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Total Syntheses of Disorazoles A_1 and B_1 and Full Structural Elucidation of Disorazole B_1

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Supporting Information

ABSTRACT: Described herein are the first total syntheses of naturally occurring antitumor agents disorazoles A_1 and B_1 and the full structural assignment of the latter. The syntheses were achieved through convergent strategies employing enantioselective constructions of the required building blocks, including a novel Sharpless epoxidation/enzymatic kinetic resolution of stannane-containing substrates that led selectively to both enantiomeric forms of an epoxy vinyl stannane, and a series of coupling reactions, including a Wittig reaction, a Suzuki coupling, a Stille coupling, a Yamaguchi esterification and a Yamaguchi macrolactonization.

The disorazoles[1] are a distinguished class of tubulin binding antitumor agents due to their unique mode of action and high potencies against a broad range of cancer cell lines.[2] Although too cytotoxic to be used as anticancer drugs, these natural products may become powerful payloads for antibody–drug conjugates (ADCs),[3] a hotly pursued paradigm for targeted personalized cancer therapies. Elegant total syntheses[4] of disorazole C_1[1] and related synthetic studies[5] have been reported. From the members of this family of compounds, disorazole A_1 (**1**, Figure 1) stands as the flagship, not only because it is the most studied, but also due to its single digit picomolar potencies and synthetically challenging structure.[1,6] Indeed, a total synthesis of disorazole A_1 has not been reported, despite several studies directed toward this goal.[5c,7] Disorazole B_1,[1] whose structure has only been partially assigned as **2** (C_2 symmetric) or **3** (6,8,23,25-tetra-*epi*-disorazole B_1, Figure 1) presents another challenging calling to both structural elucidation and total synthesis. In this Communication, we report: (a) total synthesis of disorazole A_1 (**1**); (b) total synthesis of disorazole B_1 (**2**) and 6,8,23,25-tetra-*epi*-disorazole B_1 (**3**); and (c) full assignment of disorazole B_1 as structure **2**.

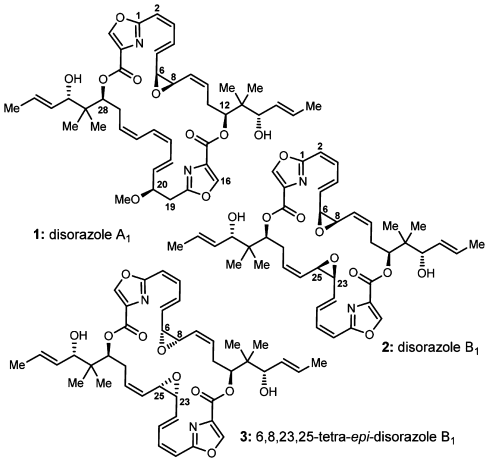

Figure 1. Structures of disorazole A_1 (**1**) and B_1 (**2**) and 6,8,23,25-tetra-*epi*-disorazole B_1 (**3**).

Figure 2 summarizes the retrosynthetic analysis of disorazoles A_1 (**1**) and B_1 (**2**). Thus, disorazole A_1 was traced to key building blocks **4**–**7** and (−)-**8** through the strategic bond disconnections indicated on structure **1** (Wittig reaction, Stille coupling, Suzuki coupling, Yamaguchi esterification and Yamaguchi macrolactonization). By virtue of its symmetrical nature, disorazole B_1 (**2**) required only building blocks **5**, **7**[8] and (−)-**8**, revealed through a simpler disconnection pattern requiring two identical Wittig and Stille couplings, a Yamaguchi esterification, and a Yamaguchi macrolactonization as shown in structure **2** (Figure 2).

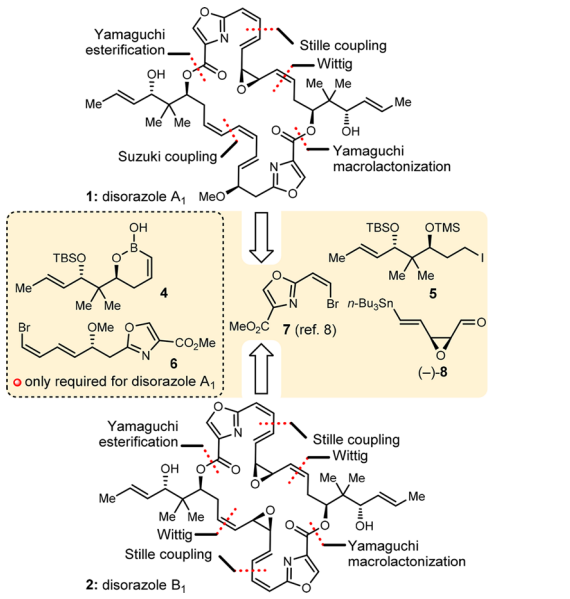

Figure 2. Retrosynthetic analyses of disorazoles A_1 (**1**) and B_1 (**2**).

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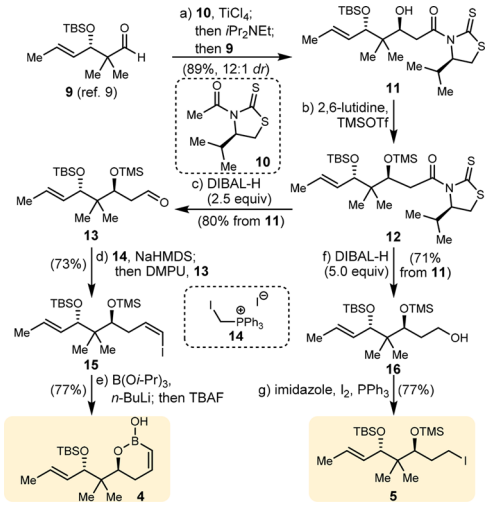
Scheme 1 depicts the asymmetric synthesis of intermediates **4** and **5** starting with building blocks **9**[9] and **10**. Thus, reaction of **9**

Scheme 1. Synthesis of Vinyl Boronic Acid 4 and Iodide 5[a]

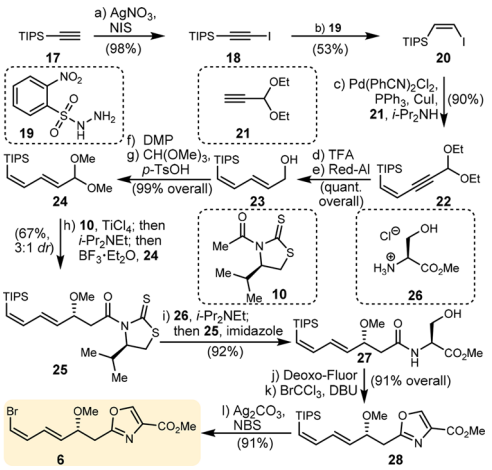


[a]Reagents and conditions: (a) **10** (1.0 equiv), $TiCl_4$ (1.5 equiv), CH_2Cl_2, 0 °C, 5 min; then −78 °C, *i*-Pr_2NEt (1.1 equiv), 30 min; then −50 °C, 2 h; then −78 °C, **9**[9] (1.0 equiv), 1 h, 89%, 12:1 *dr*; (b) 2,6-lutidine (3.0 equiv), TMSOTf (2.0 equiv), CH_2Cl_2, 0 °C, 25 min; (c) DIBAL-H (2.5 equiv), Et_2O, −78 °C, 2 h, 80% from **11**; (d) **14** (1.5 equiv), NaHMDS (1.5 equiv), THF, 0 to 23 °C, 5 min; then −78 °C, DMPU (7.5 equiv), **13** (1.0 equiv), 1 h; then 23 °C, 30 min, 73%; (e) **15** (1.0 equiv), $B(Oi\text{-}Pr)_3$ (1.1 equiv), *n*-BuLi (1.15 equiv), −78 °C, 30 min; then TBAF (1.4 equiv), 23 °C, 48 h, 77%; (f) DIBAL-H (5.0 equiv), Et_2O, −78 to 23 °C, 2 h, 71% from **11**; (g) imidazole (1.5 equiv), I_2 (1.35 equiv), PPh_3 (1.2 equiv), 23 °C, 1 h, 77%. TMSOTf = trimethylsilyl trifluoromethanesulfonate, DIBAL-H = diisobutylaluminum hydride, NaHMDS = sodium bis(trimethylsilyl)amide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TBAF = tetra-*n*-butylammonium fluoride.

with Nagao auxiliary **10**[10] ($TiCl_4$; then *i*-Pr_2NEt) led stereoselectively to alcohol **11** (89% yield, ca. 12:1 *dr*). Protection of the latter (TMSOTf, 2,6-lut.) gave TMS ether **12**, whose reduction with 2.5 equiv of DIBAL-H afforded aldehyde **13** in 80% yield from **11**. Reaction of **13** with the ylide generated from iodophosphonium iodide **14** (NaHMDS; then DMPU) gave selectively (*Z*)-vinyl iodide **15** in 73% yield. Conversion of **15** to the desired boronic acid (**4**) required sequential treatment with *n*-BuLi, $B(Oi\text{-}Pr)_3$, and TBAF (77% yield). Iodide **5** was obtained from common intermediate **12** (Scheme 1) through a two-step sequence involving reduction of the latter to the corresponding primary alcohol (5.0 equiv of DIBAL-H, 71% yield from **11**) followed by an Appel reaction[11] [I_2, PPh_3, imidazole (77% yield)].

Intermediate **6** was synthesized asymmetrically from TIPS-acetylene (**17**) (Scheme 2). Thus, **17** was converted to iodide **18** (NIS, $AgNO_3$, 98% yield) and then to (*Z*)-vinyl iodide **20** through the action of hydrazine **19** (53% yield). Coupling of **20** with acetylene **21** [$Pd(PhCN)_2Cl_2$, PPh_3, CuI, *i*-Pr_2NH, 90% yield] furnished enyne diethoxy ketal **22**, whose sequential treatment with TFA and Red-Al led to hydroxy TIPS diene **23** in quantitative yield. Oxidation (DMP) of the latter, followed by exposure of the resulting aldehyde to $CH(OMe)_3$ and *p*-TsOH (cat.) furnished dimethyl acetal **24** in 99% overall yield. Sequential treatment of **24** with Nagao auxiliary **10**[10] and $TiCl_4$, *i*-Pr_2NEt and $BF_3{\cdot}Et_2O$ afforded intermediate **25**[12]

Scheme 2. Synthesis of Vinyl Bromide 6[a]



[a]Reagents and conditions: (a) $AgNO_3$ (0.1 equiv), NIS (1.2 equiv), acetone, 23 °C, 10 min, 98%; (b) **19** (0.9 equiv), 5:2 THF:*i*-PrOH, 23 °C, 16 h, 53%; (c) $Pd(PhCN)_2Cl_2$ (0.05 equiv), PPh_3 (0.1 equiv), CuI (0.07 equiv), **21** (1.5 equiv), *i*-Pr_2NH, 23 °C, 1 h, 90%; (d) 50% aq. TFA (10 equiv), 23 °C, 30 min; (e) Red-Al (2.05 equiv), 0 to 23 °C, 0.5 h, Et_2O, quant. from **22**; (f) DMP (2.0 equiv), CH_2Cl_2, 0 to 23 °C, 2 h; (g) $CH(OMe)_3$ (1.0 equiv), *p*-TsOH (0.01 equiv), CH_2Cl_2, 23 °C, 1 h, 99% from **23**; (h) **10** (1.0 equiv), $TiCl_4$ (1.1 equiv), CH_2Cl_2, 0 °C, 5 min; then −78 °C, *i*-Pr_2NEt (1.1 equiv), 30 min; then −50 °C, 2 h; then −78 °C, $BF_3{\cdot}Et_2O$ (1.0 equiv), **24** (1.0 equiv), 1 h, 67%, ca. 3:1 *dr*; (i) **26** (1.5 equiv), *i*-Pr_2NEt (2.0 equiv), THF, 23 °C, 10 min; then **25** (1.0 equiv), imidazole (3.0 equiv), 23 °C, 16 h, 92%; (j) Deoxo-Fluor (1.2 equiv), CH_2Cl_2, −20 °C, 30 min; (k) $BrCCl_3$ (4.0 equiv), DBU (4.0 equiv), CH_2Cl_2, 0 to 23 °C, 16 h, 91% from **27**; (l) Ag_2CO_3 (1.0 equiv), NBS (1.25 equiv), HFIP, 0 °C, 2 h, 91%. NBSH = 2-nitrobenzenesulfonylhydrazide, Red-Al = sodium bis(2-methoxyethoxy)aluminum, *p*-TsOH = *p*-toluenesulfonic acid, HFIP = hexafluoro-2-propanol.

(chromatographically separated), whose reaction with ammonium salt **26** in the presence of *i*-Pr_2NEt and imidazole afforded hydroxy amide **27** in 92% yield.[13] Conversion of **27** to oxazole intermediate **28** was achieved through sequential exposure of the latter to Deoxo-Fluor and $BrCCl_3$/DBU (91% overall yield).[14] Finally, the targeted intermediate **6** was generated from **28** through the action of NBS in the presence of Ag_2CO_3 (91% yield).

The asymmetric synthesis of advanced intermediate **37** started from propargyl alcohol (**29**) and proceeded as shown in Scheme 3. Thus, AIBN facilitated addition of *n*-Bu_3SnH to **29**, followed by buffered DMP oxidation of the resulting alcohol, led to the formation of vinyl tin aldehyde **30** in 42% overall yield. Still–Gennari reaction of the latter with the anion generated from phosphonate ester **31** (KHMDS, 18-crown-6) followed by DIBAL-H reduction of the resulting methyl ester furnished alcohol **32** in 85% overall yield. Sharpless asymmetric epoxidation of **32** [*t*-BuOOH, $Ti(Oi\text{-}Pr)_4$, (−)-DET] gave epoxide **33** (61% yield), albeit in low enantiomeric excess (43% *ee*). This result was remedied through kinetic resolution of **33**. Thus, acetylation of hydroxy epoxide **33** with vinyl acetate in the presence of Amano lipase PS[15] furnished enantiomerically enriched hydroxy epoxide (+)-**33** (71% yield, >95% *ee*) and enantiomerically enriched acetoxy epoxide (−)-**34** (25% yield, >95% *ee*). The absolute configuration assignments of (+)-**33** and (−)-**34** were made tentatively based on the use of (−)-DET that was expected to afford (+)-**33** as the major enantiomer. These

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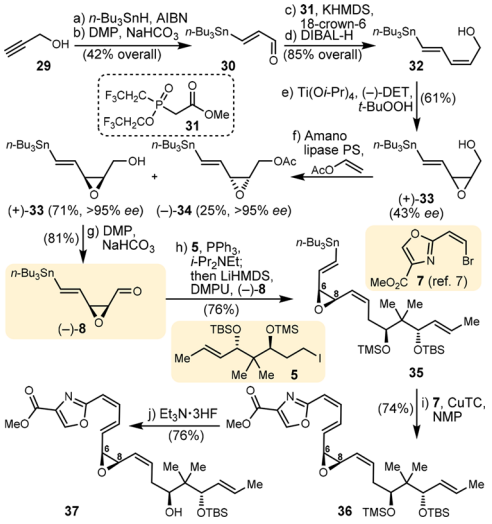
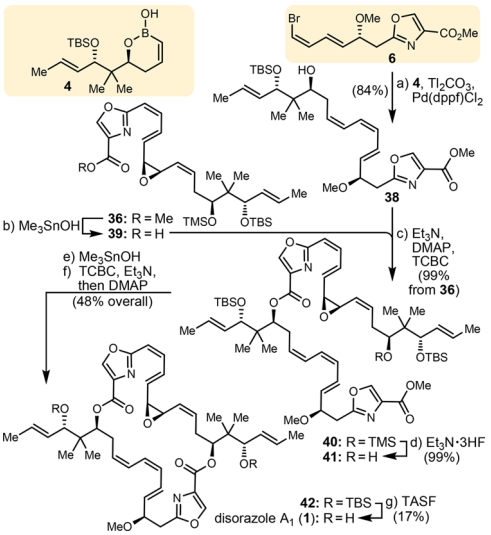
Scheme 3. Enantioselective Synthesis of Epoxide Fragment 37[a]



[a]Reagents and conditions: (a) *n*-Bu_3SnH (1.3 equiv), AIBN (0.08 equiv), 80 °C, 2.5 h, 49%; (b) DMP (1.2 equiv), $NaHCO_3$ (1.2 equiv), CH_2Cl_2, 23 °C, 1 h, 86%; (c) 18-crown-6 (4.0 equiv), **31** (1.3 equiv), KHMDS (1.2 equiv), THF, −78 °C, 0.5 h, 92%; (d) DIBAL-H (2.5 equiv), Et_2O, −78 °C, 1 h, 92%; (e) Ti(O*i*-Pr)$_4$ (1.0 equiv), (−)-DET (1.4 equiv), *t*-BuOOH (3.0 equiv), CH_2Cl_2, −20 °C, 16 h, 61%, 43% *ee*; (f) Amano lipase PS from *Burkholderia cepacia* (100%, *w*/*w*), vinyl acetate (2.0 equiv), CH_2Cl_2, 23 °C, 48 h, 71%, >95% *ee* for (+)-**33**, 25%, >95% *ee* for (−)-**34**; (g) DMP (1.3 equiv), $NaHCO_3$ (1.3 equiv), CH_2Cl_2, 23 °C, 1 h, 81%; (h) **5** (1.05 equiv), PPh_3 (1.75 equiv), *i*-Pr_2NEt (7.0 equiv), 90 °C, 16 h; then −78 °C, LiHMDS (1.05 equiv), DMPU (0.6 equiv), (−)-**8** (1.0 equiv), THF, 15 min; then 23 °C, 1 h, 76%; (i) **7** (1.0 equiv), CuTC (1.5 equiv), NMP, 23 °C, 1 h, 74%; (j) Et_3N·3HF (3.0 equiv), THF, 23 °C, 1 h, 76%. AIBN = 2,2′-azobis(2-methylpropionitrile), DMP = Dess−Martin periodinane, KHMDS = potassium bis(trimethylsilyl)amide, LiHMDS = lithium bis(trimethylsilyl)amide, CuTC = copper(I) thiophene-2-carboxylate.

Scheme 4. Total Synthesis of Disorazole A_1 (1)[a]



[a]Reagents and conditions: (a) **4** (1.4 equiv), Tl_2CO_3 (5.0 equiv), $Pd(dppf)Cl_2$ (10 mol %), THF:H_2O 3:1, 23 °C, 16 h, 84%; (b) Me_3SnOH (10 equiv), DCE, 80 °C, 3 h; (c) **39** (2.0 equiv), **38** (1.0 equiv), Et_3N (6.0 equiv), DMAP (8.0 equiv), TCBC (3.0 equiv), toluene, 23 °C, 1.5 h, 99%; (d) Et_3N·3HF (3.0 equiv), THF, 23 °C, 1 h, 99%; (e) Me_3SnOH (10 equiv), DCE, 80 °C, 1.5 h; (f) TCBC (10 equiv), Et_3N (11 equiv), toluene, 23 °C, 1 h; then DMAP (4.0 equiv), 23 to 40 °C, 29 h, 48% from **41**; (g) TASF (12 equiv), H_2O, DMF, 41 °C, 72 h, 17%. DCE = dichloroethane, TCBC = 2,4,6-trichlorobenzoyl chloride.

assignments were confirmed by successful synthesis of disorazole A_1 (**1**), whose absolute configuration was known.[16] This resolution presented us with the opportunity to synthesize enantioselectively disorazole A_1 (**1**) and the two diastereoisomers (**2** and **3**, Figure 1) of disorazole B_1 (whose relative configuration and absolute structure were not known).[1,16] Based on biosynthetic considerations, we reasoned the likelihood of both disorazoles featuring the same configuration at their epoxide sites was higher than being antipodal. We, therefore, opted to pursue first the synthesis of disorazole B_1 (**2**), rather than its diastereoisomer (**3**). To this end, hydroxy epoxide (+)-**33** was oxidized to aldehyde (−)-**8** (DMP, 81% yield), and then reacted with the ylide generated from iodide **5** (PPh_3, *i*-Pr_2NEt; LiHMDS, DMPU) to afford selectively (*Z*)-olefin vinyl tin triene epoxide **35** in 76% yield. Coupling of vinyl stannane **35** with bromide **7**[8] under palladium-free conditions (thus evading potential side reactions caused by the multiple olefinic bonds present in the two substrates)[17] then led to key intermediate **36** (74% yield), whose desilylation (Et_3N·3HF) furnished key fragment **37** (76% yield).

Scheme 4 summarizes the completion of the total synthesis of disorazole A_1. Thus, Suzuki coupling of boronic acid **4** with vinyl bromide **6** [$Pd(dppf)Cl_2$ cat., Tl_2CO_3] furnished conjugated hydroxy triene **38** (84% yield), which was reacted with carboxylic acid **39** (obtained from methyl ester **36** through the action of Me_3SnOH,[18] Scheme 4) under Yamaguchi conditions to afford diester **40** in 99% overall yield from **38**. The more labile TMS silyl ether was cleaved from **40** (Et_3N·3HF) leading to hydroxy methyl ester **41** (99% yield). The methyl ester of the latter was selectively hydrolyzed using Me_3SnOH,[18] and the resulting hydroxy acid was cyclized under Yamaguchi conditions to afford macrolactone **42** in 48% overall yield. Finally, the TBS groups were cleaved from **42** by treatment with TASF[19] (17% yield), furnishing disorazole A_1 (**1**). Synthetic disorazole A_1 exhibited identical ^1H- and ^{13}C NMR spectroscopic data and comparable specific rotation {$[\alpha]_D^{25} = -85$ (*c* = 0.08, MeOH); Lit.[1] $[\alpha]_D^{22} = -77$ (*c* = 0.75, MeOH)} with the natural product. Further improvements in this challenging and rather puzzling step are in progress.

Disorazole B_1 (**2**) was synthesized as summarized in Scheme 5. Thus, esterification of hydroxy compound **37** (see Scheme 3) with carboxylic acid **39** (see Scheme 4) under Yamaguchi conditions led to ester **43** in 98% yield (based on **36**). Selective desilylation of the latter with Et_3N·3HF (−TMS group) furnished hydroxy methyl ester **44**, whose exposure to Me_3SnOH[18] afforded the corresponding hydroxy acid. Yamaguchi macrolactonization of the so-obtained crude seco acid led to precursor **45** (48% overall yield), from which disorazole B_1 (**2**) was liberated through TASF-mediated desilylation (64% yield). Synthetic disorazole B_1 exhibited identical ^1H- and ^{13}C NMR spectral data and comparable specific rotation value {$[\alpha]_D^{25} = -59$ (*c* = 0.61, MeOH:CH_2Cl_2 1:1, *v*/*v*); Lit.[1] $[\alpha]_D^{22} = -65$[20] (*c* = 0.5, MeOH:CH_2Cl_2 1:1, *v*/*v*)} to those of the natural product.

Starting with acetoxy epoxide (−)-**34** (Scheme 3) and following a similar sequence, we synthesized disorazole B_1 diastereoisomer **3**, whose spectral data were in agreement with

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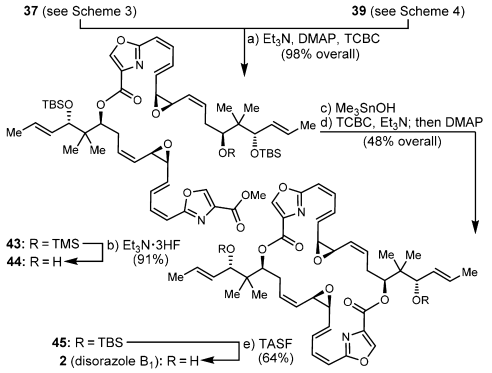
Scheme 5. Total Synthesis of Disorazole B_1 (2)[a]



[a]Reagents and conditions: (a) **37** (1.0 equiv), **39** (2.0 equiv), Et_3N (6.0 equiv), DMAP (8.0 equiv), TCBC (3.0 equiv), toluene, 23 °C, 1 h, 98% (for 2 steps); (b) $Et_3N{\cdot}3HF$ (3.0 equiv), THF, 23 °C, 1 h, 91%; (c) Me_3SnOH (10 equiv), DCE, 80 °C, 1.5 h; (d) TCBC (10 equiv), Et_3N (11 equiv), toluene, 23 °C, 1 h; then DMAP (4.0 equiv), 23 to 40 °C, 29 h, 48% (for 2 steps); (e) TASF (11.5 equiv), H_2O, DMF, 40 to 45 °C, 72 h, 64%.

its structure but differed from those of disorazole B_1 (**2**) (see Supporting Information).

Representing the first total syntheses of disorazoles A_1 (**1**) and B_1 (**2**), and revealing the full structural assignment of disorazole B_1, the described chemistry could lead to wide scope explorations of structure–activity relationships (SARs) through analogue design, synthesis and biological evaluation within the disorazole family of compounds, from which highly potent cytotoxic agents may emerge as potential payloads for antibody–drug conjugates (ADCs).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09843.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) It should be noted the sign for the specific rotation was inadvertently reported erroneously as positive in the original isolation paper (ref 1). We are grateful to Dr. Rolf Jansen for this clarification and for providing us with a scan of the lab book entry of the initial isolation indicating the true sign for the specific rotation as negative.

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