of alkyne **3** to aldehyde **2**. Subsequent treatment of the resultant internal alkyne with a hydrosilylation/protodesilylation[9] sequence should conveniently allow for reduction of the alkyne group to the requisite C9–C10 *trans* olefin present in **1**. The completion of **1** was then envisioned to arise from a late-stage macrolactonization.[10]

The hemiketal portion of **1** was envisioned to arise from treatment of ketone **3** ($R^2 = H$) with acid. The α-alkoxyketone



Scheme 1. Retrosynthetic analysis. BDMS = benzyldimethylsilyl, Bn = benzyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

3 was then proposed to arise from oxidation of epoxysilane **4**. We have previously demonstrated the utility of epoxysilanes as masked α-hydroxyketones, wherein Tamao–Fleming oxidation of the epoxysilane conveniently unmasks this group.[11] Furthermore, these epoxysilane groups are readily prepared from an alkyne functional group by hydrosilylation and subsequent epoxidation. Thus, an alkyne group serves as a convenient synthon for an α-hydroxyketone to facilitate the formation of a C–C bond and minimizing the use of protecting groups. Installation of the requisite stereochemistry at C6 and C7 in **4** could arise from a substrate-controlled diastereoselective aldol condensation between ketone **6** and aldehyde **7** while forming the C6–C7 bond. Finally, aldehyde **2** was envisioned to arise from alkyne **5** by a catalyst-controlled acetylide addition of the alkyne to benzaldehyde using the dinuclear zinc catalyst system[12] developed in our laboratory. Furthermore, alkyne **5** in turn derives from ring opening of an epoxide with a terminal alkyne. Both terminal alkynes have

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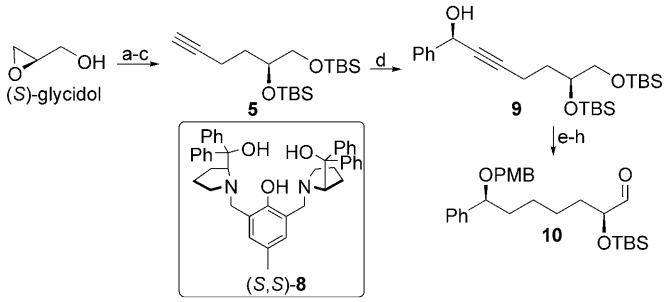
their origin in 1-propyne where it serves as a lynchpin for our synthesis. After utilizing the terminal alkyne of 1-propyne as a nucleophile, zipping[13] it recreates a new terminal alkyne that can repeat its function as a new nucleophile. This reactivity profile provides two strategies for controlling absolute stereochemistry: 1) use of the chiral pool and 2) catalyst-controlled asymmetric induction.

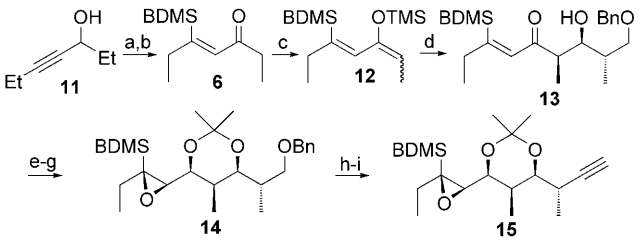
Synthesis of the aldehyde fragment began with the preparation of alkyne **5** in three steps from (*S*)-glycidol (Scheme 2). Opening of the epoxide ring with the lithium acetylide of propyne, subsequent isomerization of the internal alkyne to the terminal position using potassium 3-aminopropylamide,[13] and protection of the diol with TBS gave **5**. Coupling of **5** with benzaldehyde using 10 mol% of (*S*,*S*)-**8** as



Scheme 2. Synthesis of the aldehyde fragment **10**. Reagents and conditions: a) propyne, *n*BuLi, THF/DMPU (10:1), −78 °C to RT, 20 h, 68%; b) 1,3-diaminopropane, Li, KO*t*Bu, 66%; c) TBSCl, imidazole, DMF, 0 °C to RT, 2 h, 78%; d) 10 mol% (*S*,*S*)-**8**, benzaldehyde, **5**, $ZnMe_2$, toluene, 4 °C, 48 h, 88% (18:1 dr); e) H_2 (1 atm), 5 mol% $PtO_2 \cdot H_2O$, EtOAc, RT, 1 h, 92%; f) TBAI, KHMDS, PMBCl, THF, RT, 90%; g) HF·py, py, THF, 50% and 20% diol; h) $COCl_2$, DMSO, Et_3N, CH_2Cl_2, 98%. DMF = *N*,*N*-dimethylformamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, DMSO = dimethyl sulfoxide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, py = pyridine, TBAI = tetra-*n*-butylammonium iodide, THF = tetrahydrofuran.

the ligand furnished the desired propargylic alcohol **9** in excellent yield and diastereoselectivity. Exhaustive reduction of the alkyne to the alkane using Adams' catalyst[14] proceeded in excellent yield with minimal reduction of the benzylic alcohol (as is often observed when using Pd/C as the catalyst).[15] The benzylic secondary alcohol was then protected as a PMB ether followed by selective deprotection of the primary TBS ether using HF·py. Finally, Moffatt–Swern oxidation provided aldehyde **10** in excellent yield.

The alkyne fragment was prepared starting from 4-heptyn-3-ol (**11**, Scheme 3). Oxidation and subsequent hydrosilylation afforded ketone **6**. At this point, attempts at a chelation-controlled diastereoselective aldol condensation between ketone **6** and aldehyde[16] **7** was examined. Classical metal–enolate aldols that use the enolate generated from LDA or by soft enolization techniques ($TiCl_4/NR_3$) were futile and led to the decomposition of **6** along with recovery of **7**. Next we turned to a Mukaiyama aldol process, where deprotonation of **6** with LDA and subsequent trapping with TMSCl allowed for the synthesis of silyl enol ether **12** as an

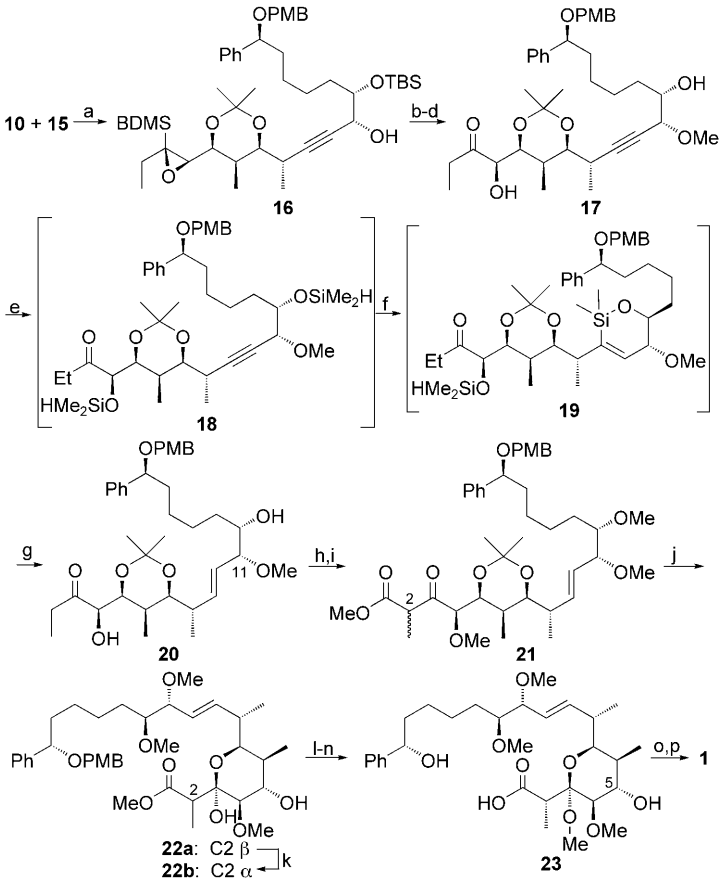


Scheme 3. Synthesis of the alkyne fragment. Reagents and conditions: a) $NaHCO_3$, 10 mol% KBr, 1 mol% TEMPO, NaOCl, RT, 1 h, 75%; b) 0.5 mol% $[Cp^*Ru(MeCN)_3]PF_6$, benzyldimethylsilane, 0 °C to RT, 30 min, 86%; c) LDA, TMSCl, THF, −78 °C to RT, >99%, ca. 1:1 *E*/*Z*; d) aldehyde **7**, $TiCl_4$, CH_2Cl_2, −78 °C, 73% (major diastereomer, 9:1 d.r.); e) Et_2BOMe, $NaBH_4$, THF/MeOH (1:1), −78 °C, 4 h; 30% H_2O_2, 84% (>50:1 d.r.); f) *m*CPBA, CH_2Cl_2, −25 °C, 36 h, , 75% (desired epimer, 8:1 d.r.); g) 2-methoxypropene, PPTS, CH_2Cl_2, RT, 1 h, 82%; h) H_2 (1 atm) 10 wt% Pd/C, EtOAc, RT, 24 h, 91%; i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; dimethyl-1-diazo-2-oxopropylphosphonate, NaOMe, THF, −78 °C to −40 °C, 81% over two steps. Cp* = pentamethylcyclopentadienyl, LDA = lithium diisopropylamide, *m*CPBA = *m*-chloroperbenzoic acid, PPTS = pyridinium toluene-*p*-sulfonate, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl.

approximate 1:1 mixture of *E* and *Z* isomers. As the diastereoselectivity of some Mukaiyama aldol reactions have been shown to be independent of silyl enol ether geometry, presumably owing to the involvement of open transition states,[17] the mixture of enols (**12**) was subjected to these types of reaction conditions. Gratifyingly, the use of $TiCl_4$ as the Lewis acid furnished the *syn*-aldol adduct **13**. Subsequent 1,3-*syn* reduction of enone **13**,[18] followed by alcohol directed epoxidation of the vinyl silane, and protection of the 1,3-diol allowed for stereoselective synthesis of epoxysilane **14**. The terminal alkyne was installed by hydrogenolysis of the primary benzyl ether, Moffatt–Swern oxidation of the primary alcohol, and final conversion into the alkyne was achieved using the Ohira–Bestmann reagent.[19]

With aldehyde **10** and alkyne **15** in hand, conditions for coupling the two fragments through a Felkin-controlled metal acetylide addition were explored (Scheme 4). Interestingly, use of the alkynyl titanate of **15** (not shown) gave the product of formal chelation-controlled addition in good diastereoselectivity (9:1 d.r.) despite the tendency of these reagents to give good Felkin-controlled addition.[20] Only the lithium acetylide of **15** was found to slightly favor the Felkin addition product **16**. Various additives which are potential lithium atom chelators were examined with the hypothesis that this chelation may increase the steric bulk of the lithium acetylide and thereby increase selectivity for the Felkin product. Ultimately, use of TMEDA as an additive led to the formation of **16** in 4.8:1 d.r. and excellent yield. However, the diastereomers could not be separated at this point and the mixture was carried forward.

With access to **16**, we turned our attention to Tamao–Fleming oxidation[21] of the epoxysilane moiety of **16** to unmask the α-hydroxyketone. First, the secondary alcohol was methylated with Meerwein's salt before Tamao–Fleming oxidation was explored. The use of aqueous H_2O_2, under reaction conditions first reported by Hosomi and co-work-



Scheme 4. Completion of the synthesis. Reagents and conditions: a) TMEDA, *n*BuLi, THF, −78 °C to −20 °C, 92% (4.8:1 d.r.); b) Me_3OBF_4, proton sponge, CH_2Cl_2, RT, 1.5 h, 89%; c) UHP, TBAF (syringe-pump addition), THF, 0 °C to RT, 2 h, 75%; d) HF·py, py, THF, RT, 48 h, 92%; e) $NH(SiMe_2H)_2$ (neat), 85 °C, 3 h; f) 5 mol% $[CpRu(MeCN)_3]PF_6$, CH_2Cl_2, RT, 2 h; g) AgF, DMSO, MeOH, H_2O, THF, RT, 1.5 h, 60% over three steps; h) Me_3OBF_4, proton sponge, CH_2Cl_2, RT, 2 h, 88%; i) LDA (4.0 equiv), THF, −78 °C; then Et_2O, HMPA, methyl cyanoformate, 57–75% (1:1 d.r.); j) 60% AcOH, 55 °C, 3 h, 68%; k) $Mg(OMe)_2$, MeOH, RT, 12 h; 60% AcOH, 55 °C, 2 h, 53% after three cycles; l) amberlyst-15, MeOH, RT, 9 h, 70%; m) DDQ, pH 7 buffer, CH_2Cl_2, MeOH, 4 °C, 5 h, 80%; n) $Ba(OH)_2{\cdot}8H_2O$, MeOH, 55 °C, 12 h, 75%; o) MNBA, DMAP, toluene, M.S. (4 Å), syringe-pump addition of **23**, 17 h, 25%; p) 1 M HCl, THF, RT, 25 min, >99%. Cp = cyclopentadienyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, MNBA = 2-methyl-6-nitrobenzoic acid anhydride, M.S. = molecular sieves, TBAF = tetra-*n*-butylammonium fluoride, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, UHP = urea hydrogen peroxide.

ers[22] and which we have previously exploited for this transformation,[11] led to substantial amounts of protodesilylation product. However, when using anhydrous conditions developed in our laboratory,[11] which employ the urea hydrogen peroxide (UHP) complex as the oxidant, clean oxidation was observed in good yield with only small amounts of the protodesilylation product (ca. 10-15%). The secondary TBS ether was not removed during the oxidation, and subsequent removal was achieved using HF·py to afford **17**.

Synthesis of the C9–C10 *trans* olefin by hydrosilylation/protodesilylation of the internal alkyne of **17** was next examined. Silylation of the secondary alcohols of **17**, and subsequent hydrosilylation[9] afforded vinylsilane **19**, which was subjected to protodesilylation without purification. A variety of protodesilylation conditions were examined, however, only AgF was successful in this system[23] thus allowing access to **20** in good overall yield from **17**. It was at this point that the epimeric mixture at C11 could be separated by chromatography.

To complete the total synthesis, formation of the hemiketal portion of **1** and macrolactonization was required. Global methylation of the free alcohol groups in **20**, and subsequent Mander carboxylation of the enolate (formed from kinetic deprotonation of the ketone) provided **21** as an inseparable epimeric mixture at C2. Heating this mixture in aqueous acetic acid removed the acetonide protecting group and facilitated cyclization to furnish hemiketals **22a** and **22b**, which were separable by chromatography. Subjection of the incorrect epimer (**22a**) to basic conditions allowed access to the open form of **22a**, and subsequent treatment with acid reformed the cyclic hemiketal and allowed for epimerization of **22a** to give an approximate 1.4:1 mixture of **22a**/**22b** in 75% yield for this equilibration step. Separation and recycling of **22a** allowed for the conversion of **22a** into **22b** in 53% overall yield after three cycles.

At this point all that remained to complete the synthesis of **1** was formation of the macrocycle. The desired seco-acid **23** was prepared by initial conversion of hemiketal **22b** into the corresponding methyl ketal, subsequent removal of the PMB protecting group, and lastly saponification of the methyl ester. Previous studies by Höfle and coworkers[1c] had shown that a related analogue to **23** bearing a protecting group on the hydroxy group at C5 was inert to typical macrolactonization procedures that rely on activation of the carboxylic acid functionality. However, Höfle was able to effect macrolactonization of this system through a four-step sequence utilizing activation of the alcohol moiety. While our synthesis is amenable to this approach by protection of the hydroxy group at C5 of **22b** prior to removal of the PMB group and saponification, this route is somewhat cumbersome. Furthermore, it was envisioned that the absence of a protecting group at C5 might allow for more efficient macrolactonization. Therefore, we chose to examine the viability of directly converting **23** into the desired macrolactone using this approach. Gratifyingly, macrolactonization of **23** using the method of Shiina et al.[24] furnished the desired macrolactone. Subsequent removal of the methyl ketal[1c] afforded synthetic **1** whose spectroscopic data was consistent with those of the natural product.

In conclusion, we have prepared soraphen A (**1**) in 25 linear and 34 total steps beginning from commercially available materials **11**, glycidol, and methyl (*S*)-3-hydroxy-2-methylpropiolate.[16] This synthesis further illustrates the versatility of the alkyne functional group in the synthesis of complex molecules.

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[16] Aldehyde **7** was prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropiolate in 67% overall yield, see the Supporting Information.

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