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Synthetic studies toward the disorazoles: synthesis of a masked northern half of disorazole D_1 and a cyclopropane analog of the masked northern half of disorazole A_1

Lars Ole Haustedt, Sreeletha B. Panicker, Mike Kleinert, Ingo V. Hartung, Ulrike Eggert, Barbara Niess and H. M. R. Hoffmann*

Department of Organic Chemistry, University of Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

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Dedicated to Professor K. C. Nicolaou with respect and admiration

Abstract—The synthesis of a masked northern half of the natural product disorazole D_1 and a cyclopropane analog of the masked northern half of disorazole A_1 is described. The synthesis involves in both cases as key steps a *Z*-selective Wittig olefination and a Sonogashira cross-coupling reaction.

1. Introduction

The disorazoles comprise a family of 29 closely related macrodiolides which were isolated in 1994 from the myxobacterium *Sorangium cellulosum* by Höfle and co-workers (Fig. 1).[1] Disorazole A_1 initiates decay of microtubules in subnanomolar concentration and arrests the cell cycle in the G2/M phase.[2] Disorazole A_1 binds irreversibly to the vinblastin binding site of tubulin.[3] For the cryptophycines,[4] maytansine[5] and rhizoxin,[6] which are epoxide bearing macrocycles, an irreversible binding to the vinblastine binding site of tubulin by way of nucleophilic epoxide opening was discussed. As the role of the epoxide moiety of disorazole A_1 is to date unknown there is a great need for epoxide analogs which mimic either electronic and/or steric behavior (e.g. hydrogen bond acceptor, conformational clasp). In SAR studies on the epothilones[7] and radicicols[8] a cyclopropane was used as substitute for the labile epoxide moiety, leading to more stable derivatives of the natural products with comparable bioactivity profiles. In this context, it is of interest to investigate if the natural relatives of disorazole A_1 without the C9–C10 epoxide are bioactive as well.

Due to their extraordinary biological activity in combination with a synthetically demanding array of double bonds and oxygen functionality the disorazoles are a challenging target for total synthesis. The ensemble of a polyketide chain with a masked amino acid in form of an oxazole may be biosynthesized by a PKS/NRPS assembly line.[9] To investigate some of these aspects we started a program toward the synthesis of a masked northern half of disorazole D_1 as well as a cyclopropane analog of the masked northern half of disorazole A_1.

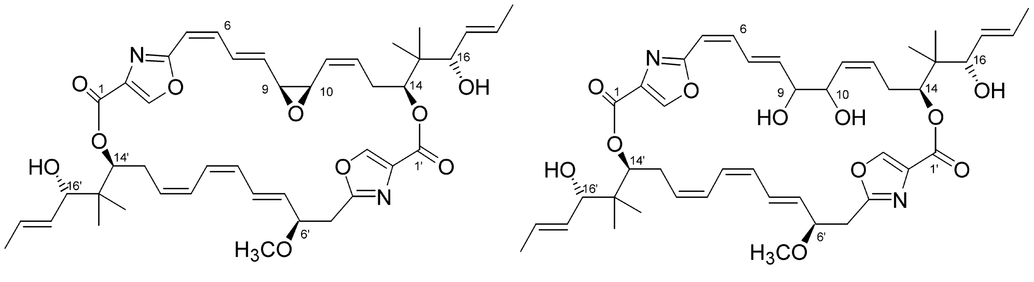

Figure 1. Disorazole A_1 and disorazole D_1.

Keywords: disorazoles; macrodiolides; cell cycle modulation; cyclopropane.
* Corresponding author. Tel.: +49-5117624611; fax: +49-5117623011; e-mail: hoffmann@mbox.oci.uni-hannover.de

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2. Results and discussion

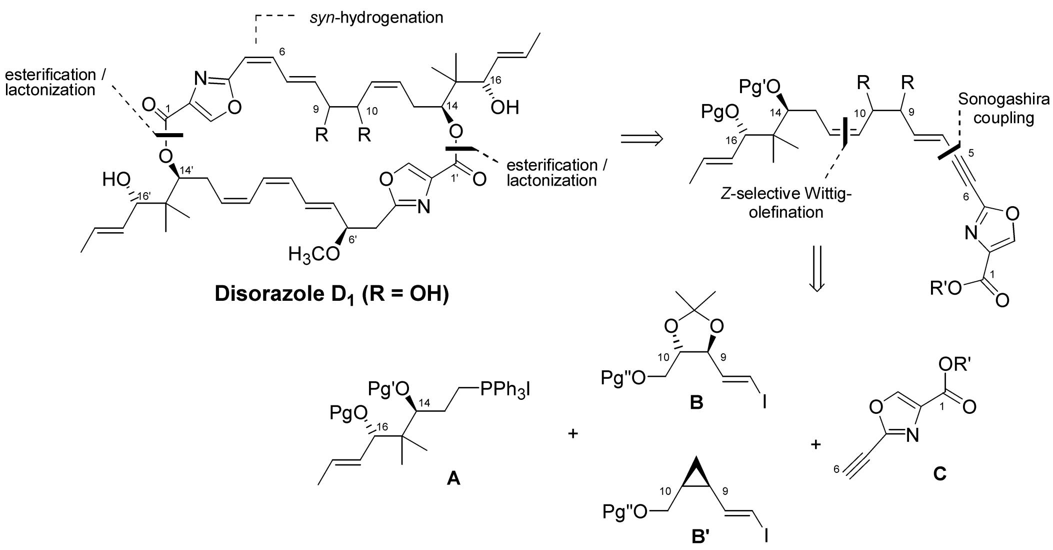
2.1. Retrosynthesis

Our retrosynthetic analysis of disorazole D_1 is outlined in Scheme 1. The C5–C6 and C11–C12 *Z*-double bonds were thought to be sensitive toward isomerization. Thus, the C5–C6 *Z*-olefin was protected in form of a triple bond. By way of a *syn*-selective hydrogenation and macrodilactonization the disorazole skeleton was planned to be assembled from masked southern and northern halfs.[10] The southern half of disorazole D_1 is identical to that of disorazole A_1. Our synthesis of the masked southern half of disorazole A_1 was published recently.[11] The northern half was thought to be accessible in a convergent and flexible manner by a *Z*-selective Wittig olefination and a Sonogashira cross-coupling reaction necessitating phosphonium salt **A**, vinyl iodide **B** and the oxazole alkyne **C** as synthetic precursors. Our retrosynthetic approach allows a straightforward substitution of vinyl iodide **B** (e.g. with cyclopropane bearing analog **B′**) to access derivatives of the northern half of disorazole A_1 and D_1.[12] The so far unknown absolute stereochemistry of the C9 and C10 stereocenters of the northern half of disorazole D_1 had to be determined by synthesis.[13]

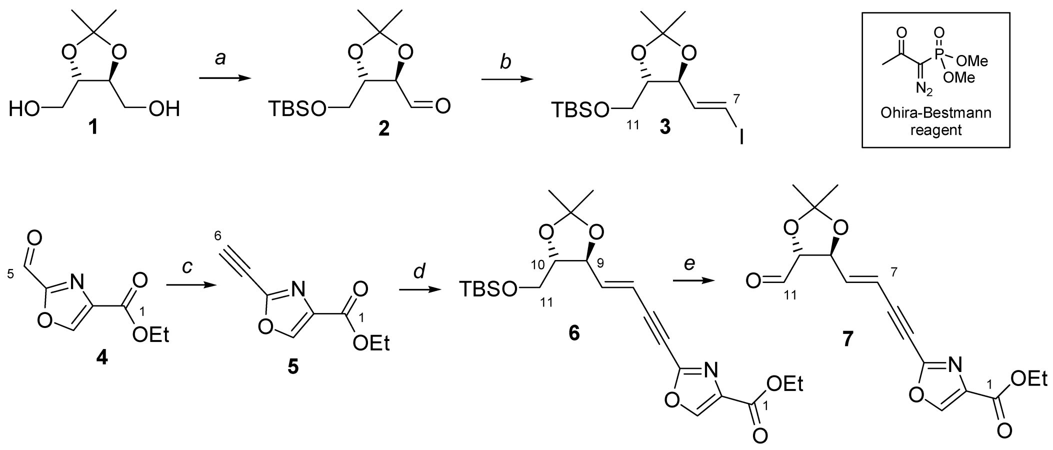
2.2. Synthesis of C1–C11 fragments

The synthesis of the C7–C11 vinyl iodide **B** started from tartaric acid diethyl ester using the Seebach protocol[14] delivering the C_2-symmetric diol **1** (Scheme 2). After monoprotection and oxidation the *E*-configured vinyl iodide **3** was prepared by a Takai reaction.[15]

Oxazole aldehyde **4** was generated using a Hantzsch protocol further modified by Panek.[16] This 2,4-disubstituted oxazole was converted into oxazole alkyne **5** under mild conditions using the Ohira–Bestmann diazophosphono ester.[17] A Sonogashira cross-coupling was used for the assembly of the protected C1–C11 enyne **6**.[18] Best yields were achieved by addition of alkyne **5** after premixing the catalyst, copper salt and vinyl iodide **3** in degassed DMF.



Scheme 1. Retrosynthetic analysis.



Scheme 2. *Reaction conditions*: (a) *i*: NaH, TBSCl, THF, rt, 85%; *ii*: SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0°C, 96%; (b) $CrCl_2$, CHI_3, THF, rt, 14 h, 72%, *E*/*Z*>10:1; (c) EtOH, K_2CO_3, Ohira–Bestmann reagent, 0°C→rt, 50%; (d) $PdCl_2(PPh_3)_2$, CuI, DMF, **3**, Et_3N, rt, 86%; (e) *i*: TBAF, THF, 0°C, 99%; *ii*: Dess–Martin periodinane (2.0 equiv.), py (4.0 equiv.), CH_2Cl_2, 0°C, 75%.

The sensitive aldehyde **7** was generated after silyl deprotection with TBAF and oxidation using buffered Dess–Martin periodinane. Alternative oxidation methods including PCC, Swern or TEMPO/BAIB oxidation protocols led to significantly lower yields.[19]

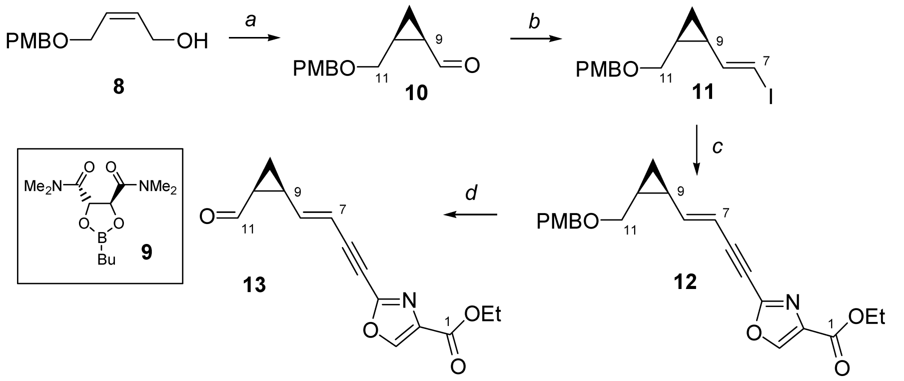
The synthesis of vinyl iodide **B′** commenced with the asymmetric Charette cyclopropanation[20] of mono-PMB protected *cis*-butene diol **8** (Scheme 3). Oxidation of the primary alcohol followed by Takai reaction afforded the *E*-vinyl iodide **11**. Sonogashira cross-coupling[21] of oxazole alkyne **5** and vinyl iodide **11** under conditions as above yielded protected C1–C11 cyclopropane enyne **12** in 48% isolated yield. It is instructive that the more sensitive epoxy analog of **11** afforded the Sonogashira product in at best 15% yield! Removal of the PMB group followed by oxidation of the so formed alcohol using buffered Dess–Martin periodinane provided the cyclopropane carbaldehyde **13**.

2.3. Synthesis of the C12–C19 phosphonium iodide

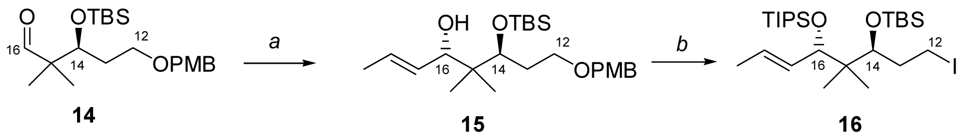
The C12–C19 phosphonium iodide **16** was prepared from the bisprotected triol **15**, which was synthesized from 1,3-propane diol in seven steps as reported in our synthesis of the masked southern half of disorazole A_1 (Scheme 4).[11]

The C17–C19 propenyl side chain was introduced without diastereomeric control by nucleophilic addition of excess *trans*-propenyl lithium formed in situ from *trans*-bromopropene and *t*-butyl lithium below −90°C, to the C16 aldehyde **14**.[11] The desired *anti*-diastereomer was separated from the resulting diastereomeric mixture by chromatography and was further transformed in four steps to the C12–C19 iodide **16** (88% overall yield). As an improvement of our synthesis and for future SAR studies the C16 stereocenter remains to be installed in a stereocontrolled fashion.

In our initial retrosynthetic planning the propenyl side chain was masked as an alkyne. The desired allylic alcohol should be set free by aluminate reduction of the propargylic alcohol **19**.[22] (Scheme 5) To this end, aldehyde **17** was converted into alkynone **18** in quantitative yield by Grignard addition and subsequent Dess–Martin oxidation. For the construction of the C16 stereogenic center both chiral and achiral reducing agents were tested (see Table 1).



Scheme 3. *Reaction conditions*: (a) *i*: Et_2Zn, CH_2Cl_2, 0°C, CH_2I_2, dioxaborolane **9**, 4.5 h, 81%; *ii*: Dess–Martin periodinane (1.5 equiv.), $NaHCO_3$ (4.0 equiv.), CH_2Cl_2, rt, 88%; (b) $CrCl_2$, CHI_3, THF, 0°C, 4 h, 49%; (c) $PdCl_2(PPh_3)_2$, CuI, DMF, **5**, Et_3N, 45 min, rt, 49%; (d) *i*: DDQ (2.5 equiv.), CH_2Cl_2/H_2O, rt; *ii*: Dess–Martin periodinane, $NaHCO_3$ (3 equiv.), rt, 20 min, 71% (from **12**).

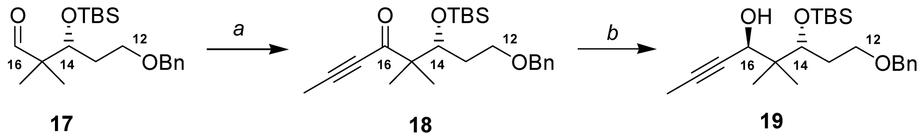


Scheme 4. *Reaction conditions*: (a) *i*: *trans*-1-bromo-propene, *t*-BuLi, Et_2O/THF 1:1, −95°C, 99% (*anti*/*syn*∼1:1); *ii*: separation of diastereomers; (b) *i*: TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 99%; *ii*: DDQ, CH_2Cl_2/H_2O 10:1, 0°C, 99%; *iii*: MsCl, Et_3N, DMAP, THF, 0°C, 99%; *iv*: NaI, $NaHCO_3$, acetone, reflux, 91%.

Table 1.

Reducing conditions	Yield of 19 [%]	*Anti*/*syn*[a]
$LiBH_4$, $CeCl_3$·7 H_2O, MeOH/THF	94	1.0:1.5
(*S*)-Me-CBS (0.5 equiv.), BH_3·DMS (1.0 equiv.), CH_2Cl_2, −20°C	58[b]	5.3:1.0
(*S*)-Me-CBS (1.0 equiv.), catechol borane (2.0 equiv.), CH_2Cl_2, −20°C → rt	66[c]	1.7:1.0
Terashima reagent (2.1 equiv.), Et_2O, −78°C	82	2.0:1.0

[a] Based on ^1H NMR integration.
[b] 35% Recovered starting material.
[c] 28% Recovered starting material.



Scheme 5. *Reaction conditions*: (a) *i*: propynylmagnesium bromide, THF, 0°C, 99% (*anti*/*syn*∼1:1); *ii*: Dess–Martin periodinane, CH_2Cl_2, 0°C →rt, 99%. (b) see Table 1.

Although high levels of 1,2-reduction were achieved under modified Luche reduction conditions[23] (entry 1), only poor diastereoselectivity slightly favouring the *syn*-diastereomer was observed in this case. Competing 1,4-reduction caused by the steric demand of the geminal dimethyl group hampered the application of most other achiral reducing agents (e. g. L-selectride gave the saturated ketone in quantitative yield). CBS-reduction[24] using borane dimethylsulfide complex as stoichiometric reductant provided predominantly the desired *anti*-diastereomer (entry 2), whereas with catechol borane[25] a significant decrease in diastereoselectivity was observed (entry 3). The Terashima reagent[26] led to a 2:1 diastereomeric mixture in high yield also favoring the desired *anti*-diastereomer (entry 4).

Surprisingly, the aluminate reduction of propargylic alcohol **19** with $LiAlH_4$ or Red-Al failed following various published procedures.[27] We speculate that the aluminate is chelated by the C14 oxygen and therefore does not attack the C17/C18 triple bond.

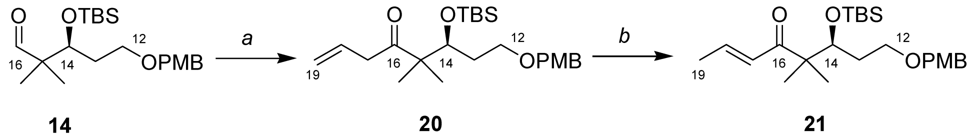
As a further approach to C16 stereocontrol we modified our synthetic strategy by employing enone **21** as substrate for diastereoselective reductions. Enone **21** was readily available from aldehyde **14** by a three step sequence including allylmagnesium bromide addition, oxidation and isomerization to the α-enone (Scheme 6).

The isomerization was best achieved with a stoichiometric amount of DBU, whereas triethylamine required elevated temperature and prolonged reaction time and transition metal catalysts failed to give satisfying yields and *E*-selectivities. Unfortunately, enone **21** was even more susceptible towards 1,4-reduction than the corresponding alkynone **18**. For example, reduction of **21** using the aforementioned modified Luche conditions ($LiBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH) produced a complex mixture (58% 1,2-reduction accompanied by 24% 1,4-reduction) slightly favouring the *syn*-diastereomer (*anti*/*syn*=1.0:1.6). L-Selectride, $LiAlH_4$, $LiHBEt_3$ or $Zn(BH_4)_2/CeCl_3{\cdot}7H_2O$ delivered predominantly to exclusively the 1,4-reduction product. Similarly, the saturated ketone was produced in 84% yield under Terashima conditions. Employing the (*S*)-Me-CBS reagent[28] enone **21** (natural C14 configuration) was converted with high diastereoselectivity into *syn*-diol **22** (Scheme 7). Stereoisomeric, enone **24** (non-natural C14 configuration) was converted under similar reaction conditions into *anti*-diol **26**. In the latter case the diastereoselectivity was significantly lower which might be due to a matched-mismatched incident. Attempts to convert the natural enone **21** into the natural *anti*-diol **23** were unrewarding as in reductions of **21** with the (*R*)-Me-CBS reagent the 1,4-reduction product was formed predominantly!

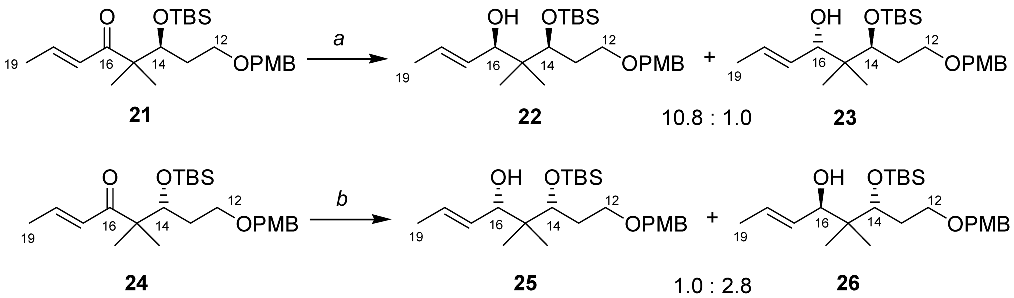
In conclusion, all four possible C12/C19 stereoisomers (**22**, **23**, **25** and **26**) were synthesized either by direct propenyl lithium addition to a C16 aldehyde and subsequent separation of diastereomers or by diastereoselective reduction of a C12–C19 α-enone.

2.4. Fragment assembly via *Z*-selective Wittig olefination

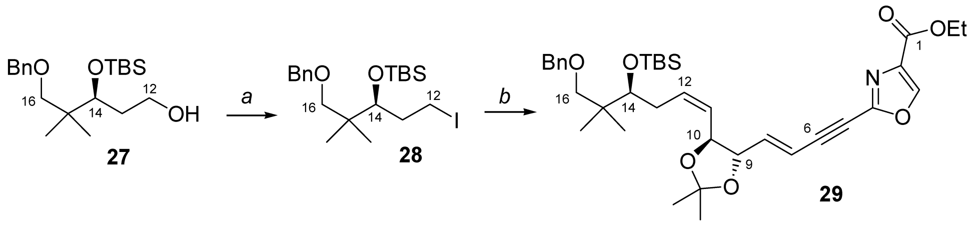
The performance of the *Z*-selective Wittig reaction for fragment assembly was critical for the success of our synthetic plan. Therefore we prepared a less complex



Scheme 6. *Reaction conditions*: (a) *i*: allylmagnesium bromide, THF, 0°C; *ii*: Dess–Martin periodinane, CH_2Cl_2, 0°C→rt; (b) DBU (1.1 equiv.), CH_2Cl_2, 0°C→rt, 75% (from **14**), *E*/*Z*>40:1.



Scheme 7. *Reaction conditions*: (a) (*S*)-Me-CBS reagent (2.1 equiv.), $BH_3{\cdot}DMS$ (5.0 equiv.), THF, −30°C, 3 h, 78% (+17% 1,4-reduction); (b) (*S*)-Me-CBS reagent (2.0 equiv.), $BH_3{\cdot}DMS$ (5.0 equiv.), THF, −30→−20°C, 6 h, 72% (+18% 1,4-reduction).



Scheme 8. *Reaction conditions*: (a) *i*: MsCl, DMAP, Et_3N, THF, 0°C, 93%; *ii*: NaI, acetone, $NaHCO_3$, reflux, 3 h, 78%; (b) *i*: PPh_3, *i*-Pr_2NEt, 90°C, 18 h; *ii*: LiHMDS, THF/HMPA 10:1, **7**, −78°C→rt, 1 h, 37% (from **28**), *Z*/*E* 2.8:1.

phosphonium iodide for model reactions. Once generated, iodide **28** might also be useful for the synthesis of analogs of the northern halfs of disorazole A_1 and D_1 for SAR investigations.

The preparation of the known alcohol **27**[29] involved as key step a Brown asymmetric allylation.[30] After silylation and ozonolysis, the iodide **28** was again prepared from alcohol **27** via the corresponding mesylate (Scheme 8).

Attempts at generating the phosphonium salt by reaction of iodide **28** in a neat triphenylphosphine melt and following chromatographic purification resulted in low yields. By using Hünig's base as an additive and increasing the pressure (sealed flask, 90°C) the phosphonium salt was formed smoothly. Conveniently, the phosphonium iodide could be used after removal of the excess triphenylphosphine with *n*-pentane without further purification steps.

Conditions for *Z*-selective Wittig olefinations of unstabilized phosphonium salts with highly functionalized aldehydes are strongly substrate dependent.[31] After some experimentation it was found that the combination of LiHMDS and HMPA as co-solvent provided the C1–C16 fragment **29** in 37% yield starting from iodide **28** (Scheme 8).

Analogously, iodide **16** was converted into the corresponding phosphonium iodide. The ylide was again generated by action of LiHMDS in THF/HMPA and after addition of aldehyde **7** the masked northern half of disorazole D_1 **30** was isolated in 32% yield starting from iodide **16** (Scheme 9). To our delight the *Z*-selectivity (*Z*/*E* 10:1) was much higher than observed with the model system. Under the same conditions the cyclopropane analog of the northern half of disorazole A_1 **31** was generated in 40% yield starting from iodide **16** (*Z*/*E*≥5:1).

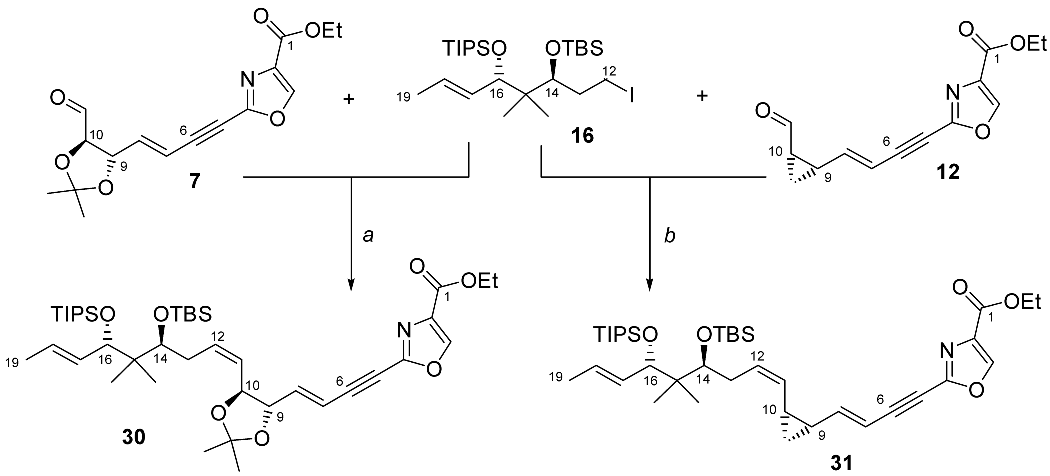
3. Conclusions

A masked northern half of disorazole D_1 and a cyclopropane analog of the masked northern half of disorazole A_1 were constructed by chemical synthesis. Both halfs were assembled in a flexible and convergent manner using a Sonogashira cross-coupling and a *Z*-selective Wittig olefination. Our strategy is well suited for the synthesis of various derivatives required for SAR studies of the disorazoles.

4. Experimental

4.1. General

Infrared spectra were recorded on a Perkin–Elmer 1710 infrared spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVS 400 and Bruker AVM 500 spectrometer in deuterated chloroform or acetone with tetramethylsilane as internal standard. ^1H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (0 ppm) as internal standard. The following abbreviations are used to describe spin multiplicity: s=singlet, br s=broad singlet, d=doublet, t=triplet,



Scheme 9. *Reaction conditions*: (a) *i*: PPh_3, *i*-Pr_2NEt, 90°C, 18 h; *ii*: LiHMDS, THF/HMPA 10:1, −78°C→rt, 32%, *Z*/*E* 10:1; (b) *i*: PPh_3, *i*-Pr_2NEt, 90°C, 20 h; *ii*: LiHMDS, HMPA/THF 10:1, −78°C→rt, 40%, *Z*/*E*≥5:1.

q=quartet, m=multiplet, dd=doublet of doublets, etc. 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 $^1H-^1H$-COSY and HMQC experiments. 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.

4.1.1. Vinyl iodide 3. To 2.73 g (17.04 mmol) SO_3·py in 12.8 mL of CH_2Cl_2 were added 3 mL of DMSO and Et_3N (3 mL), followed by 1.17 g (4.26 mmol) of alcohol **1** in 5 mL of CH_2Cl_2 at 0°C. After 4 h at 0°C the reaction was quenched with sat. NH_4Cl solution. The mixture was extracted with MTB ether. The combined organic layers were dried (Na_2SO_4). The crude product was purified by column chromatography (CH/MTBE 4:1) to furnish 1.12 g (96%) of aldehyde **2** as a slightly yellow oil. Due to its instability, aldehyde **2** was immediately used for the Takai reaction. ^1H NMR (400 MHz, $CDCl_3$, TMS): 9.80 (d, J=1.6 Hz, 1H, H-8); 4.35 (dd, J=7.3, 1.6 Hz, 1H, H-9); 4.17 (dt, J=7.3, 4.4 Hz, 1H, H-10); 3.83 (d, J=4.4 Hz, 2H, H-11); 1.50 (s, 3H, C(CH_3)$_2$); 1.45 (s, 3H, C(CH_3)$_2$); 0.93 (s, 9H, TBS); 0.12 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 200.8 (C_q, C-8); 111.0 (CH, C-9); 109.0 (C_q, C(CH_3)$_2$); 81.9 (CH, C-10); 62.9 (CH_2, C-11); 26.8 (CH_3, C(CH_3)$_2$; 26.3 (CH_3, C(CH_3)$_2$); 18.3 (CH_3, TBS); 13.8 (C_q, TBS); −5.5 (CH_3, TBS).

To a suspension of 1.0 g (8.14 mmol) of $CrCl_2$ in 32 mL of THF a mixture of 802 mg (2.04 mmol) of CHI_3 and 446 mg (1.63 mmol) of aldeyhde **2** in 6.4 mL of THF was added dropwise. After being stirred over night at rt the reaction mixture was quenched with water. The mixture was extracted with MTB ether and the combined organic layers were dried (Na_2SO_4). The crude product was purified by column chromatography (CH/MTBE 20:1) to yield 465 mg (72%) of compound **3** as an orange oil. $[\alpha]_D^{20}=-11.59°$ (c=0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 6.49 (dd, J=14.5, 6.3 Hz, 1H, H-8); 6.49 (dd, J=14.5, 0.8 Hz, 1H, H-7); 4.32 (dt, J=6.4, 0.8 Hz, 1H, H-9); 3.8 (m, 2H, H-11); 3.70 (m, 1H, H-10); 1.40 (s, 6H, C(CH_3)$_2$); 0.89 (s, 9H, TBS); 0.07 (s, 6H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 143.3 (CH, C-8); 109.5 (Cq, C(CH_3)$_2$); 80.6 (CH, C-10); 80.3 (CH, C-9); 79.5 (CH, C-7); 62.6 (CH, C-11); 26.9 (CH_3, C(CH_3)$_2$); 26.9 (CH_3, C(CH_3)$_2$); 25.9 (CH_3, TBS); 25.8 (CH_3, TBS); 25.8 (CH_3, TBS); 18.3 (C_q, TBS); −5.3 (CH_3, TBS); −5.3 (CH_3, TBS); IR (neat, cm^{-1}): 2986, 2954, 2929, 2857, 1611, 1471, 1463, 1371, 1330, 1252, 1163, 1144, 1092, 1034, 1006, 944, 836, 812, 777, 673; MS: m/z (%) 397 (M^+-1; 3); 383 (18); 297 (13); 283 (100); 253 (19); 224 (14); 215 (21); 195 (9); 185 (35); 156 (78); 141 (44); 126 (73).

4.1.2. Oxazole alkyne 5. 150 mg (0.89 mmol) of oxazole aldehyde **4** was dissolved in 6 mL of EtOH and treated subsequently with 241 mg (1.75 mmol) of K_2CO_3 and 256 mg (1.33 mmol) of the Ohira–Bestmann reagent at 0°C. Having been stirred over night, the reaction was treated with 1N HCl. The mixture was extracted with MTB ether, the organic layers were dried (Na_2SO_4). The crude product was purified by column chromatography eluting with CH/MTBE 4:1 to yield 70.5 mg (50%) of a colourless solid. mp: 73°C; ^1H NMR (400 MHz, $CDCl_3$, TMS): 8.18 (s, 1H, H-3); 4.37 (q, J=7.1 Hz, 2H, H-1′); 3.27 (s, 1H, H-6); 1.37 (t, J=7.1 Hz, 3H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 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 (CH_2, C-1′); 14.2 (CH_3, C-2′); IR (neat, cm^{-1}): 3199, 3163, 3125, 2994, 2908, 2126, 1716, 1575, 1533, 1476, 1449, 1367, 1312, 1299, 1211, 1154, 1114, 1022, 984, 946, 867, 830, 771, 748, 712, 611, 552; MS: m/z (%) 166 (M^++1; 12); 165 (M^+; 84); 138 (22); 137 (100); 120 (56); 109 (18); 93 (12); 81 (11); HRMS: calcd for $C_8H_7NO_3$: 165.0426; found: 165.0427.

4.1.3. Enyne 6. 25 mg of $PdCl_2(PPh_3)_2$ (0.035 mmol) and 13.4 mg of CuI (0.070 mmol) were dissolved in degassed DMF (3.4 mL), stirred for 15 min at rt and treated dropwise with 278 mg (0.70 mmol) of vinyl iodide **3** in DMF (3.5 mL). After addition of 3.4 mL Et_3N it was stirred for another 45 min. Finally 150 mg (0.91 mmol) of alkyne **5** in DMF (3.5 mL) were added slowly and stirring was continued for 7 h. The reaction was quenched with a solution of sat. NH_4Cl, extracted with MTB ether and the organic layers were dried (Na_2SO_4). Purification by column chromatography (CH/MTBE 20:1) furnished enyne **6** (85%) as yellow oil. $[\alpha]_D^{20}=-5.61°$ (c=0.89, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 8.15 (s, 1H, H-3); 6.43 (dd, J=15.9, 5.5 Hz, 1H, H-8); 5.97 (dd, J=15.9, 1.5 Hz, 1H, H-7); 4.43 (dt, J=7.5, 1.5 Hz, 1H, H-9); 4.34 (q, J=7.2 Hz, 2H, H-1′); 3.72 (m, 1H, H-10); 3.71 (m, 2H, H-12) 1.36 (s, 3H, O_2C(CH_3)$_2$); 1.35 (s, 3H, O_2C(CH_3)$_2$); 1.32 (t, J=7.2 Hz, 3H, H-2′); 0.86 (s, 9H, Si(CH_3)$_2$)C(CH_3)$_3$; 0.03 (s, 6H, Si(CH_3)$_2$)C(CH_3)$_3$; ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 160.4 (C_q, C-1), 147.0 (C_q, C-4); 145.7 (CH, C-8); 144.2 (CH, C-3); 134.5 (C_q, C-2); 109.8 (C_q, O_2C(CH_3)$_2$); 108.7 (CH, C-7); 90.5 (C_q, C-6); 80.8 (CH, C-10); 78.4 (CH, C-9); 76.8 (C_q, C-5); 62.7 (CH_2, C-11); 61.3 (CH_2, C-1′); 26.9, 26.8 (CH_3, O_2C(CH_3)$_2$); 26.7 (CH_3, O_2C(CH_3)$_2$); 25.8 (CH_3, TBS); 18.3 (C_q, TBS); 14.2 (CH_3, C-2′); −5.4 (CH_3, TBS), −5.5 (CH_3, TBS); IR (neat, cm^{-1}): 3151, 2985, 2954, 2930, 2857, 2219, 2131, 1746, 1723, 1572, 1543, 1463, 1370, 1463, 1370, 1331, 1305, 1237, 1141, 1112, 1024, 980, 957, 925, 834, 775, 713, 670, 612, 568, 540; MS: m/z (%): 435 (M^+; 20.0); 420 (26.2); 378 (17.5); 320 (100.0); 290 (43.5); 246 (25.3); 204 (72.6); 117 (17.1); HRMS: calcd for $C_{22}H_{33}N_1O_6Si$: 435.2078; found: 435.2077.

4.1.4. Aldehyde 7. To a solution of 720 mg (1.52 mmol) of silyl ether **6** in 4 mL of THF was added dropwise 1.82 mL (1.824 mmol) of TBAF (1M in THF) at 0°C. After 15 min the reaction mixture was quenched with water, and the mixture was extracted with MTB ether. Drying (Na_2SO_4) and purification by column chromatography (CH/MTBE 2.5:1) afforded 483 mg (99%) of the alcohol as yellow oil. $[\alpha]_D^{20}=-0.85°$ (c=0.89, $CHCl_3$); ^1H NMR:(400 MHz, $CDCl_3$, TMS): 8.17 (s, 1H, H-3); 6.38 (dd, J=15.9, 6.0 Hz, 1H, H-8); 5.98 (dd, J=15.9, 1.4 Hz, 1H, H-7); 4.45 (dt, J=6.0, 1.4 Hz, 1H, H-9); 4.35 (q, J=7.0 Hz, 2H, H-1′); 3.80 (m, 2H, H-11); 3.64 (m, 1H, H-10); 2.09 (bs, 1H, OH); 1.42, (s, 3H, O_2C(CH_3)$_2$); 1.41 (s, 3H, O_2C(CH_3)$_2$); 1.34 (t, J=7.2 Hz, 3H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 160.5 (C_q, C-1); 146.9 (C_q, C-4); 144.8 (CH, C-8); 144.3 (CH, C-3); 134.5 (C_q, C-2); 110.0 (C_q, O_2C(CH_3)$_2$);

109.7 (CH, C-7); 90.1 (C_q, C-6); 80.8 (CH, C-9); 77.2 (C_q, C-5); 76.8 (CH, C10); 61.4 (CH_2, C-11); 60.7 (CH_2, C-1′); 26.9 (CH_3, $O_2C(CH_3)_2$); 26.9 (CH_3, $O_2C(CH_3)_2$); 14.2 (CH_3, C-2′); IR (neat, cm^{-1}): 3435, 3153, 2984, 2932, 2877, 2662, 2218, 2091, 1724, 1636, 1573, 1543, 1507, 1455, 1371, 1333, 1305, 1236, 1163, 1147, 1110, 1051, 1021, 981, 957, 926, 899, 856, 830, 770, 713, 669; MS: *m/z* (%) 321 (M^+, 2.1); 324 (2.4); 307 (36.7); 276 (36.5); 264 (40.3); 232 (35.3); 192 (100); 187 (35.7); 158 (43.1); HRMS: calcd for $C_{16}H_{20}N_1O_6$ (M^+ +1): 321.1212; found 322.1290.

163 mg (0.507 mmol) of this alcohol was dissolved in CH_2Cl_2 (5 mL) at 0°C. After addition of 165 μL (2.03 mmol) of pyridine and 421 mg (1.014 mmol) of Dess–Martin periodinane the reaction mixture was stirred for 6 h at 0°C. Finally the mixture was diluted with MTB ether, treated with sat. NH_4Cl solution, and extracted with MTB ether. The combined organic layers were dried (Na_2SO_4), the crude product was purified by column chromatography (CH/MTBE 1:1) to yield 75% of aldeyhde **7** as colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): 9.76 (s, 1H, H-11); 8.18 (s, 1H, H-3); 6.41 (dd, *J*=15.9, 5.7 Hz, 1H, H-8); 6.29 (dd, *J*=15.9, 1.5 Hz, 1H, H-7); 4.59 (dt, *J*=7.3, 1.6 Hz, 1H, H-9); 4.35 (q, *J*=7.2 Hz, 2H, H-1′); 4.09 (dd, *J*=7.3, 1.6 Hz, 1H, H-10); 1.49 (s, 3H, $O_2C(CH_3)_2$); 1.44 (s, 3H, $O_2C(CH_3)_2$); 1.37 (t, *J*=7.2 Hz, 3H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 199.7 (CH, C-11); 160.4 (C_q, C-1); 146.8 (C_q, C-4); 144.3 (CH, C-3); 143.5 (CH, C-8); 134.5 (C_q, C-2); 112.1 (C_q, $O_2C(CH_3)_2$); 110.1 (CH, C-7); 89.7 (CH, C-10); 84.1 (CH, C-9); 77.6 (C_q, C-6); 76.5 (C_q, C-5); 61.5 (CH_2, C-1′); 26.6 (CH_3, $O_2C(CH_3)_2$); 26.1 (CH_3, $O_2C(CH_3)_2$); 14.2 (CH_3, C-2′).

4.1.5. Aldehyde 10. To a solution of diethyl zinc (9.3 mL, 9.3 mmol, 1M in heptane) in 17 mL of CH_2Cl_2 at 0°C was added 4.33 g of CH_2I_2 (18.4 mmol) dropwise and stirred for 10 min. To this mixture was added rapidly a preformed solution of the dioxaborolane complex[20] (4.8 mmol) and mono-PMB protected *cis*-1,4-butenediol (4.2 mmol) in 30 mL of CH_2Cl_2. The reaction mixture was allowed to stir under an argon atmosphere for 4.5 h and was quenched with sat. NH_4Cl solution. The two layers were separated and the aqueous layer was washed several times with CH_2Cl_2. The organic extracts were pooled, washed with brine and dried (Na_2SO_4). After removal of the solvent the residue was purified by silica gel column chromatography (1:1 CH/MTBE) to afford 755 mg (81%) of cyclopropane alcohol as colorless oil.

To 1.02 g of cyclopropane alcohol (4.6 mmol) in 15 mL of CH_2Cl_2 were added 2.82 g of Dess–Martin periodinane (6.95 mmol) and 1.55 g of $NaHCO_3$ (18.4 mmol) and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with CH_2Cl_2. After addition of sat. $NaHCO_3$ solution, and $Na_2S_2O_3$ (30 mL, 10% solution), the resulting mixture was stirred for 1 h at rt. The aqueous phase was extracted with MTB ether and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (CH/MTBE 2:1) to afford 890 mg (88%) of aldehyde **10**. $[\alpha]_D^{20}=-22.7°$ (*c*=1.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 9.41 (d, *J*=4.6 Hz, 1H, H-8), 7.28–7.20 (m, 2H, PMB), 6.90–6.85 (m, 2H, PMB), 4.41–4.37 (m, 2H, PMB), 3.80 (dd, *J*=10.4, 5.5 Hz, 1H, $H-11_a$), 3.79 (s, 3H, OMe), 3.39 (dd, *J*=10.4, 8.4 Hz, 1H, $H-11_b$), 2.07–2.01 (m, 1H, H-9), 1.90–1.80 (m, 1H, H-10), 1.33–1.21 (m, 2H, C_p–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): 200.51 (CH, C-8), 159.26 (C_q, PMB), 130.01 (CH, PMB), 129.33 (C_q, PMB), 113.79 (CH, PMB), 72.64 (CH_2, PMB), 67.54 (CH_2, C-11), 55.21 (OMe), 26.80 (CH, C-9), 23.59 (CH, C-10), 12.33 (CH_2, C_p–CH_2); IR (neat, cm^{-1}): 2837, 2359, 1698, 1612, 1585, 1511, 1375, 1301, 1244, 1173, 1078, 1031; MS: *m/z* (%) 220 (M^+; 6.22), 164 (4.12), 137 (51.68), 121 (100.0), 109 (7.91), 91 (8.71), 77 (26.12), 66 (3.16); HRMS: calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1098.

4.1.6. Vinyl iodide 11. 1.96 g of $CrCl_2$ (15.9 mmol) was suspended in dry THF (11 mL) and cooled to 0°C. To this slurry was added a solution of 433 mg of aldehyde **10** (2.27 mmol) and 1.87 g of CHI_3 (4.77 mmol) in 15 mL of THF. The resulting mixture was stirred at 0°C for 4 h, diluted with water and extracted with MTB ether. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography affording 383 mg (49%) of the *E*-vinyl iodide. $[\alpha]_D^{20}=+18.4°$ (*c*=1.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 7.25–7.24 (m, 2H, PMB), 6.91–6.81 (m, 2H, PMB), 6.21 (dd, *J*=14.3, 8.5 Hz, 1H, H-8), 6.04 (d, *J*=14.6 Hz, 1H, H-7), 4.50–4.38 (m, 2H, PMB), 3.81 (s, 3H, OMe), 3.56 (dd, *J*=10.2, 6.0 Hz, 1H, $H-11_a$), 3.24 (dd, *J*=10.1, 8.4 Hz, 1H, $H-11_b$), 1.69–1.61 (m, 1H, H-10), 1.44–1.34 (m, 1H, H-9), 1.01–0.95 (m, 1H, C_p–H_a), 0.49–0.45 (m, 1H, C_p–H_b); ^{13}C NMR (100 MHz, $CDCl_3$): 159.21 (C_q, PMB), 144.90 (CH, C-8), 130.34 (C_q, PMB), 129.34 (CH, PMB), 113.91 (CH, PMB), 73.38 (CH, C-7), 72.48 (CH_2, PMB), 69.41 (CH_2, C-11), 55.28 (OMe), 21.83 (CH, C-10), 18.25 (CH, C-9), 10.51 (CH_2, C_p–CH_2); IR (neat, cm^{-1}): 2854, 2360, 1611, 1510, 1462, 1301, 1244, 1172, 1078, 1033, 943, 817; MS: *m/z* (%) 344 (M^+; 5.88), 313 (5.15), 273 (1.38), 217 (32.68), 199 (9.04), 175 (28.20), 147 (7.50), 121 (100), 91 (9.75), 77 (25.55); HRMS: calcd for $C_{14}H_{17}O_2$: 344.0273; found: 344.0274.

4.1.7. Cyclopropane enyne 12. 14.3 mg of CuI (0.075 mmol) and 529.8 mg of $Pd(PPh_3)_2Cl_2$ (0.75 mmol) were taken up in 3.5 mL of degassed DMF and stirred for 20 min at rt. 258 mg of vinyl iodide **11** (0.75 mmol) in 3.5 mL of DMF and Et_3N (3.5 mL) were added and the resulting mixture was stirred at rt under an atmosphere of argon for 3–4 h before adding alkyne **5** (1.13 mmol) in 3.5 mL of DMF (slow addition). The reaction mixture was stirred over night, quenched with sat. NH_4Cl solution and extracted with MTB ether. The organic extracts were pooled, washed with brine and dried (Na_2SO_4). The residue was purified by column chromatography (CH/MTBE 2:1) to obtain 141 mg (49%) of the product as viscous oil. $[\alpha]_D^{20}=+30.0°$ (*c*=1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 8.18 (s, 1H, H-3), 7.27–7.25 (m, 2H, PMB), 7.91–6.89 (m, 2H, PMB), 6.15 (dd, *J*=15.7, 9.8 Hz, 1H, H-8), 5.77 (d, *J*=15.7 Hz, 1H, H-7), 4.49–4.40 (m, 2H, PMB), 4.37 (q, *J*=7.1 Hz, 2H, H-1′), 3.70 (s, 3H, OCH_3), 3.60 (dd, *J*=10.2, 6.0 Hz, 1H, $H-11_a$), 3.24 (dd, *J*=10.2, 8.0 Hz, 1H, $H-11_b$), 1.77–1.74 (m, 1H, H-9), 1.59–1.53 (m, 1H, H-10), 1.38 (t, *J*=7.1 Hz, 3H, H-2′), 1.17–1.12 (m, 1H,

C_p–H_a), 0.62–0.58 (m, 1H, C_p–H_b); ^{13}C NMR (100 MHz, $CDCl_3$): 160.91 (C_q, C-1), 159.57 (C_q, PMB), 150.75 (CH, C-8), 147.85 (C_q, C-4), 144.21 (CH, C-3), 134.71 (C_q, C-2), 130.40 (C_q, PMB), 129.67 (CH, PMB), 114.71 (CH, PMB), 106.82 (CH, C-7), 92.44 (C_q, C-6), 75.50 (C_q, C-5), 72.80 (CH_2, PMB), 69.44 (CH_2, C-11), 61.64 (CH_2, C-1′), 55.58 (OCH_3), 20.81 (CH, C-10), 20.44 (CH, C-9), 14.5 (CH_3, C-2′), 13.20 (CH_2, C_p–CH_2); IR (neat, cm^{-1}): 2211, 1741, 1721, 1612, 1573, 1541, 1511, 1368, 1333, 1297, 1172, 1143, 1111, 1079, 1024, 977, 950, 925, 818; MS: *m/z* (%) 381 (M^+; 4.37); 279 (80.09); 261 (4.38); 239 (2.61); 218 (4.08); 198 (5.90); 167 (72.46); 149 (100); 121 (91.65); 97 (11.90); 84 (11.94); 71 (51.47); HRMS: calcd for $C_{22}H_{23}NO_5$: 381.1576; found: 381.1575.

4.1.8. Aldehyde 13. To a stirred solution of 64.8 mg of Sonogashira product **12** (0.17 mmol) in 2 mL of a CH_2Cl_2/water mixture (9:1) was added 38.4 mg of DDQ (0.425 mmol) at rt. The reaction mixture was stirred for 30 min (TLC showed absence of starting material), quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. After removal of the solvent the residue was used without further purification for the next step. The crude product was dissolved in CH_2Cl_2 (5 mL), 106 mg of Dess–Martin periodinane (0.25 mmol) and 43 mg of $NaHCO_3$ (0.51 mmol) were added to the solution which was stirred for about 20–30 min. Extraction and purification (MTBE/CH 3:1) afforded 31 mg of aldehyde **13** as brownish yellow liquid (71% over two steps). $[\alpha]_D^{20}=-86.8°$ (c=0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 9.57 (d, J=3.8 Hz, 1H, H-11), 8.19 (s, 1H, H-3), 6.37 (dd, J=15.8, 9.6 Hz 1H, H-8), 5.87 (d, J=15.8 Hz, 1H, H-7), 4.38 (q, J=7.1 Hz, 2H, H-1′), 2.34 (m, 1H, H-10), 2.32–2.24 (m, 1H, H-9), 1.64–1.61 (m, 1H, C_p–H_a), 1.56–1.53 (m, 1H, C_p–H_b), 1.38 (t, J=7.1 Hz, 3H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 199.03 (CH, C-11), 160.56 (C_q, C-1), 147.19 (C_q, C-4), 145.94 (CH, C-8), 144.17 (CH, C-3), 134.42 (C_q, C-2), 108.94 (CH, C-7), 90.89 (C_q, C-6), 76.22 (C_q, C-5), 61.43 (CH_2, C-1′), 30.74 (CH, C-10), 27.15 (CH, C-9), 15.87 (CH_2, C_p–CH_2), 14.25 (CH_3, C-2′); IR (neat, cm^{-1}): 2924, 2854, 2214, 1721, 1542, 1370, 1296, 1240, 1145, 1110, 1018, 957, 832, 769, 713; MS: *m/z* (%) 259 (M^+; 10.0), 258 (M^+-1;37.1), 230 (37.7), 202 (23.4), 185 (29.2), 157 (47.3), 128 (100.0), 90 (51.4), 77 (54.2); HRMS: calcd for $C_{14}H_{13}NO_4$: 259.0845; found: 259.0820.

4.1.9. Propargylic alcohol 19. *Preparation of the Terashima-Reagent*: In a flame-dried flask fitted with a reflux condenser 104 mg of $LiAlH_4$ (2.74 mmol) were suspended in 3.0 mL of dry Et_2O under a positive pressure of nitrogen. Within 30 min a solution of 490 mg of (−)-*N*-methylephedrine (2.74 mmol) in 8.0 mL of dry Et_2O was added dropwise and the resulting mixture was heated to reflux for 1 h. Subsequently, 0.69 mL of *N*-ethylaniline (5.48 mmol) were added dropwise and the mixture was again heated to reflux for 1 h.

20 mg of alkynone **18** (0.05 mmol) was solved in 0.2 mL of dry Et_2O (0.25 M). At −78°C 0.43 mL of the Terashima reagent (0.25 M in Et_2O; 0.108 mmol) was added dropwise. After 2 h at −78°C the reaction mixture was hydrolyzed with saturated $NaHCO_3$ solution (1 h, rt), extracted with MTB ether, dried (Na_2SO_4) and purified by flash chromatography yielding 16.0 mg (82%) of propargylic alcohol **19** as a colorless oil (2:1 diastereomeric mixture); ^1H NMR (500 MHz, $CDCl_3$, TMS): 7.26–7.36 (m, 5H, OCH_2*Ph*); 4.46–4.52 (m, 2H; O*CH₂*Ph); 4.45 (m, 1H, H-16); 3.81 (dd, J=7.0, 3.3 Hz, 1H, H-14); 3.46–3.62 (m, 2H; H-12); 2.22 (br s, 1H; OH); 2.04 (dtd_{dddd}, J=14.4, 7.7, 3.2 Hz, 1H, H-13a); 1.85 (d, J=2.2 Hz, 3H, H-19); 1.73 (m_{dddd}, 1H, H-13b); 1.06 (s, 3H, Me); 0.89 (s, 3H, Me); 0.88 (s, 9H, TBS); 0.10 (s, 3H, TBS); 0.06 (s, 3H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): 138.34 (C_q, Bn); 128.32 (CH, Bn); 127.59 (CH, Bn); 127.53 (CH, Bn); 81.35 (C_q, C-17/C-18); 78.55 (C_q, C-17/C-18); 76.85 (CH, C-14); 72.86 (CH_2, O*CH₂*Ph); 68.54 (CH, C-16); 67.62 (CH_2, C-12); 42.10 (C_q, C-15); 33.32 (CH_2, C-13); 25.99 (CH_3, TBS); 21.40 (CH_3, Me); 18.38 (CH_3, Me′); 18.18 (C_q, TBS); 13.55 (CH_3, C-19); −4.23 (CH_3, TBS); −4.27 (CH_3, TBS); IR (neat, cm^{-1}): 3451, 3030, 2955, 2918, 2883, 2855, 2116, 1674, 1496, 1471, 1386, 1360, 1253, 1205, 1088, 1027, 1003, 938, 880, 834, 773, 733, 696, 666, 609; MS: *m/z* (%) 333 (M^+-tBu; 2.60), 321 (1.97), 280 (2.28), 279 (8.58), 241 (2.87), 240 (4.53), 239 (23.24), 225 (4.05), 187 (4.21), 173 (23.62), 133 (12.45), 131 (32.14), 92 (9.03), 91 (100.00), 75 (14.68), 73 (13.80); HRMS: calcd for $C_{19}H_{29}O_3Si_1$ (M^+-tBu): 333.1886; found: 333.1886.

4.1.10. Enone 21. 3.68 mL of allylmagnesium bromide solution (1.0 M in Et_2O; 3.68 mmol) was added at 0°C to a solution of 1.0 g of aldehyde **14** (2.63 mmol) in 5.3 mL of dry THF (0.5 M). After 2 h at 0°C the mixture was hydrolyzed with saturated NH_4Cl solution, extracted with MTB ether, dried (Na_2SO_4) with and evaporate. The residue was dissolved in dry CH_2Cl_2 and transferred to an ice-cold suspension of 1.45 g of Dess–Martin periodinane (3.42 mmol) in 6.6 mL of dry CH_2Cl_2 (0.4 M). After being stirred for 3 h at rt the mixture was hydrolyzed with 2N NaOH, extracted with MTB ether, dried and evaporated. The residue was dissolved in 5.3 mL of dry CH_2Cl_2 (0.5 M) and 0.43 mL DBU (2.89 mmol) was added at 0°C. The reaction mixture was warmed to rt, stirred for additional 20 h, hydrolyzed with saturated NH_4Cl solution, extracted with MTB ether, dried (Na_2SO_4) and evaporated to dryness. Purification by flash chromatography yielded 832 mg (75%) of enone **21** as colorless oil. $[\alpha]_D^{20}=-3.3°$ (c=1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 7.22–7.25 (m, 2H, PMB); 6.85–6.88 (m, 2H, PMB); 6.89 (dq, J=15.1, 6.9 Hz, 1H, H-18); 6.53 (dq, J=15.1, 1.6 Hz, 1H, H-17); 4.39 (m, 2H, O*CH₂*Ar); 4.03 (dd, J=7.8, 3.0 Hz, 1H, H-14); 3.80 (s, 3H, OMe_{PMB}); 3.45 (m, 2H, H-12); 1.85 (dd, J=7.0, 1.6 Hz, 3H, H-19); 1.74 (dtd_{dddd}, J=14.1, 7.8, 3.1 Hz, 1H, H-13a); 1.58 (m_{ddt}, J=14.1, 7.8, 6.0 Hz, 1H, H-13b); 1.10 (s, 3H, Me); 1.07 (s, 3H, Me′); 0.87 (s, 9H, TBS); 0.05 (s, 3H, TBS); 0.02 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 203.07 (C_q, C-16); 159.07 (C_q, PMB); 142.37 (CH, C-18); 130.61 (C_q, PMB); 129.12 (CH, PMB); 127.22 (CH, C-17); 113.69 (CH, PMB); 73.66 (CH, C-14); 72.32 (CH_2, O*CH₂*Ar); 67.18 (CH_2, C-12); 55.24 (CH_3, OMe_{PMB}); 51.84 (C_q, C-15); 34.21 (CH_2, C-13); 26.00 (CH_3, TBS); 21.78 (CH_3, Me); 19.85 (CH_3, Me′); 18.29 (C_q, TBS); 18.17 (CH_3, C-19); −4.02 (CH_3, TBS); −4.09 (CH_3, TBS); IR (neat, cm^{-1}): 2954, 2939, 2855, 1688, 1624, 1586, 1513, 1464, 1442, 1387, 1360, 1301, 1246, 1173, 1093, 1037, 1005, 967, 924, 834, 773, 732, 673; MS: *m/z* (%) 421 (M^+, 0.53), 419 (0.73), 386 (0.55), 364 (1.76), 362 (4.91), 309 (22.97), 287 (5.79), 284 (8.19), 283 (9.30), 227 (7.14), 173 (12.80), 152 (12.16), 147 (7.57), 137 (10.19), 122 (30.89), 121 (100); HRMS: calcd for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2697; Elementary Analysis: calcd for $C_{24}H_{40}O_4Si$: C 68.53; H 9.58; found: C 67.62; H 9.46.

4.1.11. *syn*-Alcohol 22. To a solution of 48.5 mg of enone **21** (0.115 mmol) in 0.58 mL of dry THF (0.2 M) were added at −30°C simultaneously and dropwise 242 μL (*S*)-Me-CBS reagent (1.0 M in toluene; 0.242 mmol) and 288 μL BH_3·DMS solution (2.0 M in THF; 0.576 mmol). After 3 h at −30°C to −20°C the mixture was hydrolyzed with ethanol and dist. H_2O, extracted with MTB ether, dried (Na_2SO_4) and evaporated. Flash chromatography yielded 37.8 mg (78%) of the 1,2-reduction products (**22**/**23**=10.8:1.0) and 8.4 mg of the saturated ketone (17%). Spetroscopic data for *syn*-alcohol **22**: $[\alpha]_D^{20}=+2.6°$ (c=0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): 7.23–7.26 (m, 2H, PMB); 6.86–6.89 (m, 2H, PMB); 5.64 (dqd, *J*=15.3, 6.2, 0.7 Hz, 1H, H-18); 5.53 (ddq, *J*=15.3, 7.0, 1.4 Hz, 1H, H-17); 4.40–4.48 (m, 2H, OCH_2Ar); 3.95 (d, *J*=6.9 Hz, 1H, H-16); 3.80 (s, 3H, OMe_{PMB}); 3.70 (dd, *J*=5.6, 3.4 Hz, 1H, H-14); 3.45–3.57 (m, 2H, H-12); 2.77 (br. s, 1H, OH); 2.04–2.14 (m_{dddd}, 1H, H-13a); 1.71 (dd, *J*=6.5, 0.7 Hz, 3H, H-19); 1.56–1.65 (m, 1H, H-13b); 0.88 (s, 9H, TBS); 0.87 (s, 3H, Me); 0.73 (s, 3H, Me′); 0.03 (s, 3H, TBS); 0.00 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 159.27 (C_q, PMB); 130.75 (CH, C-18); 130.24 (C_q, PMB); 129.40 (CH, PMB); 127.70 (CH, C-17); 113.85 (CH, PMB); 77.72 (CH, C-16); 76.02 (CH, C-14); 72.71 (CH_2, OCH_2Ar); 68.09 (CH_2, C-12); 55.27 (CH_3, OMe_{PMB}); 42.61 (C_q, C-15); 33.71 (CH_2, C-13); 26.06 (CH_3, TBS); 19.38 (CH_3, Me); 18.70 (CH_3, Me′); 18.26 (C_q, TBS); 17.83 (CH_3, C-19); −3.69 (CH_3, TBS); −4.36 (CH_3, TBS); IR (neat, cm^{-1}): 3439, 2955, 2930, 2883, 2855, 1670, 1612, 1586, 1513, 1463, 1361, 1302, 1247, 1173, 1071, 1036, 1005, 969, 938, 925, 875, 833, 772, 733, 667, 638; MS: *m/z* (%) 423 (M^+, 1.35), 365 (1.39), 355 (1.53), 351 (1.42), 347 (1.70), 311 (2.20), 309 (14.01), 270 (3.67), 269 (11.36), 220 (11.47), 187 (5.27), 178 (4.08), 173 (11.15), 149 (3.88), 147 (3.71), 137 (11.75), 131 (16.29), 122 (32.61), 121 (100), 83 (10.60), 75 (24.00), 73 (16.76); ESI-MS ($M+Na^+$): calcd for $C_{24}H_{42}O_4SiNa$: 445.2750; found: 445.2758; Elementary Analysis: calcd for $C_{24}H_{42}O_4Si$: C 68.20H 10.02; found: C 68.02; H 10.06.

4.1.12. Iodide 28. To a solution of 273 mg (0.78 mmol) of alcohol **27** in THF was added 206 μL (1.55 mmol) of triethylamine followed by 9 mg (0.078 mmol) DMAP und 81 μL (1.09 mmol) of mesyl chloride at 0°C. After being stirred for 3 h at 0°C the reaction mixture was quenched by addition of sat. NH_4Cl-solution and extracted with MTB ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH/MTBE 20:1) to furnish 310 mg (93%) of a colourless oil. $[\alpha]_D^{20}=-12.83°$ (c=1.1, $CHCl_3$); ^1H NMR:(400 MHz, $CDCl_3$, TMS): 7.32 (m, 5H, *Ph*CH_2); 4.42–4.49 (m, 2H; PhCH_2); 4.41 (m, 1H, H-12a); 4.25 (m, 1H, H-12b); 3.73 (m, 1H, H-14); 3.24 (d, *J*=8.8 Hz, 1H, H-16a); 3.16 (d, *J*=8.8 Hz, 1H, H-16b); 2.93 (s, 3H, CH_3SO_3); 2.04 (m, 1H, H13a); 1.81 (m, 1H, H-13b); 0.91 (s, 3H, C$(CH_3)_2$); 0.88 (s, 9H, $Si(CH_3)_2C(CH_3)_3$); 0.87 (s, 3H, C$(CH_3)_2$); 0.08, 0.06 (2 s, 6H, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR:(100 MHz, $CDCl_3$, TMS): 138.72 (C_q, Ph); 128.36 (CH, Ph); 127.51 (CH, Ph); 127.50 (CH, Ph); 77.43 (CH_2, CH_2Ph); 73.26 (CH_2, C-16); 73.79 (CH, C-14); 68.22 (CH_2, C-12); 39.97 (C_q, C-15); 37.48 (CH_3, CH_3SO_3); 32.95 (CH_2, C-13); 26.13, 26.10 (CH_3, C$(CH_3)_2$); 21.50, 21.38 (CH_3, $Si(CH_3)_2)C(CH_3)_3$); 18.40 (C_q, $Si(CH_3)_2$)-$C(CH_3)_3$); 3.80, −4.22 (CH_3, $Si(CH_3)_2)C(CH_3)_3$; IR (neat, cm^{-1}): 3360, 2959, 2857, 2390, 2348, 2283, 1720, 1547, 1503, 1567, 1354, 1259, 1202, 1174, 1120, 1075, 1048, 977, 846, 778, 736, 702; (M^+, 9); 307 (6); 281 (11); 277 (19); 267 (28); 261 (18); 220 (6); 201 (18); 188 (28); 172 (21); 170 (68); 154 (21); 107 (28); ESI-MS: submitted.

A solution of 100 mg (0.232 mmol) of the above mesylate in 2.3 mL of acetone, 104 mg (0.696 mmol) sodium iodide and 97.4 mg (1.16 mmol) $NaHCO_3$ were refluxed for 2 h. A second charge of 0.696 mmol of NaI and 1.16 mmol $NaHCO_3$ was added followed by reflux for 1 h. After addition of sat. NH_4Cl-solution extraction and purification (CH/MTBE 40:1) afforded 84 mg (0.181 mmol) of a colourless oil. $[\alpha]_D^{20}=-19.32°$ (c=1.0, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$, TMS): 7.34 (m, 5H, *Ph*CH_2); 4.43–4.50 (m, 2H, PhCH_2); 3.59 (dd, *J*=7.2, 3.0 Hz, 1H, H-14); 3.31 (dt, *J*=9.4, 5.0 Hz, 1H, H-12a); 3.25 (d, *J*=8.8 Hz, 1H, H-16a); 3.14 (d, *J*=8.8 Hz, 1H, H-16b); 3.11 (dt, *J*=9.4, 7.4 Hz, 1H, H-12b); 2.15 (m, 1H, H-13a); 1.97 (m, 1H, H-13b); 0.90 (s, 3H, C$(CH_3)_2$); 0.89 (s, 3H, C$(CH_3)_2$); 0.87 (s, 9H, $Si(CH_3)_2C(CH_3)_3$); 0.09 (s, 3H, $Si(CH_3)_2C(CH_3)_3$); 0.06 (s, 3H, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 138.7 (C_q, *Ph*CH_2); 128.3 (CH, *Ph*CH_2); 127.4 (CH, *Ph*CH_2); 127.3 (CH, *Ph*CH_2); 77.1 (CH_2, C-16); 73.2 (CH_2, PhCH_2); 39.9 (C_q, C-15); 38.0 (CH_2, C-13); 26.1 (CH_3, $Si(CH_3)_2C(CH_3)_3$); 21.7 (CH_3, C$(CH_3)_2$); 21.3 (CH_3, C$(CH_3)_2$); 18.5 (C_q, $Si(CH_3)_2C(CH_3)_3$); 4.7 (CH_2, C-12); −3.5 (CH_3, $Si(CH_3)_2C(CH_3)_3$; −4.2 (CH_3, $Si(CH_3)_2$-$C(CH_3)_3$; MS: *m/z* (%) 462 (M^+, 1.8); 405 (35.3); 371 (1.8); 349 (17.3); 313 (30.8); 299 (41.6); 270 (4.0); 244 (9.3); 187 (25.5); 159 (7.9); 126 (36.6); 91 (100); HRMS: calcd for $C_{20}H_{35}IO_2Si$: 462.1451; found: 462.1449.

4.1.13. Benzyl ether 29. 68 mg (0.150 mmol) of iodide **28**, 69 mg (0.266 mmol) of PPh_3 and 181 μL (1.036 mmol) *i*-$PrNEt_2$ were heated in a sealed flask at 90°C for 18 h. *i*-Pr_2NEt was carefully removed with dry *n*-pentane in vacuo and the residue was resuspended in dry *n*-pentane. After 1 min the *n*-pentane was removed by pipette (repeated twice). After removal of the remaining solvent in vacuo the residue was dissolved in 3 mL of THF and 158 μL (0.158 mmol) of LiHMDS were added at −78°C. After stirring for 15 min a solution of 0.15 mL of HMPA and 0.15 mL of THF was added dropwise at −78°C followed by the dropwise addition of a solution of 48 mg (0.150 mmol) of aldehyde **7** in 1 mL of THF. Stirring for 15 min at −78°C and 1 h at rt was followed by addition of saturated $NaHCO_3$-solution. The solution was extracted with MTB ether and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (CH/MTBE 20:1) to furnish 35 mg (37%) of a yellow oil. $[\alpha]_D^{20}=12.08°$ (c=2.4, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$, TMS): 8.20 (s, 1H, H-3); 7.32 (m, 5H, Ph); 6.87 (m, 1H, H-12); 6.34 (dd, J=16.0, 5.9 Hz, 1H, H-8); 6.03 (dd, J=16.0, 1.3 Hz, 1H, H-7); 5.71 (dd, J=11.4, 9.2 Hz, 1H, H-11); 4.51 (m, 2H, PhCH$_2$); 4.41 (q, J=7.2 Hz, 2H, H-1′); 4.40 (m, 1H, H-9); 4.15 (m, 1H, H-10); 3.71 (m, 1H, H-14); 3.24 (d, J=8.7 Hz, 1H, H-16a); 3.17 (d, J=8.7 Hz, 1H, H-16b); 2.31 (m, 2H, H-13); 1.45 (s, 3H, C(CH_3)$_2$); 1.44 (s, 3H, C(CH_3)$_2$); 0.90 (s, 9H, TBS); 0.87 (s, 6H, C17/18); 0.02 (s, 6H, TBS); ^{13}C NMR:(100 MHz, CDCl$_3$, TMS): 160.5 (C$_q$, C-1); 146.9 (C$_q$, C-4); 144.3 (CH, C-3); 144.2 (CH, C-8); 138.8 (C$_q$, *Ph*CH$_2$); 135.4 (CH, C12); 134.5 (C$_q$, C-2); 128.2 (CH, *Ph*CH$_2$); 127.2 (CH, *Ph*CH$_2$); 127.3 (CH, *Ph*CH$_2$); 124.8 (CH, C-11); 109.8 (CH, C-7); 109.8 (C$_q$, O$_2$*C*(CH$_3$)$_2$); 90.2 (C$_q$, C-6); 80.8 (CH, C-10); 77.2 (CH$_2$, C-16); 77.1 (CH, C-9); 76.9 (C$_q$, C-5); 75.9 (CH, C-14); 73.1 (CH$_2$, Ph*CH$_2$*); 61.5 (CH$_2$, C-1′); 40.4 (C$_q$, C-15); 31.9 (CH$_2$, C-13); 27.2 (CH$_3$, O$_2$C(CH_3)$_2$); 26.7 (CH$_3$, O$_2$C(CH_3)$_2$); 26.0 (CH$_3$, TBS); 22.7 (CH$_3$, C(CH_3)$_2$); 21.5 (CH$_3$, C(CH_3)$_2$); 18.1 (C$_q$, TBS); 14.2 (CH$_3$, C-2′); −3.3 (CH$_3$, TBS); −4.6 (CH$_3$, TBS); IR (neat, cm^{-1}): 2925, 2854, 2219, 2116, 1746, 1724, 1572, 1543, 1462, 1370, 1304, 1236, 1142, 1110, 1087, 1051, 1025, 980, 955, 934, 878, 833, 811, 773, 743, 713, 697, 666. ESI-MS (M+Na$^+$): calcd for C$_{36}$H$_{51}$N$_1$Na$_1$O$_7$Si$_1$: 660.3332; found: 660.3319.

4.1.14. Masked northern half of disorazole D$_1$ 30. 40 mg (0.071 mmol) of iodide **16**, 34 mg (0.129 mmol) of PPh$_3$ and 87 μL (0.499 mmol) of *i*-PrNEt$_2$ were heated in a sealed flask at 90°C for 18 h. *i*-Pr$_2$NEt was carefully removed with dry *n*-pentane in vacuo and the residue was resuspended in dry *n*-pentane. After 1 min the *n*-pentane was removed by pipette (repeated twice). After removal of the remaining solvent in vacuo the residue was dissolved in 1.4 mL of THF and 79 μL (0.079 mmol) of LiHMDS were added at −78°C. After stirring for 15 min a solution of 0.10 mL of HMPA and 0.10 mL of THF was added dropwise at −78°C followed by the dropwise addition of a solution of 30 mg (0.093 mmol) of aldehyde **7** in 1 mL of THF. Stirring for 15 min at −78°C and 1 h at rt was followed by addition of saturated NaHCO$_3$-solution. The solution was extracted with MTB ether and the combined organic phases were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (CH/MTBE 20:1) to furnish 17 mg (32%) of a yellow oil. $[\alpha]_D^{20}=-20.33°$ (c=1.5, CHCl$_3$); ^{1}H NMR: (400 MHz, CDCl$_3$, TMS): 8.21 (s, 1H, H-3); 6.35 (dd, J=15.9, 5.9 Hz, 1H, H-8); 6.05 (dd, J=15.9, 1.26 Hz, 1H, H-7); 5.85 (dt, J=9.0, 2.0 Hz, 1H, H-12); 5.48 (m, 2H, H-17/H-18); 5.39 (dt, J=9.0, 1.5 Hz, 1H, H-11); 4.42 (m, 1H, H-9); 4.35 (q, J=7.2 Hz, 2H, H-1′); 4.16 (m, 1H, H-10); 4.00 (m, 1H, H-16); 3.53 (dt$_m$, J=4.4, 2.0 Hz, 1H, H-14); 2.28 (m, 2H, H-13); 1.71 (d, J=4.5 Hz, 3H, H-19); 1.47 (s, 3H, O$_2$C(CH_3)$_2$); 1.43 (s, 3H, O$_2$C(CH_3)$_2$); 1.40 (t, J=7.2 Hz, 3H, H-2′); 1.03 (s, 21H, TIPS); 0.90 (s, 9H, TBS); 0.86 (s, 3H, C(CH$_3$)$_2$); 0.85 (s, 3H, C(CH$_3$)$_2$); 0.04 (s, 3H, TBS); 0.03 (s, 3H, TBS); ^{13}C NMR (100 MHz, CDCl$_3$, TMS): 160.5 (C$_q$, C-1); 146.9 (C$_q$, C-4); 144.2 (CH, C-3); 144.07 (CH, C-12); 135.6 (CH, C-8); 134.6 (C$_q$, C-2); 132.1 (CH, C-18); 127.8 (CH, C-17); 124.8 (CH, C-11); 109.7 (CH, C-7);109.6 (C$_q$, *C*(CH$_3$)$_2$); 90.2 (C$_q$, C-6); 80.8 (C$_q$, C-5); 90.2 (CH, C-9); 79.3 (CH, C-16); 76.9 (CH, C-10); 76.5 (CH, C-14); 61.5 (CH$_2$, C-1′); 44.7 (C$_q$, C-15); 31.8 (CH$_2$, C-13); 29.7 (CH$_3$, C-2′); 26.8 (CH$_3$, O$_2$C(CH_3)$_2$); 26.7 (CH$_3$, O$_2$C(CH_3)$_2$); 26.7 (CH$_3$, TBS); 20.4 (CH$_3$, C(CH$_3$)$_2$); 20.2 (CH$_3$, C(CH$_3$)$_2$); 18.4 (CH$_3$, TIPS); 18.3 (CH$_3$, TIPS); 18.2 (C$_q$, TBS); 17.7 (CH$_3$, C-19); 14.2 (CH$_3$, C-2′); 12.8 (CH, TIPS); −2.9 (CH$_3$, TBS); −4.2 (CH$_3$, TBS); IR (neat, cm^{-1}): 2928, 2863, 2219, 1748, 1724, 1572, 1543, 1462, 1370, 1305, 1236, 1164, 1141, 1110, 1079, 1047, 975, 955, 930, 880, 833, 809, 772, 734, 713, 676; ESI-MS (M$^+$Na$^+$): calcd for C$_{41}$H$_{69}$NO$_7$Si$_2$Na$_1$: 766.4510; found: 766.4517.

4.1.15. Cyclopropane analog of the masked northern half of disorazole A$_1$ 31. 40 mg of iodide **16** (0.070 mmol), 34 mg of PPh$_3$ (0.127 mmol) and 86 μL of *i*-Pr$_2$NEt (0.49 mmol) were heated in a sealed flask to 85°C for 20 h. *i*-Pr$_2$NEt was carefully removed with dry *n*-pentane in vacuo and the residue was resuspended in dry *n*-pentane. After 1 min the *n*-pentane was removed by pipette (repeated twice). The residue was dissolved in 1.4 mL of dry THF (0.05 M) and cooled to −78°C. 74 μL of LiHMDS solution (1.0 M in THF, 0.074 mmol) were added to this solution. After 15 min at −78°C, 0.14 mL of HMPA (in 0.3 mL of dry THF) and 21 mg of aldehyde **12** (0.081 mmol) in 0.3 mL of dry THF were subsequently added. The mixture was gradually warmed to rt and stirred for 3 h. The mixture was hydrolyzed with saturated NaHCO$_3$ solution, extracted with MTB ether, dried (Na$_2$SO$_4$), filtered through Celite and evaporated to dryness. After flash chromatography 18.9 mg of **31** (40%) were isolated as a slightly yellow oil (*Z*/*E*>5:1); ^{1}H NMR: (400 MHz, CDCl$_3$, TMS): 8.19 (s, 1H, H-3); 6.22 (dd, J=15.8, 9.9 Hz, 1H, H-8); 5.75 (d, J=15.8 Hz, 1H, H-7); 5.55 (dt, J=10.2, 7.0 Hz, 1H, H-12); 5.48–5.50 (m, 2H, H-17 + H-18); 5.08 (t, J=9.8–10.5 Hz, 1H, H-11); 4.40 (q, J=7.1 Hz, 2H, OEt); 4.07 (d, J=8.3 Hz, 1H, H-16); 3.57 (dd, J=6.5, 3.8 Hz, 1H, H-14); 2.35–2.45 (m, 1H, H-13$_a$); 2.22–2.33 (m, 1H, H-13$_b$); 1.98–2.07 (m, 1H, H-9/H-10); 1.82–1.90 (m, 1H, H-9/H-10); 1.70 (d, J=4.4 Hz, 3H, H-19); 1.06 (br. s, 21H, TIPS); 0.93 (s, 3H, Me); 0.90 (s, 9H, TBS); 0.87 (s, 3H, Me′); 0.73–0.82 (m, 2H, C$_p$–CH$_2$); 0.04 (s, 3H, TBS); 0.03 (s, 3H, TBS); ^{13}C NMR:(100 MHz, CDCl$_3$, TMS): 160.64 (C$_q$, C-1); 151.02 (CH, C-8); 147.58 (C$_q$, C-4); 143.89 (CH, C-3); 134.42 (C$_q$. C-2); 132.08 (CH, C-17/C-18/C-11/C-12); 131.14 (CH, C-17/C-18/C-11/C-12); 127.60 (CH, C-17/C-18/C-11/ C-12); 127.37 (CH, C-17/C-18/C-11/C-12); 106.38 (CH, C-7); 92.11 (C$_q$, C-5/C-6); 79.16 (CH, C-16); 76.91 (CH, C-14); 75.19 (C$_q$, C-5/C-6); 61.35 (CH$_2$, OEt); 44.76 (C$_q$, C-15); 31.60 (CH$_2$, C-13); 26.18 (CH$_3$, TBS); 22.92 (CH, C-9/C-10); 20.18 (CH$_3$, Me); 19.85 (CH$_3$, Me′); 19.83 (CH, C-9/C-10); 18.39 (C$_q$, TBS); 18.37 (CH$_3$, TIPS); 18.25 (CH$_3$, TIPS); 17.70 (CH$_3$, C-19); 16.67 (CH$_2$, C$_p$–CH$_2$); 14.24 (CH$_3$, OEt); 12.86 (CH, TIPS); −3.07 (CH$_3$, TBS); −4.08 (CH$_3$, TBS); IR (neat, cm^{-1}): 2930, 2864, 2215, 1748, 1724, 1624, 1573, 1543, 1463, 1369, 1314, 1251, 1142, 1113, 1080, 1049, 976, 948, 882, 834, 773, 715, 679; ESI-MS (M$^+$Na$^+$): calcd for C$_{39}$H$_{65}$NO$_5$Si$_2$Na$_1$: 706.4299; found: 706.4311.

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