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# The synthesis of the monomeric moiety of disorazole $C_1$

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**Abstract**

The stereocontrolled synthesis of the monomeric subunit of the macrolide dimer disorazole $C_1$ (**1**) has been accomplished by convergent coupling of **3** and **4** using the Stille method. 

Disorazole $C_1$ (**1**) was isolated in 1994 from the fermentation broth of *Sorangium cellulosum* by Jansen et al.[1] and its crude structure was identified (Scheme 1). As part of our general interest in the synthesis of oxazole-containing natural products, we became intrigued with a synthetic route to this molecule. Unfortunately, though **1** was found to be optically active, none of the stereocenters (C6–C6′, C14–C14′, and C16–C16′) were assigned in either a relative or an absolute sense.[1] With this in mind, we set out to devise a synthesis of disorazole $C_1$, via the monomeric subunit **2**, which would be both stereocontrolled and convergent. In this way, we could access all of the stereochemical possibilities present in **1**. By direct comparison of our synthetic samples with the reported $[\alpha]_D$ and $^1$H NMR spectral data[1] for disorazole $C_1$ we might then obtain correct stereochemical information regarding this macrolide. We feel that this is the best way to determine the structure and stereochemistry of disorazole $C_1$, since none of the natural product remains[2] and, therefore, chemical degradation or X-ray techniques cannot be employed to obtain this information. Retrosynthetically, we envisioned that the synthesis of disorazole $C_1$ might involve a cyclodimerization of the hydroxyacid **2** (Scheme 1), which, in turn, could be assembled via a Stille coupling of the dienyl iodide **3** and the stannane **4**.[3] Furthermore, a successful synthesis of **2** would potentially allow access to 17 of the 29 known disorazole variants, which have this subunit in common.[1]

Synthesis of the oxazole fragment **3** began from the readily available ester **5**[4] which was saponified (2N LiOH, THF) and coupled to the methyl ester of racemic serine with 1,1′-carbonyl diimidazole[5] (1,1′-CDI) to give **6** in 67% combined yield (Scheme 2). Cyclodehydration of **6** was accomplished using diethylaminosulfur trifluoride (DAST) in $CH_2Cl_2$ at −78°C, and the resulting oxazoline was taken on without purification and treated with DBU and $BrCCl_3$ in $CH_2Cl_2$ at 0°C to give the oxazole **7** in 79% overall yield for the two steps.[6] Subsequently, the acetal in **7** was cleaved and the diol selectively converted into the hydroxy-methoxy oxazole **8** in 56% overall yield from **7**. Homologation of **8** to the α,β-unsaturated aldehyde was affected by oxidation of the primary alcohol ($SO_3$·Pyr, DMSO, $Et_3N$, $CH_2Cl_2$) to the aldehyde, which was treated with triphenylphosphoranylidene acetaldehyde in refluxing

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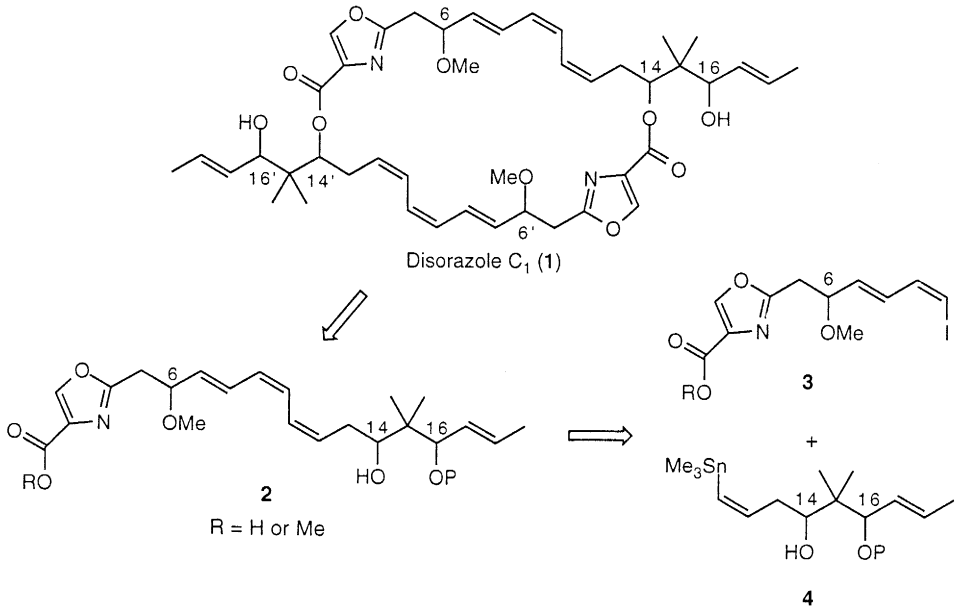
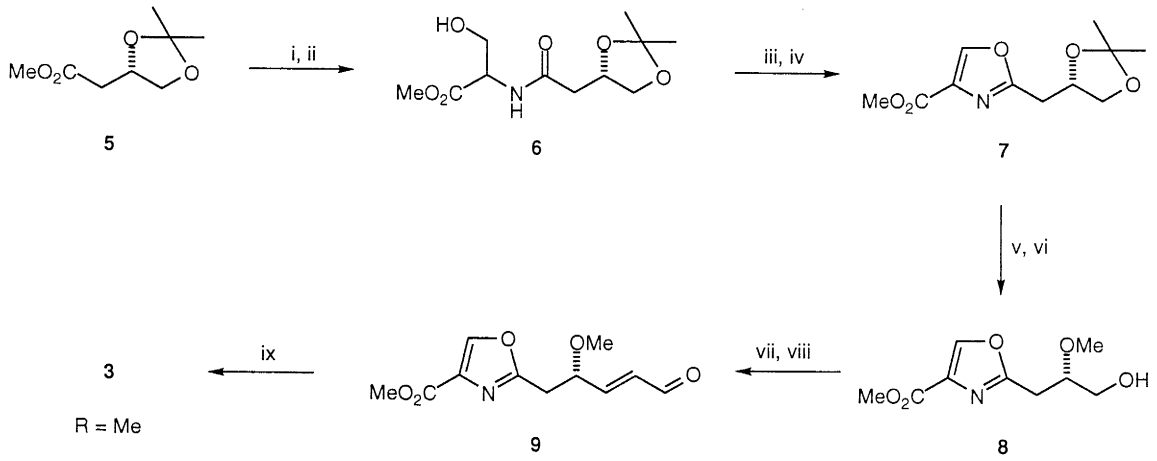



Scheme 1.

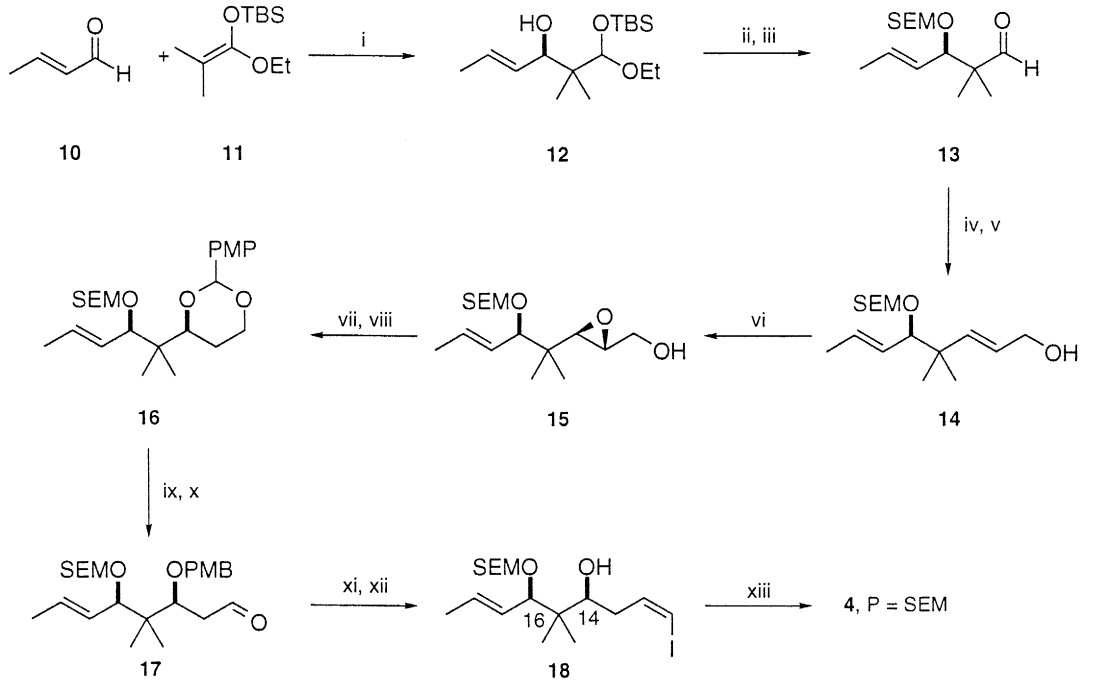
benzene to afford **9** in 62% yield. This enal **9** was converted to the (*Z*)-vinyl iodide **3** (R=Me) in 71% yield (*Z*:*E*=18:1) using a modification[7] of the Wittig coupling ($I^-Ph_3P^+CH_2I$,[8] NaHMDS, HMPA, THF, −78°C).




Scheme 2. *Reaction conditions*: (i) 2N LiOH, THF; (ii) D,L-serine·OMe, 1,1′-CDI, THF, 67% for two steps; (iii) DAST, $CH_2Cl_2$, −78°C; (iv) DBU, $BrCCl_3$, $CH_2Cl_2$, 0°C to rt, 79% for two steps; (v) (a) Dowex-$H^+$, MeOH; (b) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$ (0.05 M), −78°C, 74% for two steps; (vi) (a) MeI, $Ag_2O$, $CH_3CN$, Δ; (b) TBAF, THF, 75% for two steps; (vii) $SO_3$·Pyr, DMSO, $Et_3N$, $CH_2Cl_2$; (viii) $Ph_3P{=}CH_2CHO$, benzene, Δ, 62% for two steps; (ix) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, THF, −78°C, 71%

The first step in the reaction sequence leading to **4** (Scheme 3) involved a modified[9] Mukaiyama aldol between (*E*)-crotonaldehyde **10** and the *O*-silyl ketene acetal **11**[10] thus furnishing **12** in 73% yield and 92–93% ee.[11] The hydroxy-acetal **12** was protected with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) in the presence of diisopropylethylamine (DIEA) and the *t*-butyldimethylsilyl (TBS) ethyl acetal was hydrolyzed to give the aldehyde **13** in 79% yield for the two steps. This aldehyde was subjected to a Horner–Emmons reaction to install an (*E*)-α,β-unsaturated ester, which was immediately reduced with Dibal at −78°C affording the allylic alcohol **14** (76% from **13**). Sharpless epoxidation[12] (D-(−)-

DIPT, *t*-BuOOH, Ti(O*i*Pr)$_4$, 3 Å mol sieves, $CH_2Cl_2$, −30°C) of **14** gave the epoxy alcohol **15** (95% yield, ≥15:1 de) which was reduced with Red-Al,[13] and protected as the *p*-methoxybenzylidene acetal **16** in 79% overall yield for the three steps. The acetal **16** was selectively ring opened with Dibal at −78°C,[14] followed by oxidation of the primary hydroxyl group with Dess–Martin periodinane[15] to afford the aldehyde **17** (76%). Subsequent reaction of this aldehyde with iodomethyl triphenylphosphonium ylide according to the Stork/Zhao modification[7] of the Wittig method and oxidative removal of the *p*-methoxybenzyl group (DDQ, $CH_2Cl_2$:$H_2O$) led to the (*Z*)-vinyl iodide **18** in 53% (*Z*:*E*=18:1) for the two steps. This iodide was converted to the stannane **4** in 74% yield by reaction with hexamethylditin in THF in the presence of catalytic $Pd(PPh_3)_2Cl_2$ at rt.[16–18]




Scheme 3. *Reaction conditions*: (i) $BH_3$·THF, *N*-Ts-L-valine, $CH_2Cl_2$, −78°C, 73%; (ii) SEMCl, Hünigs base, $CH_2Cl_2$, −78°C; (iii) 80% AcOH, 79% for two steps; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH (oil-free), toluene, THF, >95%; (v) Dibal, $CH_2Cl_2$, −78°C, 76%; (vi) D-(−)-DIPT, *t*-BuOOH, Ti(O*i*Pr)$_4$, $CH_2Cl_2$, −30°C, 95%; (vii) Red-Al, THF, −20°C; (viii) *p*-methoxybenzylidene dimethyl acetal, PPTS, $CH_2Cl_2$, 83% for two steps; (ix) Dibal, $CH_2Cl_2$, −78°C, 92%; (x) Dess–Martin periodinane, pyridine, *t*-BuOH, $CH_2Cl_2$, 83%; (xi) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, THF, −78°C, 67%; (xii) DDQ, $CH_2Cl_2$, $H_2O$, 79%; (xiii) $Pd(Ph_3P)_2Cl_2$, $(Me_3Sn)_2$, $Li_2CO_3$, THF, rt, 74%

With both coupling partners **3** and **4** in hand, a Stille coupling was attempted in order to assemble the target monomer **2** (R=Me, P=SEM). In practice, this was accomplished by addition of the stannane **4** to a solution of the dienyl iodide **3** in DMF in the presence of a catalytic amount of $Pd(CH_3CN)_2Cl_2$ to give **2** in 76% yield.[19] $^1$H NMR of this monomeric product **2** (Scheme 1) revealed that this material contained many of the signals found in the natural product **1**, particularly in the olefinic region.[20]

In conclusion, we have constructed the monomeric moiety **2** of the natural product disorazole $C_1$ (**1**) in a convergent and stereocontrolled fashion. It is hoped that this methodology will provide access to a number of diastereomeric derivatives of **2**, which may then be dimerized and compared to **1** via the reported $[\alpha]_D$ and spectral data for this compound. However, early attempts at double lactonization of **2** (R=H, P=SEM) to provide disorazole $C_1$ have not been promising. We continue to address this final key step.

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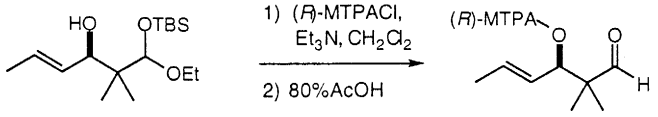
11. The enantiomeric excess (ee) of the Mukaiyama aldol reaction was determined by Mosher's ester anaylsis of **19** via HPLC and $^{19}F$ NMR:




**12** **19**

12. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
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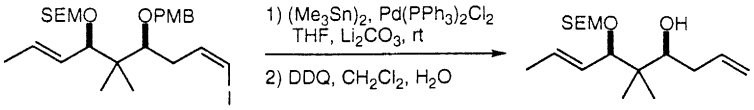
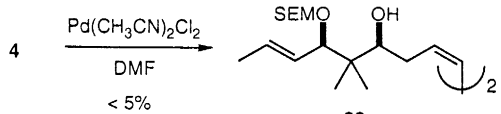
17. We found that conversion of the iodide **20** to the vinyl tin species, followed by removal of the *p*-methoxybenzyl group with DDQ resulted in destannylation, thus providing **21**:




**20** **21**

18. Elevated reaction temperatures for this transformation resulted in lower reaction yields (ca. 45%). Use of the less toxic hexabutylditin $(Bu_3Sn)_2$ in this reaction did not provide product.
19. The Stille coupling also resulted in the formation of a small of amount (<5%) of the homocoupled byproduct **22**:




**22**

20. Unfortunately, the monomer **2** is somewhat unstable and slowly isomerizes even when stored at −20°C.