Communication

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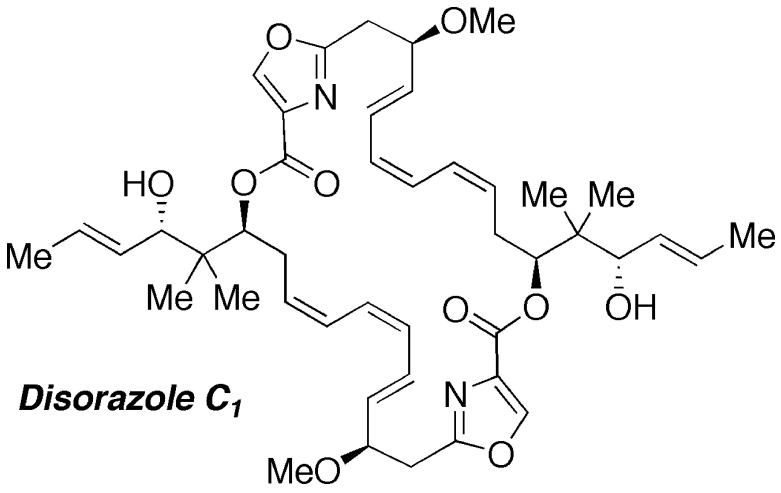

Disorazole C$_1$

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Total Synthesis of (−)-Disorazole C_1

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Disorazole C_1 (**1**) is one of 29 related macrocycles isolated in 1994 by Jansen and co-workers from the fermentation broth of the myxobacterium *Sorangium cellulosum*.[1] Myxobacteria demonstrate features of both unicellular and polycellular organisms. They are able to move in waves by gliding on surfaces of rotten wood, dead plants, and other bacteria and fungi. Over the past two decades, myxobacteria have been intensively studied, in part due to their ability to produce a wide range of anticancer, antibacterial, fungicidal, and immuno-modulating secondary metabolites.[2] Disorazoles possess significant cytotoxic and nM antitubulin activities.[3] While many of the disorazoles have pseudo-dimeric structures, their macrocyclic-heterocyclic scaffolds and labile polyene segments render them synthetically challenging,[4] and questions about their definitive structural assignment and their relative and absolute configuration have remained unresolved.[4a] We now report the asymmetric total synthesis of disorazole C_1.

Our convergent retrosynthesis paid special consideration to the known sensitivity of late stage polyene intermediates. The dimer was separated into four segments that could be assembled under mild reaction conditions with minimal protecting group manipulations (Figure 1). Two of the (*Z*)-alkenes of the triene unit were masked as alkynes. The resulting dieneyne **2** offered an opportunity for a Sonogashira segment condensation. The 1,3-diol **3** would arise from the known compound **5**.[5] The oxazole segment **4** was derived from the propargyl alcohol **6**, obtained from enantioselective addition of an alkynyl zinc reagent to the corresponding aldehyde.[6]

Homoallylic alcohol **5** was obtained in 91% yield and 92% ee by TiF_4/(*S*)-Binol-catalyzed allylation.[5] The terminal olefin was then converted to the alcohol in 88% yield by cleavage with ozone using Sudan III[7] as an indicator, followed by in situ reduction with $NaBH_4$ (Scheme 1).[8] 1,3-Diol protection and saponification led to acetonide **7** in 80% yield. Swern oxidation to the aldehyde and treatment with 1-lithiopropyne afforded a mixture of diastereomers **8** and **9** which were readily separated by chromatography on triethylamine-deactivated SiO_2.[9]

Reduction of **8** using Red-Al in THF initially gave the corresponding allylic alcohol in 68% yield. This yield was improved to 83% by rigorously degassing the THF prior to the introduction of Red-Al. Conversion to diol **10** was completed in 84% yield by first protecting the allylic hydroxyl group as the PMB ether using freshly distilled *p*-methoxybenzyl bromide with Et_3N and KHMDS in THF,[10] followed by removal of the acetonide with aqueous acetic acid in THF. Diol **10** is a key intermediate in this synthesis, since the primary hydroxyl group allows for a variety of transformations for the installation of the $C_{11}-C_{12}$ (*Z*)-alkene. In the present synthesis, a Peterson olefination with 1,3-bis(triisopropylsilyl)-propyne[11] was utilized. After protection of both hydroxyl groups in **10** as triethylsilyl ethers, selective oxidation of the terminal TES-ether under Swern conditions,[12] exposure to lithiated 1,3-bis-(triisopropylsilyl)propyne,[11] and cleavage of the TES ether with chloroacetic acid in methanol,[13] an 8:1 (*Z*/*E*)-mixture of enyne **11** was obtained. The isomers were readily separated by chromatography on SiO_2. Deprotection of (*Z*)-**11** with TBAF in THF afforded the desired diol segment **3** in 94% yield.

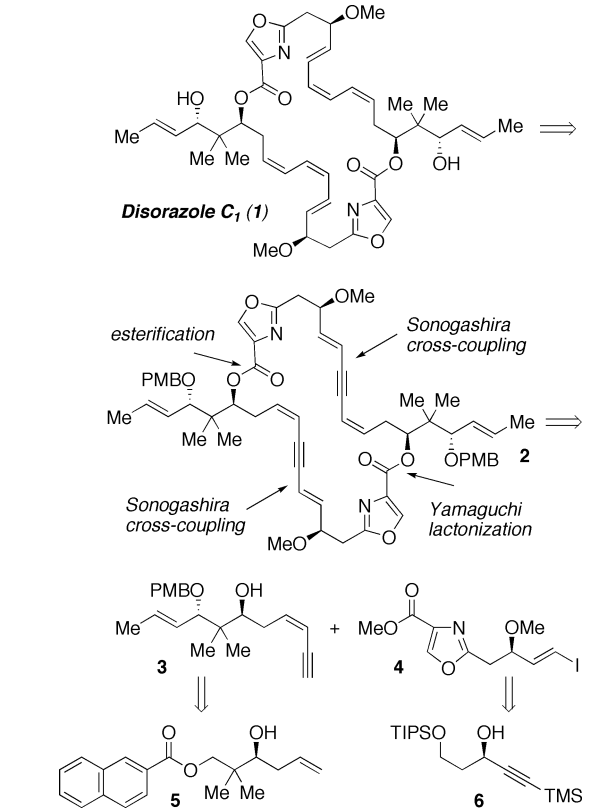
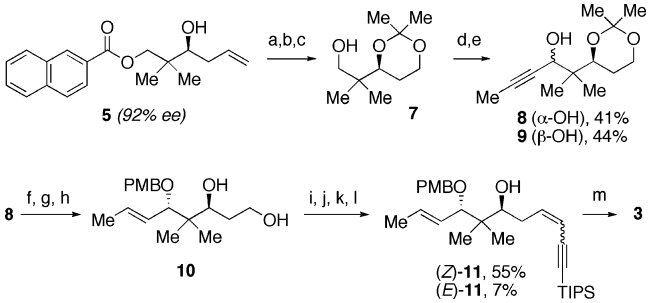


Figure 1. Retrosynthetic analysis of (−)-disorazole C_1.

Scheme 1[a]



[a] (a) O_3/O_2, Sudan III, MeOH, CH_2Cl_2, −78 °C then $NaBH_4$, −78 °C to rt, 88%; (b) 2,2-dimethoxypropane, PPTS, THF, 0 °C to rt, 36 h, 97%; (c) 1 M LiOH, THF, MeOH, 0 °C to rt, 20 h, 82%; (d) oxalyl chloride, DMSO, Et_3N, −78 °C; (e) propyne, *n*-BuLi, THF, −78 °C to 0 °C, 1.5 h; (f) Red-Al, THF (degassed), 70−75 °C, 25 h, 83%; (g) PMB-Br, Et_3N, KHMDS, THF, −78 °C, 1 h then rt, 2 h; (h) AcOH, THF, H_2O (4:1:1), 60 °C, 12 h, 84% (2 steps); (i) TES-OTf, 2,6-Lutidine, CH_2Cl_2, 0 °C, 30 min; (j) oxalyl choride, DMSO, Et_3N, CH_2Cl_2, 75% (2 steps); (k) 1,3-bis(TIPS)propyne, *n*-BuLi, THF, −78 °C, 30 min; (l) chloroacetic acid, MeOH/CH_2Cl_2, rt, 14 h; (m) TBAF, THF, 0 °C to rt, 14 h, 94%.

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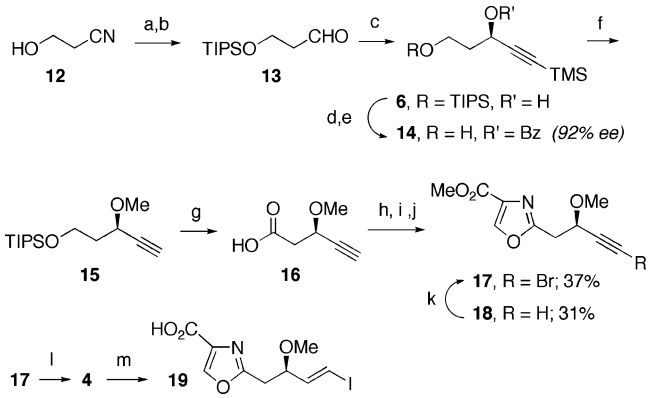
Scheme 2[a]



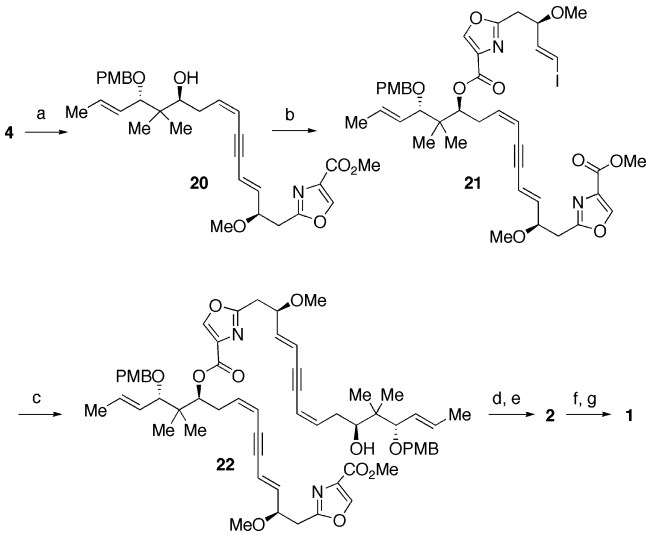
[a] (a) TIPS-Cl, imid, DMF, rt, 16 h; (b) DiBAl-H, CH_2Cl_2, −10 °C, 50 min, 78% (2 steps); (c) TMS-acetylene, Et_2Zn, toluene, reflux, 1 h, then (*S*)-Binol, Ti(O*i*-Pr)$_4$, then **13**, rt, 20 h, 66%; (d) benzoyl chloride, DMAP, pyridine, rt, 4 h, 100%; (e) HF/H_2O, CH_3CN, rt, 12 h, 93%; (f) Dimethyl sulfate, *n*-Bu_4NHSO_4, NaOH, toluene/H_2O, 0 °C to rt, 3.5 h, 95%; (g) HF, CH_3CN, rt, 24 h then NaOCl, $NaClO_2$, TEMPO, CH_3CN, phosphate buffer (pH 6.7), 45 °C, 18 h, 99%; (h) SerOMe•HCl, EDC, HOBT, NMM, CH_2Cl_2, 0 °C to rt, 16 h, 55%; (i) DAST, CH_2Cl_2, −78 °C, 1 h then K_2CO_3, −78 °C to rt, 40 min; (j) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to 4 °C, 20 h; (k) NBS, $AgNO_3$, acetone, rt, 1 h, 54%; (l) *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, −78 °C to rt, 3 h, then I_2, 0 °C, 45 min, 92%; (m) LiOH, H_2O, THF, rt, 12 h, 97%.

Silyl ether protection of hydroxy nitrile **12** followed by reduction with DiBAl-H afforded aldehyde **13** in 78% yield (Scheme 2). The transformation of **13** to the propargylic alcohol **6** utilized the methodology of Pu and co-workers.[6] The alkynyl zinc reagent derived from TMS-acetylene and diethylzinc was added to **13** in the presence of a catalyst formed in situ from Ti(*i*-OPr)$_4$ and (*S*)-Binol. For the determination of the %ee of this transformation, **6** was converted to benzoate **14** and analyzed by chiral HPLC. Dimethyl sulfate under phase-transfer conditions converted **6** to the methyl ether **15** in 95% yield with concomitant loss of the trimethylsilyl group. Carboxylic acid **16**[14] was obtained by removal of the TIPS group with aqueous HF in acetonitrile, neutralization with aqueous NaOH, and oxidation using the Merck protocol.[15] Cyclodehydration of the hydroxy amide obtained from **16** and serine methyl ester was accomplished using diethylaminosulfurtrifluoride (DAST) followed by $BrCCl_3$ and DBU[16] to afford oxazoles **17** and **18**. The alkynyl bromide **17** was an unexpected outcome, but allowed for an efficient conversion to the required vinyl iodide **4** in 92% yield by Pd-catalyzed hydrostannylation.[17] Finally, **4** was converted to the carboxylic acid segment **19** in 97% yield by saponification with aqueous LiOH in THF.

Both segments **3** and **4** were going to be utilized twice in the convergent construction of disorazole C_1. The chain extension sequence to the *seco*-macrodiolide was initiated by Sonogashira cross-coupling of **3** and **4** to afford the protected monomer **20** in 94% yield (Scheme 3). Acylation of **20** with an excess of **19** led to **21** in 80% yield. A second Sonogashira coupling between **21** and **3** afforded *seco*-disorazole C_1 in 94% yield. Selective *mono*-saponification of methyl ester **22** was followed by a Yamaguchi lactonization[18] to give macrocycle **2** in 79% yield. While thus far the segment assembly had benefited from oustanding yields and efficiency, the next steps required extensive optimization to avoid decomposition of the *oligo*-enyne scaffold of the natural product. The PMB ethers were removed with DDQ under buffered conditions to afford the diol in 61% yield. Finally, double alkyne reduction with Lindlar catalyst in the presence of excess quinoline afforded **1** in 57% yield after HPLC purification.[19]

In conclusion, the highly convergent and stereoselective synthesis of the myxobacterium metabolite (−)-disorazole C_1 was accomplished in 20 steps and 1.5% yield for the longest linear sequence. Notable features include the concise formation of iodoalkene **4** and the selective functional group manipulations including the conversion of PMB-protected hexaene-diyne **2** to the highly labile octaene natural product. This total synthesis also establishes the correct relative and absolute configuration of the disorazoles.

Scheme 3[a]



[a] (a) **3**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, −20 °C to rt, 75 min, 94%; (b) **19**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 14 h, 80%; (c) **3**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, −20 °C to rt, 75 min, 94%; (d) LiOH, H_2O, THF, rt, 13.5 h, 98%; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 2 h then DMAP, toluene, rt, 16 h, 79%; (f) DDQ, phosphate buffer, CH_2Cl_2, rt, 15 min, 61%; (g) H_2, Lindlar catalyst, quinoline, EtOAc, rt, 1 h, 57%.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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