Toward the Total Synthesis of Disorazole A_1: Asymmetric Synthesis of the Masked Northern Half

Ingo V. Hartung, Ulrike Eggert, Lars Ole Haustedt, Barbara Niess, Peter M. Schäfer, H. Martin R. Hoffmann*

Department of Organic Chemistry, University of Hannover, Schneiderberg 1B, 30167 Hannover, Germany
Fax +49(511)7623011; E-mail: hoffmann@mbox.oci.uni-hannover.de

Received 10 June 2003; revised 10 July 2003

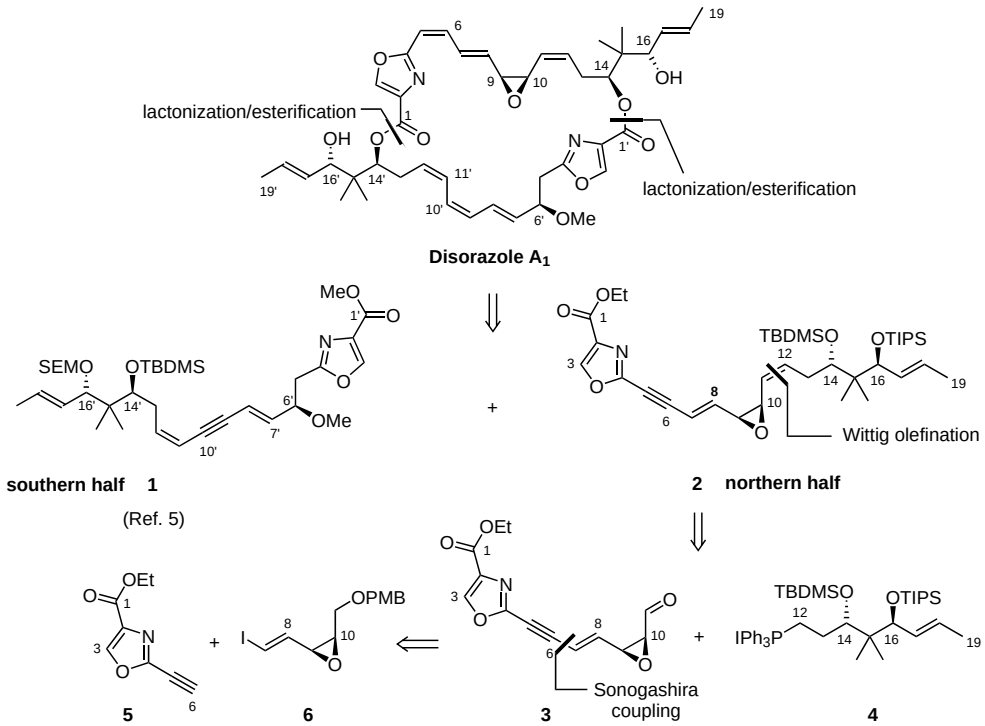
Dedicated to Prof. Wolfgang Steglich on the occasion of his 70th birthday.

Abstract: The stereoselective synthesis of the masked northern half of the antimitotic natural product disorazole A_1 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 A_1, 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 A_1.

Our retrosynthetic disconnections of disorazole A_1 are outlined in Scheme 1. The C7′–C12′ triene and C5–C8 diene of disorazole A_1 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

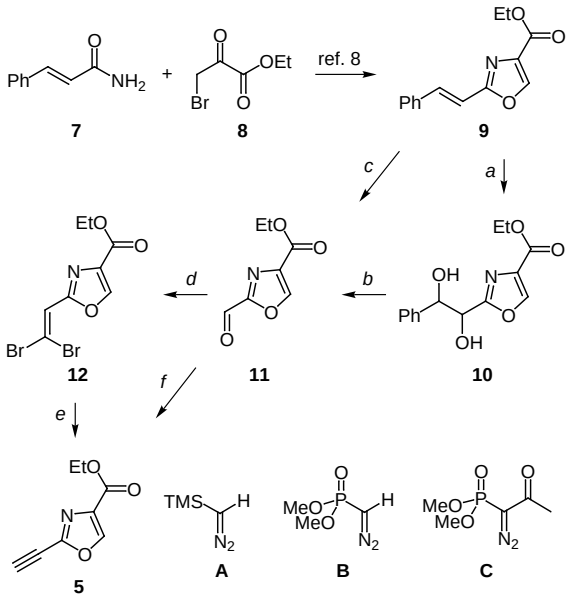


Scheme 1

Synthesis 2003, No. 12, Print: 02 09 2003. Web: 13 08 2003.
Art Id.1437-210X,E;2003,0,12,1844,1850,ftx,en;T05003SS.pdf.
DOI: 10.1055/s-2003-41033

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**.

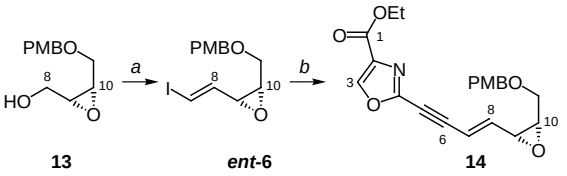
The synthesis of the oxazole alkyne **5** commenced with the transformation of *trans*-cinnamamide (**7**)[6] to the 2,4-disubstituted oxazole ester **9** by reaction with α-bromoethyl pyruvate (**8**)[7] using Panek's modification of the Hantzsch protocol (Scheme 2).[8] Oxidative cleavage of the double 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,[8] the necessary amount of toxic OsO_4 was reduced from 10 mol% to 1 mol%.[9] Ozonolysis of **9** followed by workup with Ph_3P gave the oxazole aldehyde **11** in 45% yield.



Scheme 2 *Reaction conditions:* (*a*) $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (3 equiv), OsO_4 (0.01 equiv), $(DHQD)_2PHAL$ (0.01 equiv), *t*-BuOH, H_2O, r.t., 96%; (*b*) $Pb(OAc)_4$, K_2CO_3, benzene, 0 °C, 80%; (*c*) $NaIO_4$ (3 equiv), silica gel, $RuCl_3 \cdot xH_2O$ (0.05 equiv), CH_2Cl_2, r.t., 68%; (*d*) CBr_4, Ph_3P, CH_2Cl_2, 70%; (*e*) *n*-BuLi, THF, –78 °C, 30%; (*f*) **A**, *t*-BuOK, THF, –78 °C, 30% or **C**, K_2CO_3, EtOH, 0 °C → r.t., 50% or 1. CHI_3, *t*-BuOK, CH_2Cl_2, r.t.; 2. *n*-BuLi, –100 °C, 41% (2 steps) [$(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether]

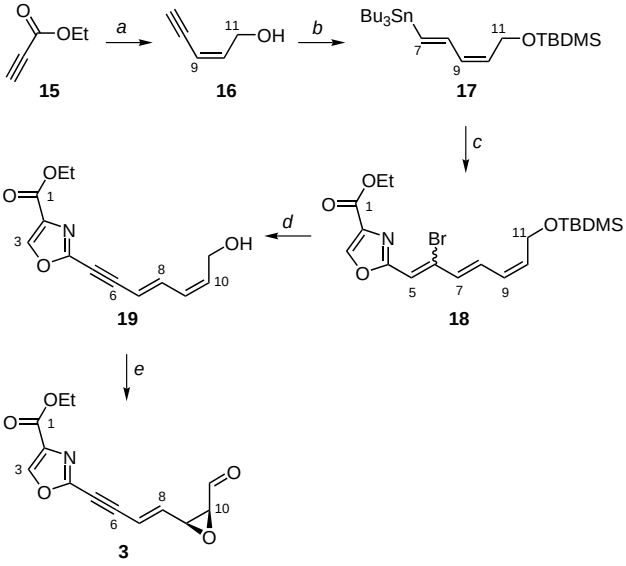
Gratifyingly, this one-step oxidative cleavage of **9** was optimized to 68% yield by using $NaIO_4$ on silica gel in the presence of a catalytic amount of $RuCl_3$.[10] Homologation to the oxazole alkyne **5** was first pursued under Corey–Fuchs conditions[11] via dibromo olefin **12**. Unfortunately, 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 C_1-transfer reagents **A**–**C**. Commercially available TMS-diazomethane **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 **13**[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.



Scheme 3 *Reaction conditions:* (*a*) 1. $SO_3 \cdot py$, Et_3N, CH_2Cl_2–DMSO, 0 °C → r.t., 95%; 2. Ph_3P, CHI_3, *t*-BuOK, THF, 75%; 3. MeLi, THF, –100 °C, 75%; (*b*) $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, **5**, r.t., 15% (PMB = *p*-methoxybenzyl]

To circumvent the low yielding alkynation 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).

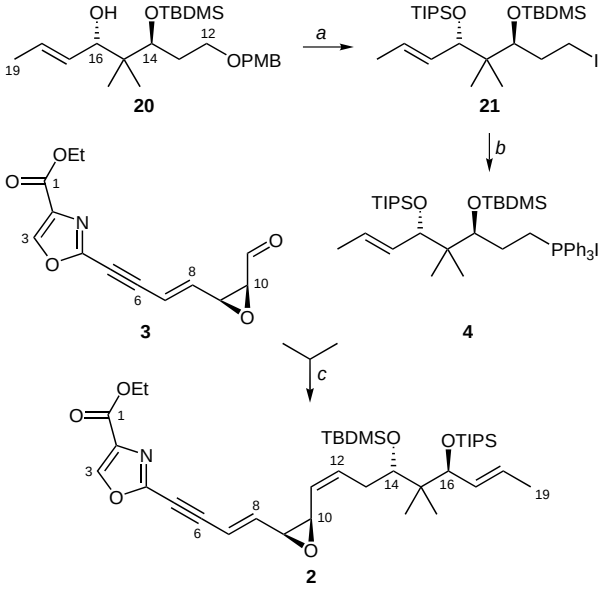


Scheme 4 *Reaction conditions*: (*a*) 1. LiBr, HOAc, MeCN; Et_3N, CuI (0.02 equiv), $PdCl_2(Ph_3P)_2$ (0.01 equiv), HC≡CSiMe$_3$, r.t., 79%; 2. DIBAH, THF, –78 → 0 °C, 85%; 3. TBAF, THF, 0 °C, 70%; (*b*) 1. TBDMSCl, imidazole, DMF, r.t., 90%; 2. CuCN, *n*-BuLi, Bu_3SnH, THF, –78 → –30 °C, 85%; (*c*) **12**, TFP (0.15 equiv), Pd_2dba_3 (0.025 equiv), toluene, 100 °C, 86%; (*d*) TBAF (3.0 equiv), THF, 0 °C, 87%; (*e*) 1. D-(–)-DET, $Ti(i\text{-}PrO)_4$, *t*-BuOOH, MS 4Å, CH_2Cl_2, –18 °C, 84% (86% ee), 2. $PhI(OAc)_2$ (1.1 equiv), TEMPO (0.1 equiv), CH_2Cl_2, r.t., 81% [TFP = tris(2-furyl)phosphine, DET = diethyl tartrate, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl]

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,[17] which was reduced and deprotected to give allylic alcohol **16**.

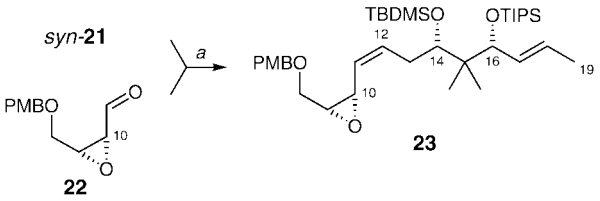
After *E*-selective stannylation,[18] diene **17** was coupled with oxazole dibromoolefin **12** giving rise to bromotriene **18** of inconsequential geometry in excellent 86% yield.[19] TBDMS-deprotection and dehydrobromination was achieved in one-step using an excess of TBAF. The synthesis of epoxy aldehyde **3** was completed by Sharpless epoxidation (86% ee)[20] and oxidation with $PhI(OAc)_2$/TEMPO.[21]

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 A_1 (Scheme 5).[5] TIPS-protection of the C16 hydroxy group,[22] 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 (Ph_3P, neat, 85 °C).[23] In contrast, by adding excess Hünig's base[24] the phosphonium iodide was formed in 83% isolated yield.



Scheme 5 *Reaction conditions*: (*a*) 1. TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 99%; 2. DDQ, CH_2Cl_2/H_2O 10:1, 0 °C, 99%; 3. MsCl, Et_3N, DMAP, THF, 0 °C, 99%; 4. NaI, $NaHCO_3$, acetone, reflux, 91%; (*b*) Ph_3P, DIPEA, sealed flask, 85 °C, 83%; (*c*) 1. **4**, LiHMDS, THF, –78 °C → r.t.; 2. HMPA, **3**, –78 °C → r.t., 43% (from **21**) [DIPEA = diisopropylamine; HMPA = hexamethylphosphoric triamide; LiHMDS = lithium hexamethyldisilazide]

The phosphonium iodide was conveniently used after removal of excess triphenylphosphine with *n*-pentane without further purification steps. First, lithium salt-free conditions were employed for the Wittig reaction of phosphonium iodide **4** and C1–C11 aldehyde **3**.[25] Using NaHMDS as base the masked northern half was isolated in only 21% yield. For optimization studies epoxy aldehyde **22** and its enantiomer were used as model systems in combination with phosphonium iodide **4** and its *syn*-diastereomer (Scheme 6). In this case, the Wittig product was formed using lithium salt free conditions in 45% yield (*Z*/*E* = 9.5:1.0). By changing the base to LiHMDS with HMPA as co-solvent[26] Wittig product **23** was isolated in 61% yield (from *syn*-**21**).



Scheme 6 *Reaction conditions*: (*a*) 1. *syn*-**21**, Ph_3P (1.8 equiv), DIPEA (7.0 equiv), sealed flask, 85 °C, 20 h; 2. removal of excess Ph_3P with *n*-pentane; 3. LiHMDS, THF, –78 °C, 15 min; 4. HMPA, **22**, –78 °C → r.t., 3 h, 61% (from *syn*-**21**)

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.[27] Nucleophilic addition reactions of the so formed lithiated oxazole could possibly involve the C11 aldehyde,[28] the C9–C10 epoxide or even the C1 ester functionality leading to diverse side products.

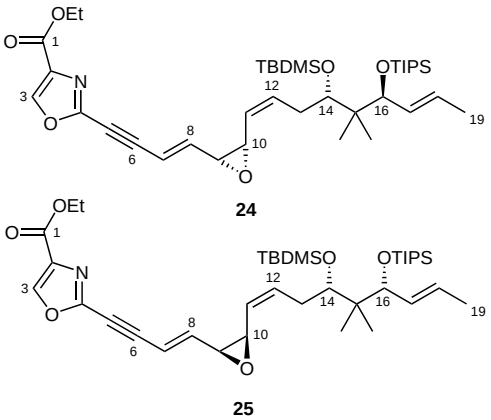


Figure 1 Structures of masked non-natural halves of disorazole A_1 **24** and **25**

We have applied our strategy for the synthesis of two masked non-natural northern halves of disorazole A_1 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 A_1 in hand, our further synthetic efforts are focused on developing cyclization strategies targeting disorazole A_1 and its C_2-symmetric homodimers disorazole B_1 and disorazole C_1.

IR spectra were recorded on a Perkin-Elmer 1710 IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVS 400 and Bruker AVM 500 spectrometers in $CDCl_3$ or acetone-d_6 with tetramethylsilane as internal standard. ^{1}H 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). ^{13}C NMR spectra were fully decoupled with chemical shifts reported relative to the solvent signal ($CDCl_3$, 77.0 ppm). Signal assignments are based on DEPT and – if necessary – on additional ^{1}H-^{1}H-COSY and HMQC experiments. The numbering of carbon and hydrogen signals refers to the numbering of the natural product. Mass spectra were performed on a Finnigan MAT 312 (70 eV) or a VG Autospec (HR-MS) spectrometer. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Petroleum ether (PE) used had bp 55–60 °C.

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

To a solution of aldehyde **11** (869 mg, 5.14 mmol, 1.0 equiv) and CBr_4 (1.79 g, 5.4 mmol, 1.05 equiv) in CH_2Cl_2 (15 mL) was added Ph_3P (2.83 g, 10.8 mmol, 2.1 equiv) in four portions (5 min intervals) at 0 °C. The mixture was stirred for 1 h at r.t. Then silica gel was added followed by PE. The solvent was evaporated and the residue filtered though a short column [PE/MTBE (methyl *tert*-butyl ether)] to afford dibromoolefin **12** (1.08 g, 65%) as a colorless solid; mp 68 °C.

IR (neat): 3135, 2911, 1719, 1568, 1310, 1245, 1161, 1101, 1025, 988 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/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, OCH_2CH_3), 1.37 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$/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 (OCH_2CH_3), 14.3 (OCH_2CH_3).

MS-MAT (80 °C): *m*/*z* (%) = 325 (47, [M^+ + 2]), 323 (26, [M^+]), 297 (100), 295 (44), 280 (14), 215 (23), 211 (25).

HRMS: *m*/*z* calcd for $C_8H_7Br_2NO_3$: 322.8792; found: 322.8792.

2-Ethynyloxazole-4-carboxylic Acid Ethyl Ester (5)

To a solution of oxazole aldehyde **11** (150 mg, 0.89 mmol, 1.0 equiv) in EtOH (6 mL) was added sequentially K_2CO_3 (241 mg, 1.75 mmol, 2.0 equiv) and the Ohira–Bestmann reagent (256 mg, 1.33 mmol, 1.5 equiv) at 0 °C. After 16 h, the reaction mixture was treated with 1 N HCl, and extracted with MTB ether. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by chromatography (cylohexane–MTBE, 4:1) to afford oxazole alkyne **5** (70.5 mg, 50%) as a colorless solid; mp 73 °C.

IR (neat): 3199, 2994, 2126, 1716, 1575, 1367, 1211, 1022, 946, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.18 (s, 1 H, H-3), 4.37 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.27 (s, 1 H, H-6), 1.37 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 160.3 (C_q, C-1), 145.9 (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 (OCH_2CH_3), 14.2 (OCH_2CH_3).

MS MAT: *m*/*z* (%) = 166 (12, [M^+ + 1]), 165 (84, [M^+]), 138 (22), 137 (100), 120 (56), 109 (18), 93 (12), 81 (11).

HRMS: *m*/*z* calcd for $C_8H_7NO_3$: 165.0426; found: 165.0427.

***tert*-Butyldimethyl-(5-tributylstannanylpenta-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 alkyne (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 NH_4Cl solution (2.5 mL) and conc. aq NH_3 solution (0.5 mL) were added. The aqueous layer was extracted with MTBE, dried ($MgSO_4$) and the solvent removed. The crude product was purified by chromatography on silica gel (PE–Et_3N, 100:1 → PE–MTBE–Et_3N, 95:5:1) to afford stannane **17** (416 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 6.78 (ddd, *J* = 18.6, 10.5, 1.1 Hz, 1 H, H-8), 6.27 (d, *J* = 18.6 Hz, 1 H, H-7), 5.90–6.03 (m, 1 H, H-9), 5.42–5.50 (m, 1 H, H-10), 4.40 (dd, *J* = 6.6, 1.3 Hz, 2 H, H-11), 1.46–1.54 (m, 6 H, 3 CH_2, Bu), 1.26–1.36 (m, 6 H, 3 CH_2, Bu), 0.87–0.93 (m, 24 H, *t*-C_4H_9,TBDMS and 3 CH_2CH_3, Bu), 0.09 (s, 6 H, 2 CH_3, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 141.55 (CH), 136.19 (CH), 132.16 (CH), 129.41 (CH), 59.72 (CH_2, C-11), 29.13 (CH_2, Bu), 27.30 (CH_2, Bu), 25.99 (CH_3, *t*-C_4H_9), 18.40 [C_q, *t*-C_4H_9), 13.69 (CH_3, Bu), 9.58 (CH_2, Bu), –5.07 (CH_3, TBDMS).

MS-MAT (80 °C): *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 $C_{23}H_{48}OSiSn$: 488.2496; found: 488.2494.

2-[2-Bromo-7-(*tert*-butyldimethylsilyloxy)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), dibromoolefin **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 Pd_2dba_3 (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 $NaHCO_3$ solution was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried ($MgSO_4$), the solvent removed, and the crude product purified by chromatography to afford **18** (190 mg, 86%) as a colorless solid; mp 93 °C.

^{1}H NMR (400 MHz, $CDCl_3$/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* = 10.9, 6.3 Hz, 1 H, H-10), 4.47 (dd, *J* = 6.3, 1.6 Hz, 2 H, H-11), 4.41 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 1.40 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 0.92 (s, 9 H, *t*-C_4H_9, TBDMS), 0.11 (s, 6 H, 2 CH_3, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 160.97 (C_q), 159.87 (C_q), 143.43 (CH), 136.19 (CH), 134.76 (C_q), 133.96 (CH), 132.08 (CH), 129.48 (C_q), 127.21 (CH), 116.81 (CH), 61.29 (CH_2), 59.92 (CH_2), 25.88 (CH_3), 18.28 (C_q), 14.23 (CH_3), –5.18 (CH_3).

MS-MAT (130 °C): *m*/*z* (%) = 443 (36), 441 (17, [M$^+$]), 387 (11), 386 (89), 384 (41), 362 (33), 306 (22), 264 (20), 236 (35), 230 (100), 202 (90), 129 (33).

HRMS: *m*/*z* calcd for $C_{19}H_{28}BrNO_4Si$: 441.0971; found: 441.0973.

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

To a solution of protected bromotriene **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, H_2O was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried ($MgSO_4$) 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.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.20 (s, 1 H, H-3), 7.17 (ddd, *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* = 15.6 Hz, 1 H, H-7), 4.40 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 4.39–4.42 (m, 2 H, H-11), 1.66 (br, 1 H, OH), 1.39 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 160.58 (C_q), 147.21 (C_q), 144.30 (CH), 140.96 (CH), 135.88 (CH), 134.51 (C_q), 128.46 (CH), 109.57 (CH), 92.17 (C_q), 78.69 (C_q), 61.53 (CH_2), 58.88 (CH_2), 14.25 (CH_3).

MS-MAT (120 °C): *m*/*z* (%) = 248 (20), 247 (53, [M$^+$]), 219 (29), 218 (80), 202 (37), 192 (19), 179 (13), 173 (77), 172 (100), 145 (39), 116 (510), 105 (43).

HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_4$: 247.0845; found: 247.0845.

2-[4-(3-Hydroxymethyloxiranyl)but-3-en-1-ynyl]oxazole-4-carboxylic Acid Ethyl Ester

To a solution of 4Å molecular sieves (206 mg), Ti(*i*-PrO)$_4$ (35 μL, 0.028 mmol, 0.14 equiv) and D-(–)-diethyl tartrate (24 mg, 0.028 mmol, 0.14 equiv) in CH_2Cl_2 (4 mL) was added *t*-BuOOH (5.5 M in decane, 0.31 mL, 1.74 mmol, 2.1 equiv) at –20 °C. The solution was stirred for 15 min and then the allylic alcohol **19** (206 mg, 0.83 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added. The resulting mixture was stored for 3 d in a refrigerator (–18 °C) and then suction-filtered through Celite. To the filtrate was added $FeSO_4$/tartaric acid solution and the mixture was stirred for 1 h at r.t. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification of the crude product by chromatography afforded the epoxide (184 mg, 84%) as a colorless solid; mp 89 °C; $[\alpha]_D^{20}$ +72.2 (*c* = 0.63, $CHCl_3$).

IR (neat): 3382, 1720, 1544, 1305, 1239, 1153, 1108, 1020, 948 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.21 (s, 1 H, H-3), 6.40 (dd, *J* = 16.0, 6.8 Hz, 1 H, H-8), 6.06 (dd, *J* = 16.1, 1.0 Hz, 1 H, H-7), 4.40 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 3.85 (dd, *J* = 12.4, 4.4 Hz, 1 H, H-11a), 3.74 (dd, *J* = 12.4, 6.2 Hz, 1 H, H-11b), 3.63 (ddd, *J* = 6.8, 4.4, 1.0 Hz, 1 H, H-9), 3.42 (dt, *J* = 6.2, 4.4 Hz, 1 H, H-10), 1.53 (br, 1 H, OH), 1.39 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 160.50 (C_q, C-1), 146.88 (C_q, C-4), 144.46 (CH), 142.13 (CH), 134.47 (C_q, C-2), 112.29 (CH), 90.01 (C_q), 77.72 (C_q), 61.57 (O*C*H$_2$CH$_3$), 60.06 (CH_2, C-11), 59.91 (CH, C-9/C-10), 55.91 (CH, C-9/C-10), 14.24 (OCH$_2$*C*H$_3$).

MS-MAT (130 °C): *m*/*z* (%) = 264 (42), 263 (100, [M$^+$]), 247 (13), 235 (14), 234 (62), 233 (84), 232 (84), 220 (89), 218 (84), 195 (56), 188 (85), 174 (83), 121 (73).

HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_5$: 263.0794; found: 263.0790.

2-[4-(3-Formyloxiranyl)but-3-en-1-ynyl]oxazole-4-carboxylic Acid Ethyl Ester (3)

A solution of the above prepared epoxy alcohol (131.6 mg, 0.5 mmol, 1.0 equiv), BAIB [bis(acetoxy)iodobenzene, 177 mg, 0.55 mmol, 1.1 equiv] und TEMPO (8 mg, 0.05 mmol, 0.1 equiv) in CH_2Cl_2 (1 mL) was stirred for 2.5 h at r.t. 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; $[\alpha]_D^{20}$ –118.2 (*c* = 0.45, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$/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, OC*H*$_2$CH$_3$), 3.86 (ddd, *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, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 196.75 (CH, C-11), 160.39 (C_q, C-1), 146.57 (C_q, C-4), 144.52 (CH, C-3), 139.01 (CH, C-7/C-8), 134.70 (C_q, C-2), 114.30 (CH, C-7/C-8), 88.82 (C_q, C-5/C-6), 78.98 (C_q, C-5/C-6), 61.56 (O*C*H$_2$CH$_3$), 59.49 (CH, C-9/C-10), 57.34 (CH, C-9/C-10), 14.25 (OCH$_2$*C*H$_3$).

MS-MAT (100 °C): *m*/*z* (%) = 262 (24), 261 (100, [M$^+$]), 233 (32), 232 (69), 216 (32), 204 (53), 187 (51), 159 (30), 149 (40), 105 (64).

HRMS: *m*/*z* calcd for $C_{13}H_{11}NO_5$: 261.0637; found: 261.0637.

3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-triisopropylsilyloxyoct-6-en-1-ol

To a solution of alcohol **20** (150 mg, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (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 r.t., H_2O was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na_2SO_4) 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 CH_2Cl_2 (25 ml) was added H_2O (2.5 mL) and DDQ (629.5 mg, 2.77 mmol, 1.3 equiv) at 0 °C. After 1 h at r.t., cyclohexa-1,4-diene (3 mL) and sat. aq $NaHCO_3$ solution were added and the aqueous layer was extracted with MTBE. The combined organic layer was dried (Na_2SO_4) and the solvent was evaporated. Purification of the crude product by chromatography afforded the free primary alcohol (977 mg, 99%) as a colorless oil; $[\alpha]_D^{20}$ –11.5 (*c* = 1.01, $CHCl_3$).

IR (neat): 3327, 2938, 1672, 1386, 1082, 1049, 1004, 834, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.40–5.55 (m, 2 H, H-18, 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_{dddd}, 1 H, H-13a), 1.68 (d, *J* = 5.0 Hz, 3 H, H-19), 1.60–1.66 (m, 1 H, H-13b), 1.04 [m, 21 H, CH(CH$_3$)$_2$, TIPS], 0.95 (s, 3 H, CH$_3$), 0.91 (s, 9 H, *t*-C$_4$H$_9$, TBDMS), 0.88 (s, 3 H, CH$_3$′), 0.07 (s, 3 H, CH$_3$, TBDMS), 0.06 (s, 3 H, CH$_3$, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 131.97 (CH, C-18), 127.66 (CH, C-17), 79.12 (CH, C-16), 74.35 (CH, C-14), 60.86 (CH_2, C-12), 44.28 (C_q, C-15), 35.69 (CH_2, C-13), 26.17 (CH_3, TBDMS), 20.32 (CH_3,), 19.68 (CH_3′), 18.34 (CH_3, TIPS), 18.22 (CH_3, TIPS), 18.09 [*C*(CH$_3$)$_3$, TBDMS], 17.66 (CH_3, C-19), 12.83 (CH, TIPS), –3.66 (CH_3, TBDMS), –3.72 (CH_3, TBDMS).

MS (80 °C): *m*/*z* (%) = 417 (1), 416 (2), 415 (5, [M$^+$]), 414 (0.6), 399 (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 (29), 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), 131 (100), 119 (36), 115 (32), 103 (27), 89 (32), 75 (47), 73 (54).

HRMS: *m*/*z* calcd for $C_{22}H_{47}O_3Si_2$: 415.3064; found: 415.3061.

Methanesulfonic Acid 3-(*tert*-Butyl-dimethylsilyloxy)-4,4-dimethyl-5-triisopropylsilyloxyoct-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.), Et_3N (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 NH_4Cl solution was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Purification of the crude product by chromatography afforded the corresponding mesylate (682.4 mg, 99%) as a colorless oil; $[\alpha]_D^{20}$ –15.3 (*c* = 1.11, $CHCl_3$).

IR (neat): 2939, 1690, 1358, 1176, 1082, 1005, 971, 881, 834, 773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.53 (dq, *J* = 15.4, 5.9 Hz, 1 H, H-18), 5.46 (ddq, *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, CH_3, 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, $CH(CH_3)_2$, TIPS], 0.92 (br s, 12 H, CH_3, TBDMS), 0.90 (s, 3 H, CH_3'), 0.09 (2 × 3 H, CH_3, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 131.47 (CH, C-18), 128.17 (CH, C-17), 79.25 (CH, C-16), 73.42 (CH, C-14), 68.08 (CH_2, C-12), 44.17 (C_q, C-15), 37.39 (CH_3, mesylate), 32.76 (CH_2, C-13), 26.12 (CH_3, TBDMS), 20.39 (CH_3), 19.84 (CH_3'), 18.44 [$C(CH_3)_3$, TBDMS], 18.37 (CH_3, TIPS), 18.25 (CH_3, TIPS), 17,73 (CH_3, C-19), 12.81 (CH, TIPS), –3.63 (CH_3, TBDMS), –3.71 (CH_3, TBDMS).

MS (100 °C): *m*/*z* (%) = 536 (1, [M^+]), 535 (2), 496 (2), 495 (3), 494 (5), 493 (13), 479 (2), 449 (3), 437 (4), 397 (9), 383 (9), 361 (12), 353 (9), 341 (137), 311 (10), 309 (20), 301 (18), 287 (24), 283 (23), 280 (20), 279 (57), 267 (46), 246 (53), 228 (54), 227 (56), 209 (100), 185 (80), 171 (72), 153 (81), 115 (53), 73 (87).

HRMS: *m*/*z* calcd for $C_{26}H_{56}O_5Si_2S$: 536.3387; found: 536.3392.

6-(*tert*-Butyldimethylsilyloxy)-8-iodo-5,5-dimethyl-4-triisopropylsilyloxyoct-2-ene (21)

To a solution of the above mesylate (450 mg, 0.84 mmol, 1.0 equiv) in acetone (9 mL) was added solid $NaHCO_3$ (422 mg, 5.03 mmol, 6.0 equiv) and NaI (503 mg, 3.35 mmol, 4.0 equiv) at r.t. After 6 h at reflux, H_2O was added and the aqueous layer was extracted with MTBE. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Purification of the crude product by chromatography afforded iodide **21** (434.1 mg, 91%) as a colorless oil; $[\alpha]_D^{20}$ –32.3 (*c* = 0.93, $CHCl_3$).

IR (neat): 2960, 1669, 1471, 1462, 1255, 1083, 1046, 833, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.53 (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 (m_{ddd}, 1 H, H-12a), 3.11 (dt, *J* = 9.4, 8.3 Hz, 1 H, H-12b), 2.12 (dtd, *J* = 14.6, 8.5, 2.4 Hz, 1 H, H-13a), 1.93 (dtd, *J* = 15.2, 7.4–8.0, 4.6 Hz, 1 H, H-13b), 1.72 (d, *J* = 5.8 Hz, 3 H, H-19), 1.07 [br s, 21 H, $CH(CH_3)_2$, TIPS], 0.93 (br s, 12 H, CH_3 and *t*-C_4H_9, TBDMS), 0.90 (s, 3 H, CH_3'), 0.13 (s, 3 H, CH_3, TBDMS), 0.11 (s, 3 H, CH_3, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 131.51 (CH, C-18), 128.18 (CH, C-17), 79.36 (CH, C-16), 77.55 (CH, C-14), 44.26 (C_q, C-15), 37.33 (CH_2, C-13), 26.24 (CH_3, TBDMS), 20.50 (CH_3), 20.18 (CH_3'), 18.58 (C_q, TBDMS), 18.38 (CH_3, TIPS), 18.26 (CH_3, TIPS), 17.72 (CH_3, C-19), 12.83 (CH, TIPS), 5.05 (CH_2, C-12), –3.19 (CH_3, TBDMS), –3.74 (CH_3, TBDMS).

MS (90 °C): *m*/*z* (%) = 568 (1, [M^+]), 567 (2), 528 (3), 527 (11), 526 (27), 525 (32), 470 (8), 469 (25), 430 (24), 429 (33), 417 (20), 416 (29), 415 (43), 375 (10), 374 (25), 373 (36), 317 (14), 315 (29), 311 (25), 300 (16), 299 (35), 297 (19), 283 (35), 245 (34), 241 (36), 231 (39), 229 (29), 228 (43), 227 (100), 203 (45), 185 (68), 153 (40), 115 (42).

HRMS: *m*/*z* calcd for $C_{22}H_{46}IO_2Si_2$: 525.2081; found: 525.2078.

Anal. Calcd for $C_{25}H_{53}IO_2Si_2$: C, 52.79; H; 9.39. Found: C, 52.47; H, 9.20.

2-(4-{3-[4-(*tert*-Butyldimethylsilyloxy)-5,5-dimethyl-6-triisopropylsilyloxynona-1,7-dienyl]oxiranyl}but-3-en-1-ynyl)oxazole-4-carboxylic Acid Ethyl Ester (2)

Iodide **21** (40 mg, 0.070 mmol, 1.0 equiv), Ph_3P (34 mg, 0.127 mmol, 1.8 equiv) and *i*-Pr_2NEt (86 μL, 0.49 mmol, 7.0 equiv) were heated in a sealed flask to 85 °C for 20 h. *i*-Pr_2NEt was carefully removed with anhyd *n*-pentane in vacuo (3 ×) and the residue was resuspended in anhyd *n*-pentane. After 1 min, the *n*-pentane was removed by pipette (repeated twice). The residue was dissolved in anhyd THF (1.4 mL), cooled to –78 °C and a 1 M solution of LiHMDS in THF (74 μL, 0.074 mmol, 1.05 equiv) was added dropwise. After 15 min at –78 °C, HMPA (0.14 ml) and aldehyde **3** (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 $NaHCO_3$ solution, extracted with MTBE, dried (Na_2SO_4), filtered through Celite, and evaporated to dryness. After chromatography, the Wittig product was isolated (20.8 mg, 43%) as a slightly yellow oil (*Z*/*E* >5:1).

IR (neat): 2928, 2863, 1745, 1465, 1306, 1251, 1143, 1081, 1051, 835, 809, 773 cm^{-1}.

^1H-^1H-COSY (400 MHz, $CDCl_3$/TMS): δ = 8.22 (s, 1 H, H-3), 6.35 (dd, *J* = 16.0, 6.8 Hz, 1 H; H-8), 6.06 (d, *J* = 16.0 Hz, 1 H, H-7), 5.87–5.94 (m, 1 H, H-12), 5.42–5.57 (m, 2 H, H-17 + H-18); 5.21 (t_{dd}, *J* = 9.5–10.5 Hz, 1 H, H-11), 4.41 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.05 (d, *J* = 7.8 Hz, 1 H, H-16), 3.88 (dd, *J* = 8.7, 4.2 Hz, 1 H, H-10), 3.67 (dd, *J* = 6.5, 4.3 Hz, 1 H, H-9), 3.59 (dd, *J* = 6.6, 3.7 Hz, 1 H, H-14), 2.35–2.49 (m, 2 H, H-13), 1.71 (d, *J* = 4.5 Hz, 3 H, H-19), 1.40 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.06 (br s, 21 H, TIPS), 0.91 (s, 3 H, CH_3), 0.90 (s, 9 H, *t*-C_4H_9, TBDMS), 0.89 (s, 3 H, CH_3'), 0.05 (s, 3 H, CH_3, TBDMS), 0.01 (s, 3 H, CH_3, TBDMS).

^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 160.48 (C_q, C-1), 146.94 (C_q, C-4), 144.29 (CH, C-3), 142.76 (CH, C-8), 138.15 (CH, C-12), 134.56 (C_q, C-2), 131.82 (CH, C-17/C-18), 127.87 (CH, C-17/C-18), 122.44 (CH, C-11), 111.81 (CH, C-7), 90.07 (C_q, C-5/C-6), 79.27 (CH, C-14/C-16), 77.61 (C_q, C-5/C-6), 76.53 (CH, C-14/C-16), 61.48 (OCH_2CH_3), 57.45 (CH, C-9), 55.59 (CH, C-10), 44.69 (C_q, C-15), 31.64 (CH_2, C-13), 26.14 (CH_3, TBDMS), 20.30 (CH_3), 19.97 (CH_3'), 18.39 [$C(CH_3)_3$, TBDMS], 18.36 (CH_3, TIPS), 18.23 (CH_3, TIPS), 17.74 (CH_3, C-19), 14.23 (OCH_2CH_3), 12.80 (CH, TIPS), –3.00 (CH_3, TBDMS), –4.00 (CH_3, TBDMS).

ESI-MS: *m*/*z* calcd for $C_{38}H_{63}NNaO_6Si_2$: 708.4092; found: 708.4059.

Acknowledgment

We are grateful to the Innovation Campaign of the University of Hannover, the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for support.

References

(1) Jansen, R.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann.* **1994**, 759.
(2) (a) Elnakady, Y. A. *PhD Thesis*; TU Braunschweig: Germany, **2001**. (b) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiotics* **1995**, *48*, 31.

(3) (a) Walsh, C. T. *ChemBioChem* **2002**, *3*, 124. (b) Staunton, J.; Weisman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (c) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63.
(4) Independently, Meyers et al. pursued a similar approach in their pioneering work toward the southern segment of disorazole A_1 and the C_2-symmetric disorazole C_1: (a) Hillier, M. C.; Price, A. T.; Meyers, A. I. *J. Org. Chem.* **2001**, *66*, 6037. (b) Hillier, M. C.; Park, D. H.; Price, A. T.; Ng, R.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 2821.
(5) Hartung, I. V.; Niess, B.; Haustedt, L. O.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3239.
(6) *trans*-Cinnamamide was prepared on a large scale in 89% yield from inexpensive *trans*-cinnamic acid chloride with $(Me_3Si)_2NH$: Pellegata, R.; Italia, A.; Villa, M.; Palmisano, G.; Lesma, G. *Synthesis* **1985**, 517.
(7) Ethyl lactate was converted into α-bromoethyl pyruvate by reacting with NBS in CCl_4: Kruse, P. F. Jr.; Geurkink, N.; Grist, K. L. *J. Am. Chem. Soc.* **1954**, *76*, 5796.
(8) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496.
(9) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.
(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(11) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *14*, 3769.
(12) (a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151.
(13) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (c) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.
(14) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
(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.
(16) Epoxy alcohol **13** was prepared from *cis*-butene diol by mono PMB protection and Sharpless epoxidation (99% ee, 75% overall yield): (a) Zhi-min, W.; Wei-shan, Z.; Guo-giang, L. *Tetrahedron Lett.* **1985**, *26*, 6221. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(17) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 2535.
(18) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.
(19) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.
(20) Quantified by conversion to the Mosher ester.
(21) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
(22) The corresponding C16 MOM and SEM ethers were not sufficiently stable under standard halogenation conditions.
(23) Smith, A. B. III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.
(24) Smith, A. B. III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.
(25) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694.
(26) (a) Corey, E. J.; Marfat, A.; Munroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077. (b) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436. (c) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.
(27) (a) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (c) Nicolaou, K. C.; Bella, M.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3495.
(28) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Pagel, M. *Tetrahedron Lett.* **1998**, *39*, 8023.