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Total Synthesis of Antheliolide A

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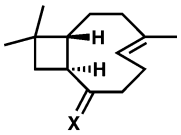
The structurally unusual and compact marine natural product antheliolide A (**1**) has remained a formidable challenge to synthetic chemists since the isolation from *Anthelia glauca* and the determination of structure almost 20 years ago.[1−3] The framework of four-, five-, six-, and nine-membered rings and the particular arrangement of functionality and multiple embedded stereocenters sharply limit the range of chemical reactions that are applicable to the synthesis. Further, there is little in the existing synthetic literature to define an effective strategy of synthesis. This paper describes the development of a logical synthetic pathway to **1** that efficiently assembles this acetoacetate−diterpenoid composite with excellent stereocontrol. The present synthesis has allowed the assignment of absolute configuration to antheliolide A (as in **1**) as well as laboratory access to this scarce natural product.

The pathway for the synthesis of **1** is outlined in Scheme 1. Conversion of the vinylic bromide **2**[4] to the corresponding vinyllithium reagent using 2 equiv of *t*-BuLi[5] and subsequent reaction with the *tert*-butyldiphenylsilyl-protected ϵ-hydroxy aldehyde **3** (R_1 = *t*-$BuPh_2Si$)[6] afforded the trienol **4**. Double bond transposition−homologation of **4** to form stereoselectively the *Z*-homoallylic alcohol **5** was effected by application of Still's methodology[7] using the following sequence: (1) deprotonation of the allylic hydroxyl of **4** with KH and etherification with Bu_3SnCH_2I and (2) Sn−Li exchange and [2,3]-sigmatropic rearrangement with *n*-BuLi in THF. Primary alcohol **5** was oxidized by periodinane into the corresponding aldehyde which was then transformed into the dimethyl acetal **6** with methyl orthoformate and a catalytic amount of pyridinium tosylate.[8] Partial acetal exchange using $HOCH_2COOCH_3$ and pyridinium tosylate converted **6** to the mixed acetal methyl ester **7**. Saponification of the ester **7** gave the corresponding carboxylic acid which was converted to the triethylammonium salt by treatment with triethylamine. Slow addition of this salt to a solution of tosyl chloride and triethylamine in toluene at reflux resulted in ketene formation and diastereoselective internal [2 + 2]-cycloaddition to produce the bicyclic ketone **8**.[9] Ethynylation of the carbonyl group of **8** by the reagent from lithium trimethylsilylacetylide and $CeCl_3$[10] in THF at −78 °C afforded the expected propargylic alcohol which was desilylated by exposure to LiOH in MeOH at 23 °C to give the ethynyl carbinol (±)-**9** as a single diastereomer.

We were pleased to find that the two enantiomers of (±)-**9** were separated with remarkable facility on a Chiral Technologies OD-H HPLC column with 97:3 hexane−*i*-PrOH as eluent because of greatly different retention times (baseline separation with the two enantiomers typically eluting at 4.75 and 6.14 min). This separation was performed on a 4.2 g sample to afford each of the oily enantiomers of **9** in pure form and >99.9% ee.[11] Each of the enantiomers of **9** was then carried forward through the steps k−q of Scheme 1 to afford the enantiomers of tricyclic ketone **13** in the following way. This sequence includes a new and potentially broadly useful method for effecting the change of a ketone, R_2CO, to a β-keto sulfone, $R_2CHCOCH_2SO_2Ph$. Treatment of **9** with benzenesulfinyl chloride, Et_3N and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 at 0 °C for 2 h provided the benzenesulfinate ester **10** which underwent Pd-catalyzed [2,3]-sigmatropic rearrangement[12] upon exposure to $Pd_2(dba)_3$ in toluene at 60 °C for 2 h to form the isomeric allenic sulfone, $R_2C{=}C{=}CHSO_2Ph$. Reaction of this intermediate with Et_2NH at 23 °C to effect conjugate addition followed by hydrolysis with aqueous 1 N HCl and desilylation produced the β-keto sulfone **11** (76% yield from **10**). The primary hydroxyl of **11** was esterified with methyl chloroformate-DMAP to afford the corresponding allylic methoxycarbonyl derivative which served as the substrate for ring closure to **12** by a method that we had applied earlier to the closure of the 11-membered rings in β-arenosene and humulene.[13] Treatment of the methoxycarbonate of **11** with a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ and 1,4-bisdiphenylphosphinobutane using the base diazabicycloundecene (DBU) in THF at 55 °C for 2 h resulted in smooth cyclization to form **12** in 75% yield. Reductive $C-SO_2$ cleavage of **12** was effected with Al(Hg)-THF-H_2O at 23 °C for 16 h to form the ketone **13** in 88% yield.[14]

Starting with the enantiomer of **9** with the shorter retention time (4.75 min) we obtained the dextrorotatory form of **13** ($[\alpha]^{23}_D$ +34 in $CHCl_3$) to which we assign the absolute stereochemistry shown in Scheme 1. From the enantiomer of **9** with the longer retention time (6.14 min) we obtained the levorotatory product, ketone *ent*-**13** ($[\alpha]^{23}_D$ −34 in $CHCl_3$). These assignments were made by comparison with a close model, the known levorotatory bicyclic ketone **19** ($[\alpha]_D$ −72 in $CHCl_3$) that had been correlated with naturally occurring β-caryophyllene (**20**).[15,16]



19, X = O
20, X = CH_2

Using the (+)-enantiomer **13**, we were able to synthesize the naturally occurring form of **1** as outlined in Scheme 1. Methylenation of the dextrorotatory ketone **13** using the Tebbe reagent,[17] $Cp_2TiCH_2{\cdot}Me_2AlCl$ in toluene at 20 °C for 2 h furnished the required triene **14**. The next task in the synthesis, the conversion of the lactal **14** to the corresponding lactol and lactone **15**, turned out to be a challenge because of the great sensitivity of the caryophyllene-like subunit to acids, electrophiles, and oxidants. The only satisfactory solution that we were able to find involved sequential treatment of **14** with (1) $PhSeAlMe_2$[18] in CH_2Cl_2 at 23 °C for 2 h to replace methoxy by phenylseleno, (2) $AgNO_3$ in Me_2CO-H_2O to replace phenylseleno by hydroxyl, and (3) oxidation with catalytic Pr_4N^+ RuO_4^- (TPAP) and *N*-methylmorpholine *N*-oxide in CH_2Cl_2 which gave the desired lactone **15**.[19] Conversion of **15** to the potassium enolate with potassium hexamethyldisilazide

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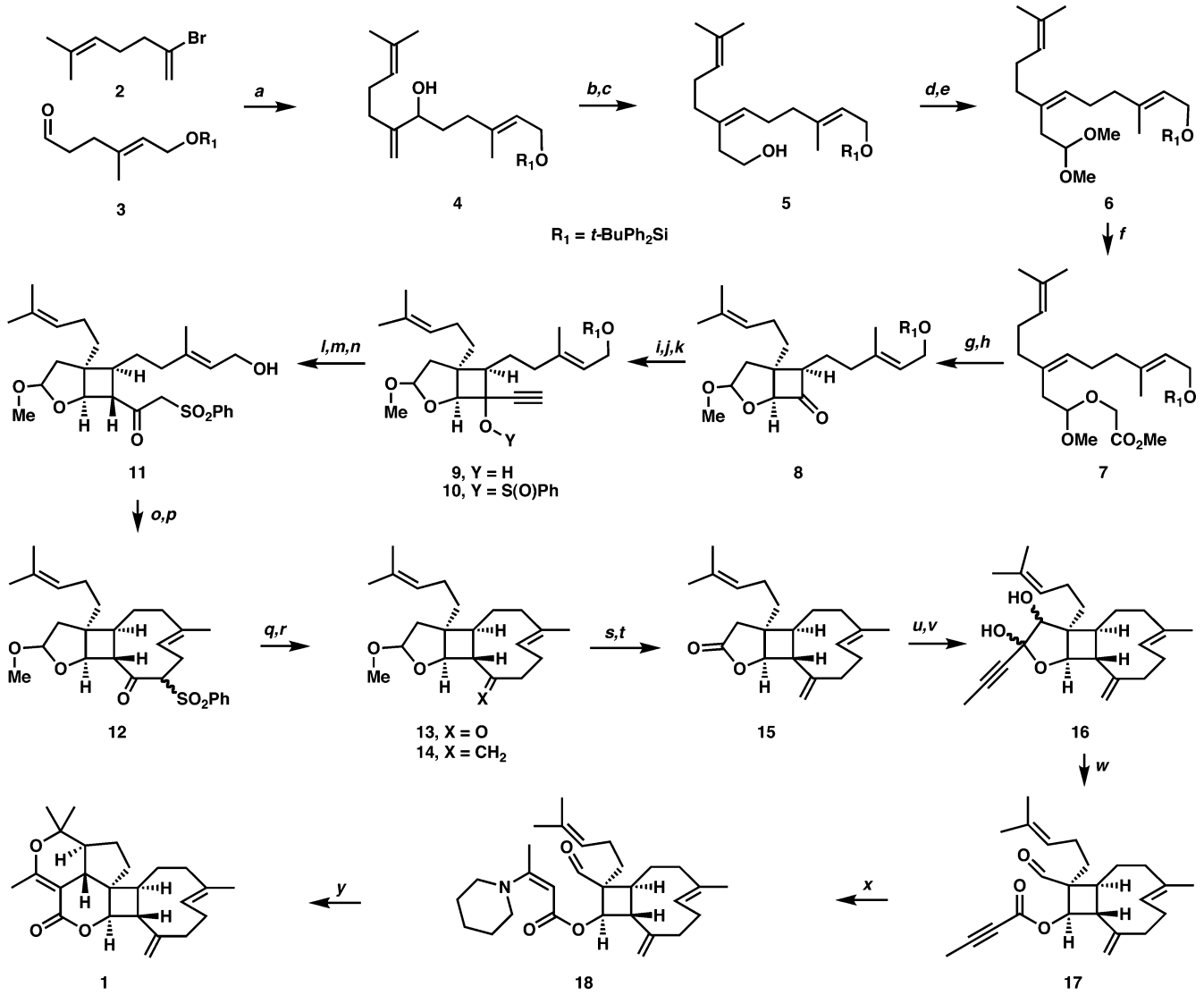
Scheme 1 [a]

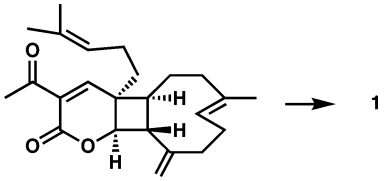


[a] Reagents and conditions: (a) 2-equiv *t*-BuLi, **2**, Et_2O, −78 °C; −20 °C, 6 h; then **3**, −78 °C, 2 h; (90%); (b) KH, THF, −40 °C, 30 min; then Bu_3SnCH_2I at −40 °C; 0 °C, 16 h; (c) *n*-BuLi, THF, −78 °C, 3 h (61% from **4**); (d) Dess−Martin periodinane, CH_2Cl_2, 23 °C, 30 min; (e) $HC(OMe)_3$, pyH^+ TsO^-, 23 °C, 12 h (85% from **5**); (f) $HOCH_2COOMe$, pyH^+ TsO^-, 60−65 °C, 1.5 h (73%); (g) LiOH, MeOH, 22 °C, 2 h; adjust to pH 3.3 and extract with Et_2O; (h) *p*-TsCl, Et_3N, C_7H_8, at reflux for 7 h (66%); (i) $TMSC{\equiv}CCeCl_2$, THF, −78 °C, 3 h; (j) 3*N*-LiOH, MeOH−H_2O, 23 °C, 2 h; (k) PhS(O)Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h (87% from **8**); (l) $Pd_2(dba)_3$, C_7H_8, 60 °C, 2 h; (m) Et_2NH, CH_2Cl_2, 23 °C, 1 h then 1*N*-HCl (aq) (76% of β-keto sulfone from **10**); (n) desilylation, py $(HF)_x$, py, 0−23 °C over 3 h (89% of hydroxy β-keto sulfone **11**); (o) MeOCOCl, DMAP, CH_2Cl_2, 0−23 °C over 6 h (88% of the methoxy carbonate ester of **11**); (p) $Pd_2(dba)_3{\cdot}CHCl_3$, 1,4-bis-diphenylphosphinobutane, DBU, THF, 55 °C, 2 h (75% of **12**); (q) Al(Hg), THF-H_2O 23 °C, 16 h (88% of **13**); (r) Tebbe reagent ($Cp_2TiCH_2{\cdot}Me_2AlCl$), C_7H_8, (85% of **14**); (s) $PhSeAlMe_2$, CH_2Cl_2, 23 °C, 2 h; then $AgNO_3$ in 1:1 Me_2CO-H_2O at 23 °C for 2 h; (t) TPAP, NMO, 4A mol sieves, CH_2Cl_2, 23 °C, 2 h (55% of **15** from **14**); (u) $(Me_3Si)_2NK$, THF −78 C, 45 min; then $PhCH(O)NSO_2Ph$, THF, −78 °C, 2 h followed by Me_2S and then H_2O (90% of α-hydroxy **15**); (v) $CH_3C{\equiv}CLi$, THF, −78 °C, 12 h (90% of **16** from **15**); (w) $NaIO_4$ on silica gel, CH_2Cl_2, 25 °C, 3 h (93% of **17**); (x) piperidine, THF, 23 °C, 4 h (98% of **18**); (y) silica gel, C_6H_6, 23 °C, 6 h (74% of **1** from **18**).

in THF and subsequent treatment with the Davis oxaziridine afforded a 5:1 mixture of diastereomeric α-hydroxy lactones[20] which upon reaction with 1-propynyllithium were transformed into **16**.[21] Oxidative cleavage of **16** with sodium periodate supported on silica gel[22] provided aldehyde ester **17** in excellent yield. Exposure of **17** to piperidine at 23 °C gave the vinylogous enamide aldehyde **18** cleanly. Antheliolide A was produced in a single step from **18** simply by stirring in C_6H_6 solution with silica gel at 23 °C for 6 h. Since the absolute configuration of antheliolide A had not been determined previously, we also employed the sequence shown in Scheme 1 to synthesize *ent*-antheliolide A (from *ent*-**13**) and racemic antheliolide A (from (±)-**9** via (±)-**13**). We found that the enantiomers of antheliolide A are cleanly separated by HPLC using a Chiral Technologies Chiralpak-AD column with 97:3 hexane−*i*-PrOH for elution (23 °C, 1 mL/min flow rate): *ent*-antheliolide A eluted at 14.01 min; synthetic or naturally occurring antheliolide A (**1**) eluted identically at 20.28 min.[23] The ^1H and ^{13}C NMR data for synthetic **1** agreed completely with that reported for antheliolide A, including the observation in the ^1H NMR spectrum of two conformational forms of the nine-membered ring that interconvert slowly on the NMR time scale.[24] Although we measured the optical rotation of synthetic antheliolide A, $[\alpha]^{23}_D$ −111 (c = 0.2, CH_2Cl_2), it was not possible to make a comparison with the natural product since that rotation had not been reported and since there was insufficient reference sample available to us. The assignment of the absolute configuration **1** to antheliolide A brings it in line with the absolute stereochemistry of the majority of the related xenicane family of marine natural products.[25,26] It is noteworthy

that the absolute stereoarrangement of **1** is opposite to that of the plant-derived natural product β-caryophyllene (**20**).

Many of the steps used in the synthesis of antheliolide A described above have implications beyond the present work, as well as being of crucial importance to the success of this project. These include (1) formation of the mixed acetal **7**, (2) the diastereoselective bicyclization to form **8** in which stereocenters are correctly established at each carbon of the four-membered ring, (3) the chain extension **8** → **11**, (4) the efficient closure of the nine-membered ring of **12**, (5) the mild oxidative cleavage sequence **14** → **17**, and (6) the successful and quick formation of the last three rings of **1** from aldehyde **17** via **18**. It seems logical that the one-step conversion of **18** to **1** occurs via the intermediate **21** by [2 + 4]-cycloaddition which is made even more facile by steric acceleration. The same pathway may be involved in the biosynthesis of **1**. The approach described above for the synthesis of **1** is completely different from that employed in these laboratories earlier for the construction of the structural relative β-caryophyllene.[27]



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Although the xenicane family of marine natural products is sizable and growing steadily,[28] only a few studies have appeared on approaches to their synthesis.[29] Structurally intricate and rigid polycylic natural products such as **1** are likely to possess interesting biological activity. The availability of synthetic **1** should facilitate the study of this possibility.

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Supporting Information Available: Experimental procedures and characterization data for all reactions and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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