Toward the Total Synthesis of Disorazole A₁: Asymmetric Synthesis of the Masked Northern Half

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Dedicated to Prof. Wolfgang Steglich on the occasion of his 70th birthday.

Abstract: The stereoselective synthesis of the masked northern half of the antimitotic natural product disorazole A₁ is described involving as key step a Z-selective Wittig olefination of a C1–C11 epoxy aldehyde with a C12–C19 phosphonium iodide.

Key words: total synthesis, cell cycle modulation, polyketides, oxazoles, Wittig reactions

The disorazoles are a family of 29 complex macrodiolides isolated in 1994 from the fermentation broth of the gliding bacterium Sorangium cellulosum.¹ Disorazole A₁, by far the major component of the crude extraction residue, causes beyond its antifungal activity, decay of microtubules in subnanomolar concentration, initiates cell cycle arrest in G2/M phase and competes in vitro with vinblastin for the tubulin binding site.² Structurally, the macrocycle forming hydroxy acids consist of an unsaturated polyketide chain with an amino acid terminus masked as an oxazole. This ensemble may have its biosynthetic origin in the joint action of a polyketide synthase (PKS) and a nonribosomal peptide synthetase (NRPS).³ In view of its interesting biological profile and its challenging structural features we have embarked on a program toward the total synthesis of disorazole A₁.

Our retrosynthetic disconnections of disorazole A₁ are outlined in Scheme 1. The C⁷–C₁₂ triene and C₅–C₈ diene of disorazole A₁ were expected to be prone to light or heat-induced isomerization. Therefore, we decided to mask these sensitive functionalities by installing triple bonds in place of Z-olefins.⁴ Retrosynthetic cleavage of the dilactone provides the masked southern half ¹ and northern half ². Our stereoselective synthesis of the

![Scheme 1](image-url)
masked southern half 1 has been reported recently.\(^5\) The masked northern half was thought to be assembled by a Z-selective Wittig olefination of epoxy aldehyde 3 with phosphonium iodide 4. A Sonogashira coupling between oxazole alkyne 5 and E-configured vinyl iodide 6 was initially envisaged as a key step for the synthesis of the C1–C11 fragment 3.

The synthesis of the oxazole alkyne 5 commenced with the transformation of trans-cinnamamide (7)\(^6\) to the 2,4-disubstituted oxazole ester 9 by reaction with 4-bromoethyl pyruvate (8)\(^7\) using Panek's modification of the Hantzsch protocol (Scheme 2).\(^8\) Oxidative cleavage of the double bond was initially achieved in two steps by Sharpless dihydroxylation and subsequent glycol cleavage with Pb(OAc)\(_4\) in 77% yield. By applying the Sharpless dihydroxylation protocol instead of trimethylamine oxide/OsO\(_4\) oxidation, the necessary amount of toxic OsO\(_4\) was reduced from 10 mol% to 1 mol%.\(^9\) Ozonolysis of 9 followed by workup with Ph\(_3\)P gave the oxazole aldehyde 11 in 45% yield.

[Diagram showing the synthesis of oxazole alkyne 5]

Gratifyingly, this one-step oxidative cleavage of 9 was optimized to 68% yield by using NaIO\(_4\) on silica gel in the presence of a catalytic amount of RuCl\(_3\).\(^8\) Homologation to the oxazole alkyne was first pursued under Corey–Fuchs conditions\(^11\) via dibromo olefin 12. Unfortunately, treatment of 12 with n-butyllithium produced the desired alkyne 5 in only 30% yield. The direct conversion of aldehyde 11 into alkyne 5 was investigated using C3-transfer reagents A–C. Commercially available TMS-diazo-methane A\(^12\) produced the oxazole alkyne 5 in 30% yield, whereas with the Gilbert–Seyferth reagent B none of the desired alkyne 5 was formed.\(^13\) Instead, oxazole alkyne 5 was formed in 50% yield under very mild conditions using the Ohira–Bestmann diazophosphono ester C.\(^14\)

E-Configured vinyl iodide ent-6\(^15\) was synthesized from epoxy alcohol\(^16\) in three steps (Scheme 3). Our synthetic plan required next the Sonogashira coupling of vinyl iodide ent-6 with oxazole alkyne 5. Even after extensive optimization efforts involving variations of catalyst, solvent, base, temperature, concentration and order of addition, enyne 14 was isolated at best in discouraging 15% yield.

[Diagram showing the synthesis of oxazole alkyne 5 and its coupling with oxazole alkyne ent-6]

To circumvent the low yielding alknyation Sonogashira coupling sequence, we revised our synthetic strategy by applying a Stille coupling and postponing the introduction of the sensitive C9–C10 epoxide to a later stage of the synthesis (Scheme 4).

[Diagram showing the revised synthetic strategy]

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Starting from ethyl propiolate, in situ formation of Z-vinyl bromide and trapping under Sonogashira conditions with TMS-acetylene led to a TMS-protected enyne ester, which was reduced and deprotected to give allylic alcohol 16.

After E-selective stannylation, diene 17 was coupled with oxazole dibromolefin 12 giving rise to bromotriene 18 of inconsequential geometry in excellent 86% yield. TBDMS-deprotection and dehydrobromination was achieved in one-step using an excess of TBAF. The synthesis of epoxy aldehyde 3 was completed by Sharpless epoxidation (86% ee) and oxidation with PhI(OAc)2/TEMPO.

The C12–C19 phosphonium iodide 4 was prepared from the bisprotected triol 20, which was synthesized from propane-1,3-diol in seven steps as reported in our synthesis of the masked southern half of disorazole A1 (Scheme 5). TIPS-protection of the C16 hydroxy group, PMB-cleavage and transformation of the primary alcohol to the iodide 21 proceeded in 88% overall yield. Treatment of iodide 21 with triphenylphosphine under standard conditions (MeCN, reflux) afforded the phosphonium iodide 4 in less than 50% yield accompanied by significant decomposition of starting material. Similar results were obtained using solvent-free conditions (Ph3 P, neat, 85 °C). In contrast, by adding excess Hünig's base the phosphonium iodide was formed in 83% isolated yield.

By applying the optimized conditions to the Wittig olefination of oxazole epoxy aldehyde 3, the masked northern half of disorazole was formed in 43% yield as a 5:1 Z/E mixture (Scheme 5). The decrease in yield compared to Wittig olefinations of model aldehyde 22 is most likely due to the presence of the oxazole. The hydrogen atom of 2,4-disubstituted oxazoles is known to be sufficiently acidic to be abstracted by common lithium bases. Nuclideophilic addition reactions of the so formed lithiated oxazoles could possibly involve the C11 aldehyde, the C9–C10 epoxide or even the C1 ester functionality leading to diverse side products.
We have applied our strategy for the synthesis of two masked non-natural northern halves of disorazole A₁ with inverted configurations at C9/C10 (Figure 1, 24) and C16 (25), respectively. The modularity of our synthesis plan thus proved to be applicable for future SAR studies.

With routes for both masked halves of disorazole A₁ in hand, our further synthetic efforts are focused on developing cyclization strategies targeting disorazole A₁ and its C₅-symmetric homodimers disorazole B₁ and disorazole C₁.

IR spectra were recorded on a Perkin-Elmer 1710 IR spectrometer. 1H NMR and 13C NMR spectra were recorded on Bruker AVS 400 and Bruker AVM 500 spectrometers in CDCl₃ or acetone-d₆ with tetramethylsilane as internal standard. 1H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (0 ppm) as internal standard. Coupling constants (J) are reported in Hertz (Hz). 13C NMR spectra were fully decoupled with signal assignments are based on DEPT and – if necessary – additional 1 H–1 H-COSY and HMQC experiments. The numbering of carbon and hydrogen signals refers to the numbering of the 

1H NMR (400 MHz, CDCl₃/TMS): δ = 8.25 (s, 1 H, H-3), 7.54 (s, 1 H, H-5), 4.39 (q, J = 7.3 Hz, 2 H, OCH₂CH₃), 1.37 (t, J = 7.3 Hz, 3 H, OCH₂CH₃).

13C NMR (100 MHz, CDCl₃/TMS): δ = 160.8 (C q , C-1), 158.4 (C q , C-4), 143.5 (CH, C-3), 134.6 (C q , C-2), 123.4 (CH, C-5), 99.5 (C q , C-6), 61.5 (OCH₂CH₃), 143.0 (OCH₃CH₂).

MS-MAT (80 °C): m/z calcd for C₈H₇NO₃: 165.0427; found: 165.0426; 297 (100), 295 (44), 280 (14), 215 (23), 211 (25).

HRMS: m/z calcd for C₈H₇Br₂NO₃: 297 (100), 295 (44), 280 (14), 215 (23), 211 (25).

tert-Butyldimethyl(5-tritylstannanylpenta-2,4-dienyloxy)silane (17)

To a suspension of CuCN (104 mg, 1.16 mmol, 1.16 equiv) in THF (7 mL) was added n-BuLi (1.6 M in hexane, 1.4 mL, 2.3 mmol, 2.3 equiv) dropwise at –78 °C. The mixture was allowed to reach –30 °C to become homogeneous and was then cooled to –78 °C. Tributyltin hydride (0.6 mL, 2.3 mmol, 2.3 equiv) was added dropwise. The yellow-orange solution was warmed to 30 °C and the alkyn (196 mg, 1.0 mmol, 1.0 equiv) in THF (3 mL) was added dropwise. After 1 h, the reaction was complete (TLC control). Sat. aq NH₄Cl solution (2.5 mL) and conc. aq NH₄OH solution (0.5 mL) were added. The aqueous layer was extracted with MTBE, dried (MgSO₄) and the solvent removed. The crude product was purified by chromatography on silica gel (PE–EtOAc–PE/CH₂Cl₂–PE/acetone/PE). 

IR (neat): 3135, 2911, 1719, 1568, 1310, 1245, 1161, 1101, 1025, 830 cm⁻¹.

HRMS: m/z calcd for C₈H₇Br₂NO₃: 322.8792; found: 322.8792.

2-(2,2-Dibromovinyl)-oxazole-4-carboxylic Acid Ethyl Ester (12)

A solution of aldehyde 11 (869 mg, 5.14 mmol, 1.0 equiv) and CBr₄ (1.79 g, 5.4 mmol, 1.05 equiv) in CH₂Cl₂ (15 mL) was added dropwise over 3 h with stirring at 0 °C. After stirring for 1 h at r.t. Then silicagel was added followed by PE. The solvent was evaporated and the residue filtered through a short column [PE/MTBE (methyl tert-butyldimethylsilyloxy)hepta-1,3,5-trienyl] to afford dibromoolefin 12 (1.08 g, 65%) as a colorless solid; mp 68 °C.

IR (neat): 3199, 2994, 2126, 1716, 1575, 1367, 1211, 1022, 946, 830 cm⁻¹.

1H NMR (400 MHz, CDCl₃/TMS): δ = 8.12 (s, 1 H, H-3), 4.37 (q, J = 7.1 Hz, 2 H, OCH₂CH₃), 3.37 (s, 1 H, H-6), 1.37 (t, J = 7.1 Hz, 3 H, OCH₂CH₃).

13C NMR (100 MHz, CDCl₃/TMS): δ = 159.5 (C q , C-1), 143.5 (C q , C-4), 144.5 (CH, C-3), 134.3 (C q , C-2), 81.2 (C q , C-5), 70.4 (CH, C-6), 61.6 (OCH₂CH₃), 14.2 (OCH₂CH₃).

MS MAT: m/z (%) = 488 (3, [M⁺]), 487 (4), 436 (15), 435 (27), 433 (70), 432 (47), 431 (100), 430 (93), 429 (92), 427 (91), 365 (50), 291 (22), 249 (83), 247 (87), 193 (89), 191 (79).

HRMS: m/z calcd for C₁₅H₁₈O₃Si: 488.2496; found: 488.2494.

2-(2-Bromo-(tert-butylidimethylsilyloxy)hepta-1,3,5-trienyl)oxazole-4-carboxylic Acid Ethyl Ester (18)

A solution of stannane 17 (292 mg, 0.6 mmol, 1.2 equiv), dibromomidolefin 12 (163 mg, 0.5 mmol, 1.0 equiv) and TFP (17.4 mg, 0.075 mmol, 0.15 equiv) in toluene (2.5 mL) was degassed with argon for 30 min. Then Pd₂dba (12.9 mg, 0.0125 mmol, 0.025 equiv) was added and the mixture was heated to 100 °C. After 1 h, no starting material was detectable by TLC. Sat. aq NaHCO₃ solution was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (MgSO₄), the solvent removed, and the crude product purified by chromatography to afford 18 (190 mg, 86%) as a colorless solid; mp 93 °C.

1H NMR (400 MHz, CDCl₃/TMS): δ = 8.28 (s, 1 H, H-3), 7.21 (dd, J = 14.3, 11.9 Hz, 1 H, H-8), 6.98 (s, 1 H, H-5), 6.36 (d, J = 14.3 Hz, 1 H, H-7), 6.17–6.24 (m, 1 H, H-9), 5.81 (dt, J = 6.6, 1.6 Hz, 2 H, H-11), 4.47 (dd, J = 6.3, 1.6 Hz, 2 H, H-12), 4.41 (q, J = 7.2 Hz, 2 H, OCH₂CH₃), 1.40 (t, J = 7.2 Hz, 3 H, OCH₂CH₃), 0.92 (s, 9 H, t-C₄H₉), TBDMs, 0.11 (s, 6 H, 2 CH₂, TBDMs).

13C NMR (100 MHz, CDCl₃/TMS): δ = 159.7 (C q , C-1), 154.3 (CH), 136.19 (CH), 134.76 (CH), 133.96 (CH), 132.08 (CH), 129.48 (CH), 127.21 (CH), 116.81 (CH), 61.29 (CH₂), 59.92 (CH₂), 25.88 (CH₃), 18.28 (CH₂), 14.23 (CH₃), –5.18 (CH₂).

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PAPER

Synthesis of the Northern Half of Disorazole A₁

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2-(7-Hydroxy-hepta-3,5-dien-1-ynyl)oxazole-4-carboxylic Acid Ethyl Ester (19)

To a solution of protected bromonitrile 18 (442 mg, 1.0 mmol, 1.0 equiv) in THF (10 mL) was added TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) dropwise at 0 °C. After 30 min, H2O was added and the aqeous layer was extracted with MTBE. The combined organic layers were dried (MgSO4) and the solvent was evaporated. The crude product was purified by chromatography to afford allylic alcohol 19 (216 mg, 87%) as colorless needles; mp 91 °C.

1H NMR (400 MHz, CDCl3/TMS): δ = 8.20 (s, 1 H, H-3), 7.17 (dd, J = 15.6, 11.7, 1.4 Hz, 1 H, H-8), 6.15–6.23 (m, 1 H, H-9), 5.82–5.89 (m, 1 H, H-10), 5.81 (d, J = 7.2 Hz, 2 H, OCH2CH3), 4.39–4.42 (m, 2 H, H-11), 1.66 (br, 1 H, OH), 1.39 (J = 7.2 Hz, 3 H, OCH2CH3)

13C NMR (100 MHz, CDCl3/TMS): δ = 160.58 (Cq), 147.21 (Cq), 144.30 (CH), 140.96 (CH), 135.88 (CH), 134.51 (Cq), 128.46 (CH), 109.57 (CH), 92.17 (Cq), 78.69 (CHq), 61.55 (CH3), 58.88 (CH3), 14.25 (CH3)

MS-MAT (130 °C): m/z (%) = 264 (42), 263 (100, [M]+), 247 (13), 235 (14), 234 (62), 233 (84), 224 (80), 218 (84), 195 (56), 188 (85), 174 (83), 121 (73).

HRMS: m/z calc for C19H18NO4: 263.0794; found: 263.0790.

2-(7-[Formylmethylidene]oxy)-3-ethenyl-4-sulfonyl-3-ethyl-1H-imidazole-3-carboxylic Acid Ethyl Ester (3)

A solution of the above prepared epoxy alcohol (131.6 mg, 0.5 mmol, 1.0 equiv) in CH2Cl2 (1 mL) was stirred for 2.5 h at rt. Silica gel was added and the solvent removed. The crude product was purified by chromatography (EtOAc–PE, 1:2) to afford aldehyde 3 (106 mg, 81%) as a colorless solid; mp 97 °C; [α]D 20 = −118.2 (c = 0.45, CHC13).

1H NMR (400 MHz, CDCl3/TMS): δ = 9.44 (d, J = 5.2 Hz, 1 H, H-11), 8.22 (s, 1 H, H-3), 6.36 (dd, J = 15.9, 7.0 Hz, 1 H, H-8), 6.24 (dd, J = 15.9, 0.6 Hz, 1 H, H-7), 4.40 (q, J = 7.2 Hz, 2 H, OCH2CH3), 3.86 (dd, J = 7.0, 4.5, 0.6 Hz, 1 H, H-9), 3.64 (dd, J = 5.3, 4.6 Hz, 1 H, H-10), 1.39 (t, J = 7.2 Hz, 3 H, OCH2CH3)

13C NMR (100 MHz, CDCl3/TMS): δ = 196.75 (CH, C-1), 160.39 (Cq, C-1), 146.57 (Cq, C-3), 144.52 (CH, C-3), 139.01 (CH, C-7/C-8), 134.70 (Cq, C-2), 114.30 (CH, C-7/C-8), 88.82 (Cq, C-5/C-6), 78.98 (Cq, C-5/C-6), 61.56 (OCH2CH3), 59.49 (CH, C-9/C-10), 57.34 (CH, C-9/C-10), 142.5 (OCH2CH3)

MS-MAT (100 °C): m/z (%) = 262 (24), 261 (100, [M]+), 233 (32), 232 (69), 216 (32), 184 (53), 187 (51), 159 (30), 149 (40), 105 (64).

HRMS: m/z calc for C20H17NO4: 261.0637; found: 261.0637.

3-( tert-Butyldimethylsilyloxy)-4,4-dimethyl-5-triisopropylsilyl-oxycet-6-en-1-ol

To a solution of alcohol 20 (150 mg, 0.35 mmol, 1.0 equiv) in CH2Cl2 (0.7 mL) was added DMAP (cat.), 2,6-lutidine (124 µL, 1.06 mmol, 3.0 equiv) and TIPSOTf (124 µL, 0.46 mmol, 1.3 equiv) at 0 °C. After 16 h at rt., H2O was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na2SO4) and the solvent was evaporated. Purification of the crude product by chromatography afforded the TIPS ether (201 mg, 99%) as a colorless oil. To a solution of this PMB ether (1235 mg, 2.13 mmol, 1.0 equiv) in CH2Cl2 (25 mL) was added H2O (2.5 mL) and DDQ (629.5 mg, 2.77 mmol, 1.3 equiv) at 0 °C. After 1 h at rt., cyclohexene-1,4-diene (3 mL) and sat. aq NaHCO3 solution were added and the aqueous layer was extracted with MTBE. The combined organic layer was dried (Na2SO4) and the solvent was evaporated. Purification of the crude product by chromatography afforded the free primary alcohol (977 mg, 99%) as a colorless oil; [α]D 20 = −11.5 (c = 1.01, CHCl3).

IR (neat): 3327, 2938, 1672, 1386, 1082, 1049, 1004, 834, 773 cm⁻¹.

1H NMR (400 MHz, CDCl3/TMS): δ = 5.40–5.55 (m, 2 H, H-1, H-17), 4.03 (d, J = 8.2 Hz, 1 H, H-16), 3.71–3.77 (m, 1 H, H-12a), 3.59–3.68 (m, 1 H, H-12b), 3.56 (dd, J = 7.9, 2.7 Hz, 1 H, H-14), 1.78–1.86 (m, 2H, H-13a, H-13a), 1.68 (d, J = 5.0 Hz, 3 H, H-19), 1.60–1.66 (m, 1 H, H-13b), 0.04 [m, 21 CH(2H)2, TIPS], 0.95 (s, 3 H, CH3), 0.91 (s, 9 H, t-C6H13, TBDMS), 0.88 (s, 3 H, CH3), 0.07 (s, 3 H, CH3, TBDMS), 0.06 (s, 3 H, CH3, TBDMS).

13C NMR (100 MHz, CDCl3/TMS): δ = 131.97 (CH, C-18), 127.66 (CH, C-17), 79.12 (CH, C-16), 74.35 (CH, C-14), 60.86 (CH2, C-12), 44.28 (Cq, C-5), 35.69 (CH3, C-13), 26.17 (CH3, TBDMS), 20.32 (CH3), 19.68 (CH3), 18.34 (CH2, TIPS), 18.22 (CH3, TIPS), 18.09 (CH2, TIPS), 17.66 (CH3, C-19), 12.83 (CH3, TBDMS), −3.66 (CH3, TBDMS), −3.72 (CH3, TBDMS).

MS (80 °C): m/z (%) = 417 (1), 416 (2), 415 (5, [M]+), 414 (0.6), 413 (2), 359 (2), 345 (1), 326 (2), 320 (4), 319 (14), 315 (9), 305 (4), 284 (6), 283 (18), 263 (7), 245 (5), 243 (5), 242 (14), 241 (34), 229 (41), 228 (39), 227 (89), 213 (12), 203 (20), 199 (9), 190 (16), 189 (40), 187 (31), 186 (32), 185 (53), 173 (41), 171 (57), 157 (32), 153 (33), 151 (100), 119 (36), 115 (32), 103 (27), 89 (32), 75 (47), 73 (54).

HRMS: m/z calc for C42H74Si6O3: 415.3064; found: 415.3061.
Methanesulfonic Acid 3-(tert-Butyl-dimethylsilyloxy)-4,4-dimethyloxiranyl-5,5-diisopropylsilyloxyct-6-enyl Ester

To a solution of the above primary alcohol (583 mg, 1.27 mmol, 1.0 equiv) in THF (5 mL) was added DMAP (cat.), Et₃N (0.35 mL, 2.54 mmol, 2.0 equiv) and MsCl (0.14 mL, 1.78 mmol, 1.4 equiv) at 0 °C. After 2 h at 0 °C, sat. aq NH₄Cl solution was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated. Purification of the crude product by chromatography afforded the corresponding mesylate (682.4 mg, 99%) as a colorless oil; [α]D = -15.3 (c = 1.11, CHCl₃).

IR (neat): 2960, 1669, 1471, 1462, 1255, 1083, 1046, 833, 772 cm⁻¹.

HRMS: m/z calcd for C₃₈H₆₃NNaO₆Si₂: 708.4092; found: 708.4087.

1H NMR (400 MHz, CDCl₃/TMS): δ = 5.01 (dq, J = 15.4, 5.9 Hz, 1 H, H-18), 5.46 (ddd, J = 15.5, 8.5, 1.3 Hz, 1 H, H-17), 4.37 (ddd, J = 9.6, 8.2, 4.8 Hz, 1 H, H-12a), 4.21 (dt, J = 9.5, 7.7 Hz, 1 H, H-12b), 4.01 (d, J = 8.5 Hz, 1 H, H-16), 3.60 (dd, J = 8.0, 2.6 Hz, 1 H, H-14), 3.00 (s, 3 H, CH₃, mesylate), 2.01–2.10 (m dtd, 1 H, H-13a), 1.74–1.84 (m dtd, 1 H, H-13b), 1.71 (dd, J = 5.8, 0.8 Hz, 3 H, H-19), 1.06 [br s, 21 H, CH(CH₃)₂, TIPS], 0.92 (br s, 12 H, CH₃, TBDMS), 0.90 (s, 3 H, CH₂), 0.09 (2 × 3 H, CH₃, TBDMS).

13C NMR (100 MHz, CDCl₃/TMS): δ = 101.50 (Cq, C-1), 75.94 (CH₂, C-13), 66.83 (OCH₂CH₃), 54.40 (OCH₂CH₂CH₃), 31.47 (CH₂, C-17/C-18), 26.12 (CH₃, TBDMS), 20.39 (CH₃, 19.3 mg, 0.074 mmol, 1.05 equiv) in anhyd THF, dried with LiHMDS in THF (74 μL, 0.49 mmol, 0.70 equiv) and the residue was evaporated. The mixture was gradually warmed to r.t. and stirred for 3 h. The mixture was hydrolyzed with sat. aq NaHCO₃ solution, extracted with MTBE, dried (Na₂SO₄), filtered through Celite, and evaporated to dryness. After chromatography, the Wittig product was isolated (20.8 mg, 43%) as a slightly yellow oil (ZIE = 5:1).

IR (neat): 2960, 1669, 1471, 1462, 1255, 1083, 1046, 833, 772 cm⁻¹.

HRMS: m/z calcd for C₃₈H₆₃NNaO₆Si₂: 708.4336; found: 708.4332.

6-(tert-Butyl-dimethylsilyloxy)-8-iodo-5,5-dimethyl-4-triisopropylsilyloxyct-2-ene (21)

To a solution of the crude product (120 mg) in THF (5 mL) was added anhyd LiHMDS (74 μL, 0.49 mmol, 0.70 equiv) and the residue was evaporated. The mixture was gradually warmed to r.t. After 6 h at reflux, H₂O was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated. Purification of the crude product by chromatography afforded iodide (243.4 mg, 91%) as a colorless oil; [α]D = -32.3 (c = 0.95, CHCl₃).

IR (neat): 2960, 1669, 1471, 1462, 1255, 1083, 1046, 833, 772 cm⁻¹.

HRMS: m/z calcd for C₃₈H₆₃NNaO₆Si₂: 708.4092; found: 708.4092.

1H NMR (100 MHz, CDCl₃/TMS): δ = 5.33 (dq, J = 15.4, 5.8 Hz, 1 H, H-18), 5.43–5.49 (ddq, 1 H, H-17), 3.99 (d, J = 8.4 Hz, 1 H, H-16), 3.47 (dd, J = 8.0, 2.3 Hz, 1 H, H-14), 3.36 (mdd, 1 H, H-12a), 3.11 (dt, J = 9.4, 8.3 Hz, 1 H, H-12b), 2.12 (dd, J = 14.6, 8.5, 2.4 Hz, 1 H, H-13a), 1.93 (dd, J = 15.2, 7.4–8.0 Hz, 1 H, H-13b), 1.72 (d, J = 5.8 Hz, 3 H, H-19), 1.07 [br s, 21 H, CH(CH₃)₂, TIPS], 0.93 (br s, 12 H, CH₃, 19.3 mg, 0.074 mmol, 1.05 equiv) in anhyd THF (0.3 mL) were subsequently added. The mixture was gradually warmed to r.t. and stirred for 3 h. The mixture was hydrolyzed with sat. aq NaHCO₃ solution, extracted with MTBE, dried (Na₂SO₄), filtered through Celite, and evaporated to dryness. After chromatography, the Wittig product was isolated (20.8 mg, 43%) as a slightly yellow oil (ZIE = 5:1).

IR (neat): 2960, 1669, 1471, 1462, 1255, 1083, 1046, 833, 772 cm⁻¹.

HRMS: m/z calcd for C₃₈H₆₃NNaO₆Si₂: 708.4092; found: 708.4092.

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(15) The absolute configuration of disorazole A$_1$ had not been assigned unambiguously until late 2000. Therefore, the non-natural C7/C11 fragment was used in our earlier studies.

(20) Quantified by conversion to the Mosher ester.
(22) The corresponding C16 MOM and SEM ethers were not sufficiently stable under standard halogenation conditions.