



Pergamon

Tetrahedron Letters 41 (2000) 2821–2824

TETRAHEDRON
LETTERS

The synthesis of the monomeric moiety of disorazole C₁

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Received 6 December 1999; accepted 26 January 2000

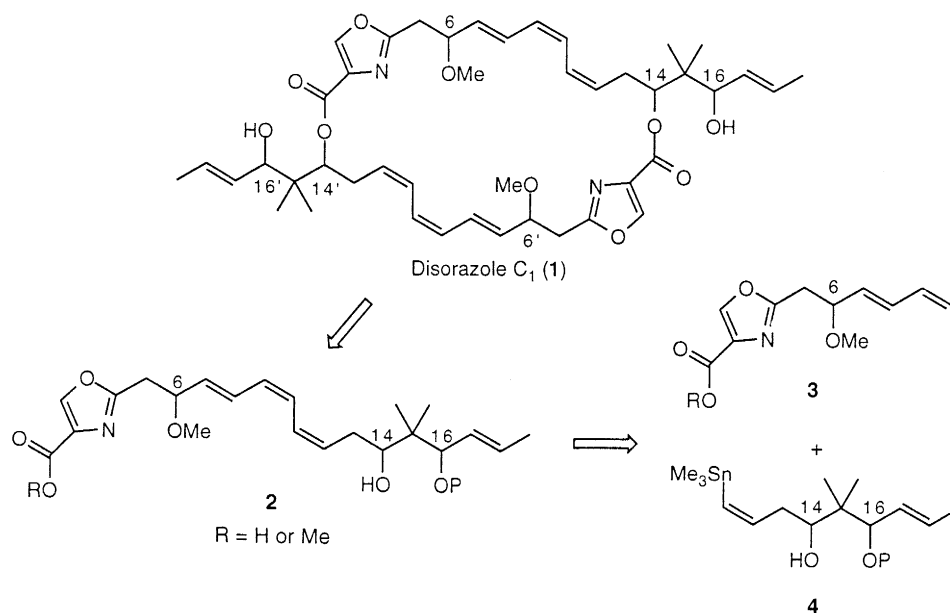
Abstract

The stereocontrolled synthesis of the monomeric subunit of the macrolide dimer disorazole C₁ (**1**) has been accomplished by convergent coupling of **3** and **4** using the Stille method. © 2000 Elsevier Science Ltd. All rights reserved.

Disorazole C₁ (**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 C₁, 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 ¹H NMR spectral data¹ for disorazole C₁ 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 C₁, since none of the natural product remains² and, therefore, chemical degradation or X-ray techniques cannot be employed to obtain this information. Retrosynthetically, we envisioned that the synthesis of disorazole C₁ 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

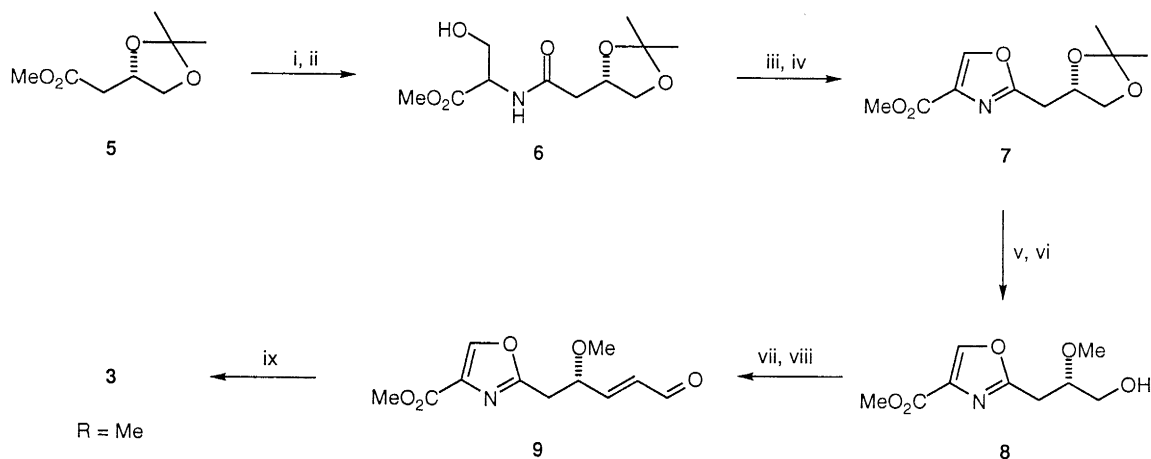
Synthesis of the oxazole fragment **3** began from the readily available ester **5**⁴ which was saponified (2N LiOH, THF) and coupled to the methyl ester of racemic serine with 1,1'-carbonyl diimidazole⁵ (1,1'-CDI) to give **6** in 67% combined yield (Scheme 2). Cyclodehydration of **6** was accomplished using diethylaminosulfur trifluoride (DAST) in CH₂Cl₂ at –78°C, and the resulting oxazoline was taken on without purification and treated with DBU and BrCCl₃ in CH₂Cl₂ 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 (SO₃·Pyr, DMSO, Et₃N, CH₂Cl₂) to the aldehyde, which was treated with triphenylphosphoranylidene acetaldehyde in refluxing

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Scheme 1.

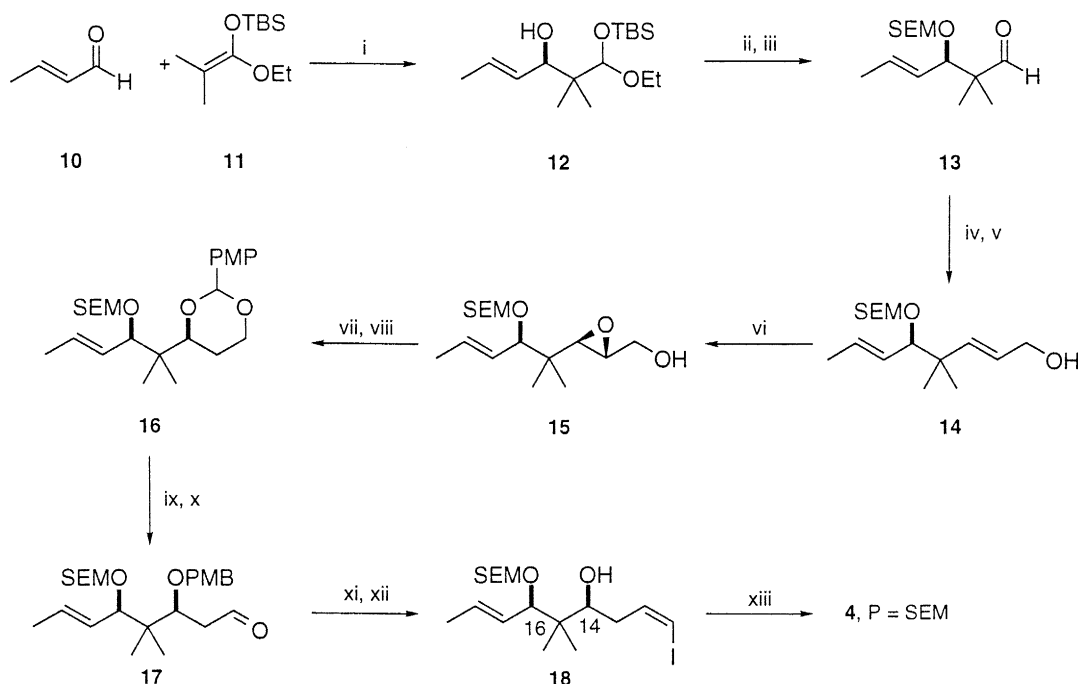
benzene to afford **9** in 62% yield. This enal **9** was converted to the (*Z*)-vinyl iodide **3** (R=Me) in 71% yield (*Z*:*E*=18:1) using a modification⁷ of the Wittig coupling ($\text{I}^- \text{Ph}_3\text{P}^+ \text{CH}_2\text{I}$,⁸ NaHMDS, HMPA, THF, -78°C).



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) $\text{SO}_3 \cdot \text{Pyr}$, DMSO, Et_3N , CH_2Cl_2 ; (viii) $\text{Ph}_3\text{P}=\text{CH}_2\text{CHO}$, benzene, Δ , 62% for two steps; (ix) $\text{I}^- \text{Ph}_3\text{P}^+ \text{CH}_2\text{I}$, NaHMDS, HMPA, THF, -78°C , 71%

The first step in the reaction sequence leading to **4** (Scheme 3) involved a modified⁹ 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 epoxidation¹² (D-(–)-

DIPT, *t*-BuOOH, Ti(O*i*Pr)₄, 3 Å mol sieves, CH₂Cl₂, –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 periodinane¹⁵ to afford the aldehyde **17** (76%). Subsequent reaction of this aldehyde with iodomethyl triphenylphosphonium ylide according to the Stork/Zhao modification⁷ of the Wittig method and oxidative removal of the *p*-methoxybenzyl group (DDQ, CH₂Cl₂:H₂O) 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(PPh₃)₂Cl₂ at rt.^{16–18}



Scheme 3. *Reaction conditions:* (i) BH₃·THF, *N*-Ts-L-valine, CH₂Cl₂, –78°C, 73%; (ii) SEMCl, Hünigs base, CH₂Cl₂, –78°C; (iii) 80% AcOH, 79% for two steps; (iv) (EtO)₂P(O)CH₂CO₂Et, NaH (oil-free), toluene, THF, >95%; (v) Dibal, CH₂Cl₂, –78°C, 76%; (vi) D-(–)-DIPT, *t*-BuOOH, Ti(O*i*Pr)₄, CH₂Cl₂, –30°C, 95%; (vii) Red-Al, THF, –20°C; (viii) *p*-methoxybenzylidene dimethyl acetal, PPTS, CH₂Cl₂, 83% for two steps; (ix) Dibal, CH₂Cl₂, –78°C, 92%; (x) Dess–Martin periodinane, pyridine, *t*-BuOH, CH₂Cl₂, 83%; (xi) I[–]Ph₃P⁺CH₂I, NaHMDS, HMPA, THF, –78°C, 67%; (xii) DDQ, CH₂Cl₂, H₂O, 79%; (xiii) Pd(Ph₃P)₂Cl₂, (Me₃Sn)₂, Li₂CO₃, 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(CH₃CN)₂Cl₂ to give **2** in 76% yield.¹⁹ ¹H 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

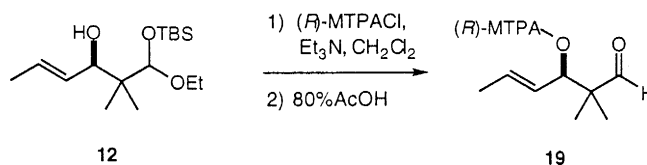
In conclusion, we have constructed the monomeric moiety **2** of the natural product disorazole C₁ (**1**) in a convergent and stereocontrolled fashion. It is hoped that this methodology will provide access to a number of diastereomeric derivatives of **2**, which may then be dimerized and compared to **1** via the reported [α]_D and spectral data for this compound. However, early attempts at double lactonization of **2** (R=H, P=SEM) to provide disorazole C₁ have not been promising. We continue to address this final key step.

Acknowledgements

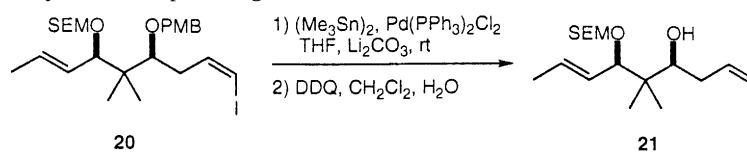
The authors are grateful to the NIH and NSF for financial support and to the American Cancer Society for a postdoctoral fellowship (M.C.H.). We thank Professor R. Jansen (Gesellschaft für Biotechnologische Forschung mbH) for providing spectral data of natural disorazole C₁ for comparison.

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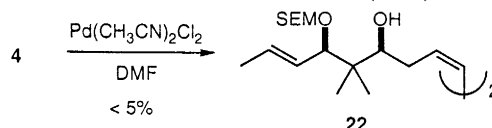
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- We found that conversion of the iodide **20** to the vinyl tin species, followed by removal of the *p*-methoxybenzyl group with DDQ resulted in destannylation, thus providing **21**:



- Elevated reaction temperatures for this transformation resulted in lower reaction yields (ca. 45%). Use of the less toxic hexabutylditin (Bu₃Sn)₂ in this reaction did not provide product.
- The Stille coupling also resulted in the formation of a small amount (<5%) of the homocoupled byproduct **22**:



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