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# Total Synthesis of (−)-Disorazole $C_1$

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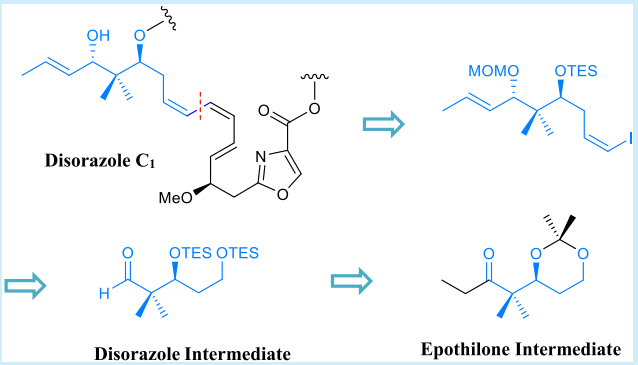
**ABSTRACT:** Disorazoles represent a powerful class of highly potent antitubulin natural products isolated from myxobacteria. Herein, we describe a scalable and robust synthesis of (−)-disorazole $C_1$ with high stereoselectivity, featuring quite simple reaction conditions that can be used to produce large quantities of this remarkable biologically active compound.






The powerful biologically active group of natural products called disorazoles were isolated for the first time by the research groups of G. Höfle and H. Reichenbach in 1994.[1]

They are secondary metabolites from myxobacterium Sorangium cellulosum (So ce12), and they show an up to picomolar biological activity as antitubulin compounds, inhibiting tubulin stabilization combined with high cytotoxicity.[2] If used in personalized medicine these compounds could be powerful payloads for antibody−drug conjugates (ADCs) in targeted cancer therapy.[3]

Besides the striking cytotoxic profile, some members (A and Z) of the disorazole family activate dendritic cells and increase the immune effector T cell activity by affecting the dynamic phosphorylation of ezrin, a key mediator of immune receptor activity.[4] Ezrin is a member of the ezrin/radixin/moesin (ERM) family and is involved in the expression of cell surface proteins. Ezrin regulates B and T cell receptor activation and downstream signaling. Moreover, ezrin-targeting compounds have been shown to block tumor metastasis, a key event in tumor progression.[5] This could lead to new immunotherapeutic approaches with natural products.

To date, more than 29 members of this family of highly potent natural products have been isolated from myxobacteria.[6]

They display a fascinating macrocyclic structure containing very sensitive unsaturated polyene units including epoxides. The structural diversity is high and spans from 24-membered macrocycles (disorazole Z) to the $C_2$-symmetric 30-membered macrocycle of disorazole $C_1$ with the very delicate (Z), (Z), (E)-triene core. In particular, disorazole $C_1$ is of interest for synthetic chemists because its yield in fermentation is rather low (0.3%), but it still shows significant high cytotoxic activity in many mammalian cancer cell lines.[7] The highly compelling biological profile of this structurally intriguing class of natural products has generated a tremendous interest in academia and pharmaceutical companies over the past decade, leading to many scientific articles and 105 active patents.[8]

In this account, we wish to report our own investigations along these lines providing a total synthesis of (−)-disorazole $C_1$ **1**, with a special emphasis on robust reactions with high yield and the potential for scale-up.[9] Up to date, three total syntheses of the title compound have been reported by Wipf et al.,[10] Hoveyda et al.,[11] and Hulme et al.,[12] respectively (Figure 1). In addition, several studies addressing the synthetic challenges to construct the demanding macrocycle have been published.[13] Lastly, an account providing SAR studies with simplified analogs of disorazoles has been published by Kalesse et al.[14] Several other members of the disorazole family (A1 and B1) have been recently synthesized by Nicolaou et al.[15]

Based on the existing knowledge about the published data of disorazoles, we concluded that the choice of protecting groups would be a key issue of the entire synthesis. The molecular scaffold with the highly sensitive triene unit and the sterically demanding 1,3-diol moiety next to the geminal dimethyl unit demands a tricky selection of reagents and conditions.

Assumed on our model studies, the choice of protecting groups also influences the stereochemical outcome in the construction of the 1,3-diol unit. In addition, the overall sensitivity of the 30-membered fully functionalized macrocycle

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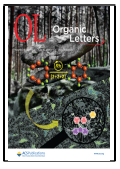


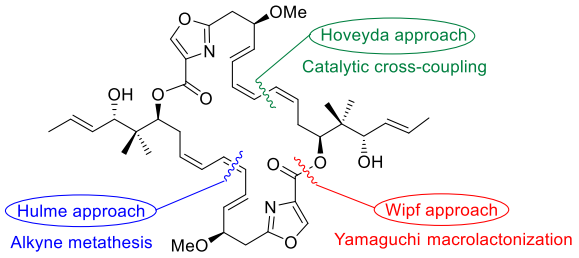
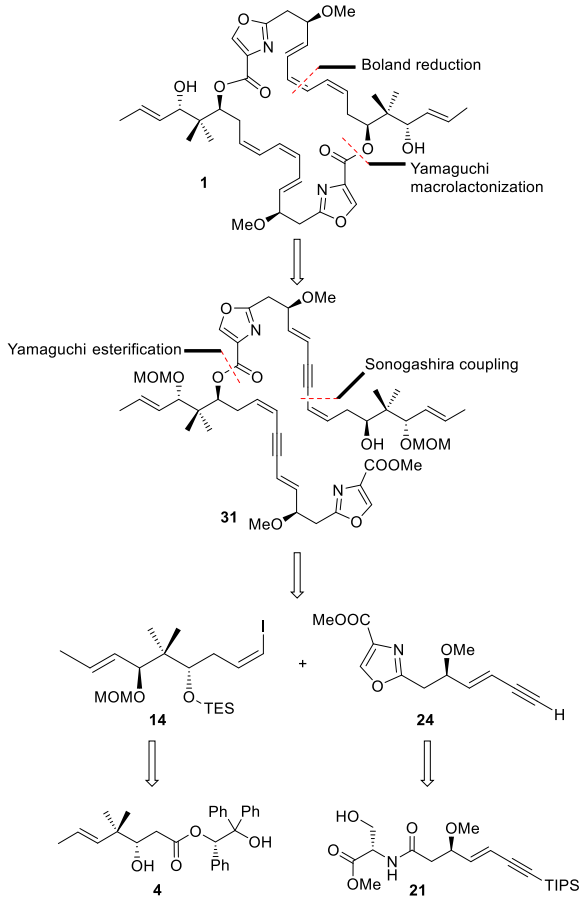



**Figure 1.** Previous strategies for the construction of the macrocycle.

**Scheme 1. Retrosynthetic Approach to (−)-Disorazole $C_1$ 1**

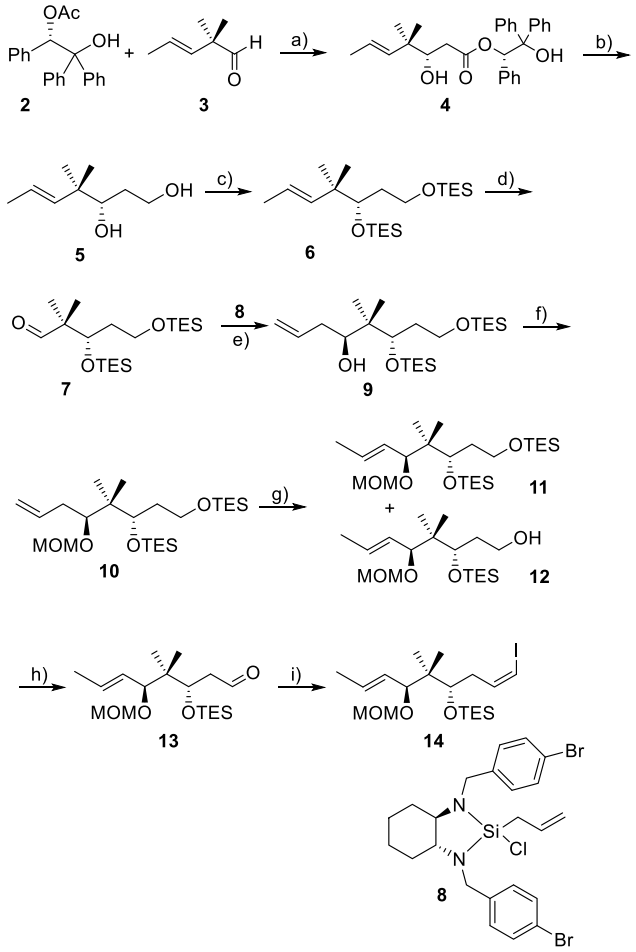



narrows the order of transformations, reagents, and conditions in the endgame of the synthesis.

Aware of all that, we designed the following retrosynthesis depicted in Scheme 1 hoping to synthesize the title compound in an efficient and robust way to obtain a significant amount of material. Reflecting the polyunsaturated scaffold of the target molecule, transition metal-catalyzed reactions will play a major role in the synthesis. Ring closure to construct the 30-membered macrolide Yamaguchi macrolactonization[16] should be the reaction of choice. For the synthesis of the heterocyclic oxazole fragment, we also used powerful methodology based on published data using chiral pool synthesis with (L)-serine and a lipase resolution.[17] The real challenge was the endgame of the synthesis along with the selective hydrogenation of the triple bonds and removal of the MOM protecting groups.

In order to solve the major stereochemical issue, we used a derivative of a key intermediate from our epothilone A synthesis,[18] followed by a Leighton reaction.[19] The synthesis

**Scheme 2. Synthesis of the Lateral Chain[a]**




[a]Reagents and conditions: (a) LDA, THF, −78 °C to 0 °C 77%; (b) $LiAlH_4$, $Et_2O$, reflux, 90%; (c) TESOTf, 2,6-lutidine, DCM, −78 °C to 0 °C, 99%; (d) $O_3$, $PPh_3$, DCM, −78 °C, 67%; (e) (*R*,*R*)-Leighton reagent **8**, $Sc(OTf)_3$, DCM, −15 °C, 85%; (f) MOMCl, DIPEA, DMAP, DCM, reflux, 92%; (g) Grubbs II, MeOH, 60 °C; (h) $(COCl)_2$, DMSO, TEA, DCM, −78 °C, 77% over two steps; (i) $ICH_2PPh_3I$, NaHMDS, DMPU, THF, −78 °C, 67%.

started from aldehyde **3**, which is commercially available or alternatively it can be easily synthesized on a large scale in a straightforward sequence using ethyl isobutyrate condensed with *n*-propinal, followed by Sicapent dehydration and adjustment of the oxidation stage.[18] Afterward, an enantioselective aldol reaction with (*S*)-HYTRA[20] (1,1,2-triphenyl-1,2-ethanediol acetate) **2** following the protocol of our epothilone A synthesis yielded the desired aldol product **4** in 77% yield and >96% de as a crystalline solid. Reductive removal of the HYTRA unit with lithium aluminum hydride accompanied by double silylation with triethylsilyl (TES) triflate and final ozonolysis provided the starting material for the enantioselective allylation. Having studied several options using boron ligands,[21] in our hands the Leighton reagent[19] in the presence of scandium triflate gave the best result generating the (*S*)-allylic alcohol **9** in 85% yield and 84% de. This procedure sets the *anti*-relation of the 1,3-diol moiety of the natural product. Methoxymethyl (MOM) protection with MOM chloride gave the protected diol fragment **10** in high yield. Subsequent isomerization of the double bond using Grubbs II catalyst[22] yielded only the *E*-isomer as a mixture of compounds **11**



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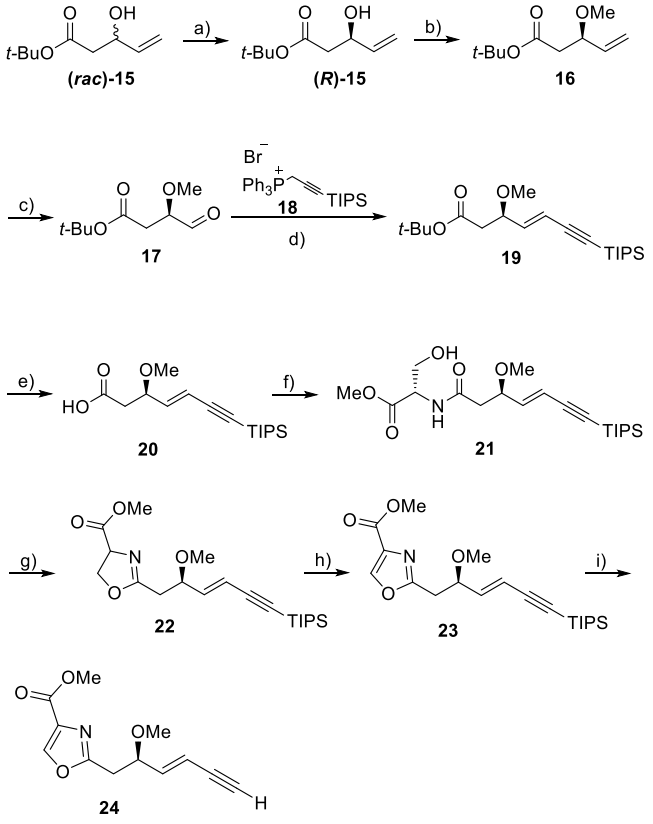
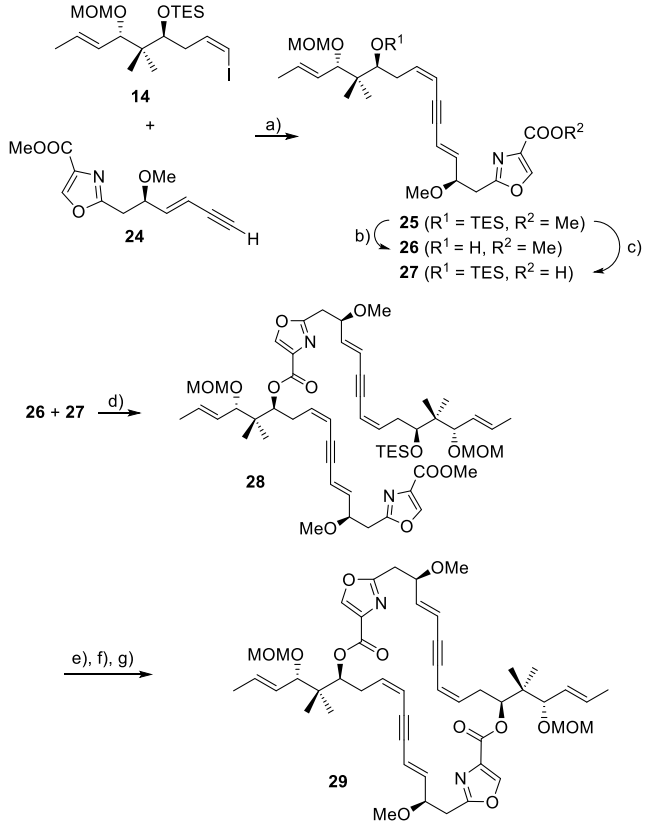
**Scheme 3. Synthesis of the Oxazole Fragment**[a]




[a]Reagents and conditions: (a) amano lipase PS, vinylacetate, MS 4 Å, pentane, 30 °C, 47% (*R*)-**15** and 48% OAc-(*S*)-**15**; (b) proton sponge, $Me_3OBF_4$, DCM, rt, 77%; (c) $O_3$, DCM/MeOH 5:1, $PPh_3$, −78 °C, 89%; (d) **18**, *n*-BuLi, THF, −78 °C to 0 °C, 60%; (e) HCOOH, rt, 99%; (f) serine methylester hydrochloride, TFFH, DIPEA, THF, rt, 90%; (g) DAST, $K_2CO_3$, DCM, −78 °C; (h) DBU, $BrCCl_3$, DCM, 0 °C to rt, 62% from **21**; (i) TBAF, THF, 0 °C to rt, 81%.

**Scheme 4. Construction of the Macrocycle**[a]




[a]Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, TEA, ACN, −10 °C to rt, 85%; (b) CSA, DCM/MeOH 1:1, 0 °C, 95%; (c) 1 M LiOH, THF, rt, 99%; (d) 1. TCBC, TEA; 2. DMAP, THF/toluene, rt, 75%; (e) CSA, DCM/MeOH 1:1, 0 °C; (f) 1 M LiOH, THF, rt; (g) 1. TCBC, TEA; 2. DMAP, THF/toluene, rt, 70% from **28**.

(15%) and **12** (80%), which were directly oxidized using a Swern protocol to yield aldehyde **13** in 77% over two steps. A modified Wittig reaction using iodomethyl triphenylphosphonium iodide[13,15a] in the presence of sodium disilazane at −78 °C gave selectively the Z iodide **14** in 67% as shown in Scheme 2.

The oxazole fragment was synthesized using known methods starting with a lipase resolution, yielding the (*R*)-enantiomer of **15** in 47%.[17] Methylation was achieved with Meerwein salt,[11] followed by ozonolysis and subsequent Wittig reaction with TIPS-protected propargyl triphenylphosphonium bromide **18** to obtain the desired *E* ene-yne-fragment **19** in 60% yield, along with 22% of the *Z* isomer; the two isomers could be easily separated by flash chromatography. Quantitative hydrolysis of the *t*-butyl ester with formic acid and later condensation with serine methyl ester provided amide **21** in 90% yield.

Cyclization in the presence of diethylaminosulfur trifluoride (DAST)[23] followed by elimination with $BrCCl_3$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[24] gave the required oxazole **23** in 62% yield over two steps. Consequent desilylation with tetra-*n*-butylammonium fluoride (TBAF) offered compound **24** in 81% yield as depicted in Scheme 3.

With all fragments in hand the final connections could be envisioned using a Sonogashira reaction to couple fragments **14** and **24** to obtain major building block **25** in high chemical yield. With compound **25** we could make use of the C2-symmetry of the target structure synthesizing compounds **26** utilizing a selective CSA-promoted desilylation and also compound **27** via saponification with LiOH all from the same starting material. Yamaguchi esterification between acid **27** and alcohol **26** gave compound **28** in 75% yield. An additional CSA-promoted desilylation, followed by another smooth hydrolysis of the methyl ester in the presence of lithium hydroxide and final macrolactonization using Yamaguchi's conditions, resulted in the formation of the symmetric macrocycle **29** in 70% yield over three steps, as depicted in Scheme 4.

At this point, the critical phase of the synthesis started because the polyunsaturated macrocycle **29** had to be treated with precaution and the final sequence of events had to be decided carefully. Many attempts to cleave the MOM group completely failed and resulted only in decomposition products.[25] In addition, partial hydrogenation of compound **29** also did not work in a satisfactory way using classical Lindlar conditions.[10,12,26] Finally, we found that reduction under Boland[27] conditions in the presence of Zn(Ag/Cu) yielded the MOM-protected natural product **30** in 65% yield.

As we expected, considering the documented problems in deprotecting these sensitive compounds, the last step proved to be one of the most difficult of the overall synthesis. After having carefully tested more than 20 published reagents for the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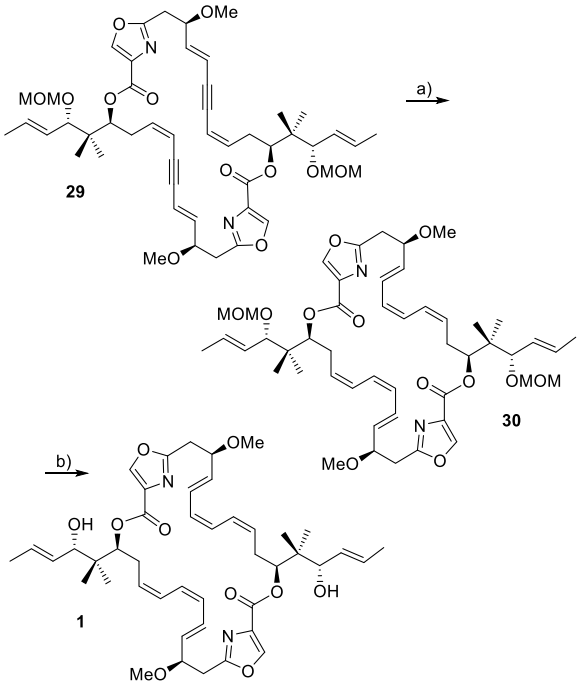
**Scheme 5. Total Synthesis of (−)-Disorazole $C_1$ 1**[a]




[a]Reagents and conditions: (a) Zn (Ag/Cu), MeOH/$H_2O$ 1:1, 50 °C, 65%; (b) HBr, ACN/$H_2O$, 0 °C, 56%.

MOM-deprotection of quite complicated molecules, many reactions with model systems, and using up more than 250 mg of compound **30**, these attempts either led to no reaction at all or fast decomposition under various conditions.[26] Finally, a drop of hydrogen bromide in acetonitrile at 0 °C provided (−)-disorazole $C_1$ **1** in 56% yield after stirring for 1 h, as demonstrated in Scheme 5.

The endgame of the synthesis taught us a nice lesson: that the sequence of the final events and the use of the appropriate reagents when treating these very delicate and complex structures are the keys to success. In particular, the choice of protecting groups at an early stage of the synthesis has a great effect on the outcome of the Leighton reaction and finally offers the simplest removal of the MOM protecting groups with HBr, after an advantageous metal-induced partial Boland reduction. For instance, replacing the double TES with a double acetate in compound **6** (Scheme 2), we observed a slight improvement in the stereoselectivity (86% instead of 84%), but the yield was significantly lower (60%); whereas with the use of an acetonide, the reaction completely failed. On the contrary, the TBS (*tert*-butyldimethylsilyl) group gave good results, with 90% yield and 83% stereoselectivity, but the removal of the secondary TBS was much more complicated than that of TES.

In conclusion, we have demonstrated that (−)-disorazole $C_1$ **1** can be synthesized in 17 steps and with an overall yield of 2.9% for the longest linear sequence. This offers the possibility to generate substantial amounts (gram-scale) of this highly active natural product in order to study its fascinating biology. In addition, it provides a broad entry to construct a large number of analogs.[28] The synthesis relies on robust chemistry and simple protocols and has the potential for real scale-up.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01123.

Experimental procedures and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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