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Toward the Total Synthesis of Disorazole A_1 and C_1: Asymmetric Synthesis of a Masked Southern Segment

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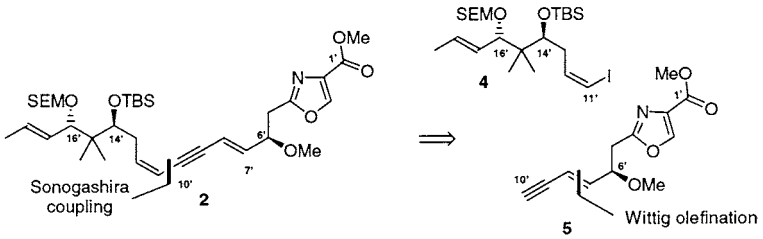
ABSTRACT



A highly convergent asymmetric synthesis of the masked southern segment of the antimitotic agent disorazole A_1 involves a Sonogashira coupling between a C1′–C10′ enyne and a suitably protected C11′–C19′ vinyl iodide. The central *E*,*Z*,*Z*-triene moiety is masked as a more stable ynediene.

The disorazoles are a family of 29 unique macrocyclic polyketides, which were isolated in 1994 from the fermentation broth of the gliding bacteria *Sorangium cellulosum* (strain So ce12) by Höfle et al.[1] Disorazole A_1 is by far the major component, being isolated in 17.2% from the crude extraction residue. While the structure of disorazole A_1 was reported in 1994, the correct absolute configuration of all seven stereocenters had not been assigned unambiguously until 2000.[2] Disorazole A_1 comprises a highly functionalized 30-membered macrodiolide, which is built up from two different hydroxy acids, whereas the C_2-symmetric disorazole C_1 is a homodimer of the southern half of disorazole A_1. Disorazole A_1 initiates decay of microtubules in subnanomolar concentrations. It causes cell cycle arrest in the G2/M phase and competes in vitro with vinblastin for the tubulin binding site.[3] With an IC_{50} value of 3 pg/mL (cell line L 929, mouse fibroblasts)[4] disorazole A_1 is too cytotoxic for a direct application in anticancer therapy, but structural derivatives and their mode of action are of great scientific and pharmaceutical interest.

In 2000 Meyers et al. reported the asymmetric synthesis of a southern half of disorazole A_1 and C_1 showing a *syn* relationship between the C14′ and C16′ hydroxy groups and the nonnatural configuration at C6′.[5]

An asymmetric synthesis of a nonnatural C12′−C19′ polyketide fragment has been published from our laboratories very recently.[6]

Herein, we report the first asymmetric synthesis of the masked southern segment of disorazole A_1 and C_1 with the natural absolute configuration of all stereocenters along with a modeling study that has guided our synthetic strategy.

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(2) Höfle, G. *GBF Annual Report* **1999/2000**, 102−103.
(3) Elnakady, Y. A. Ph.D. Thesis, TU Braunschweig, 2001.
(4) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 31−35.
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(6) Vakalopoulos, A.; Smits, R.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **2002**, *5*, 1538−1545.

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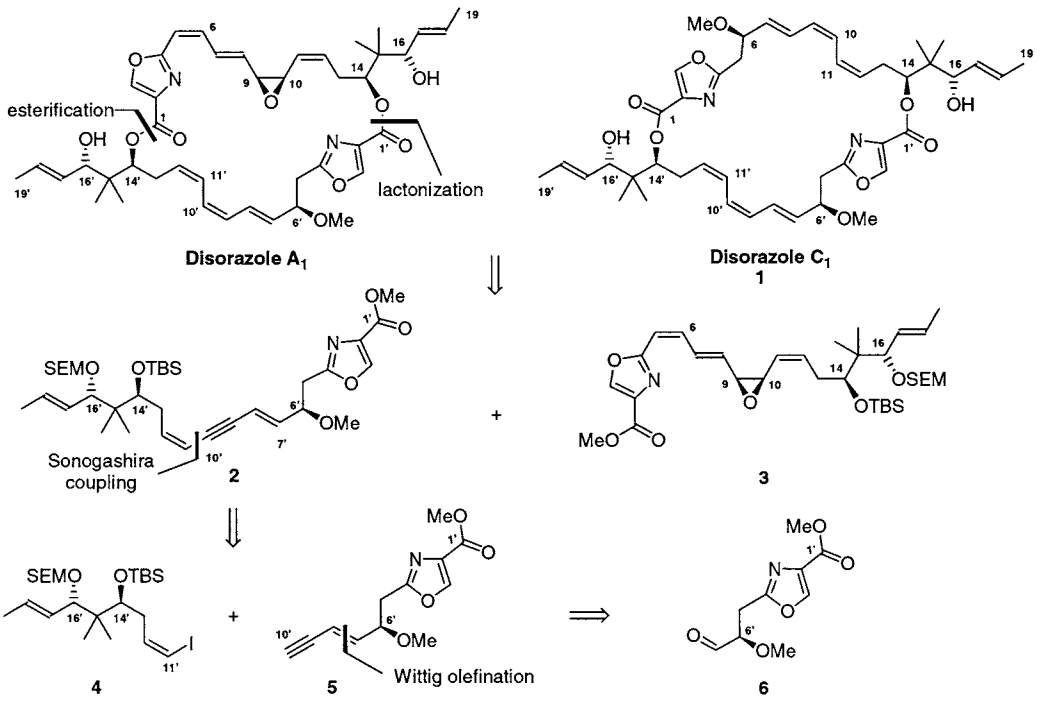
Scheme 1



Our retrosynthetic disconnections of disorazole A_1 and disorazole C_1 are outlined in Scheme 1. Cleavage of the dilactone provides the southern segment **2** and the northern segment **3**. Because of the expected instability of the triene moiety toward isomerization, we decided to mask one of the two *Z*-olefins of segment **2** as an alkyne (see below).[7] The southern segment was envisaged to be assembled in convergent fashion by a Sonogashira coupling of the suitably protected vinyl iodide **4** and terminal enyne **5**, which can be traced back to oxazole aldehyde **6**.

The position of the triple bond relative to the ring-closing functionalities at C1′ and C14′ was thought to be critical for the cyclization steps leading to disorazole C_1. A direct dimerization of the hydroxy acid to the macrodiolide would significantly shorten our synthesis. Therefore an intramolecular lactonization yielding the 15-membered macrolactone has to be suppressed. A suitably placed triple bond should preclude this unwanted intramolecular cyclization due to ring strain.

To assess the best fitting location we started a modeling study to compare the relative energies of the 30-membered macrodiolides **I** and **II** and the corresponding 15-membered macrolactones **III** and **IV** (Figure 1).

All starting geometries were minimized using the MMFF ForceField[8] within MacroModel 7.2.[9] These minimized conformations were used as input for a Monte Carlo search to find the global minimum.[10] Our calculations imply a more strained 15-membered macrolactone in the case of the C9′−C10′ alkyne, while the relative energy of the macrodiolide

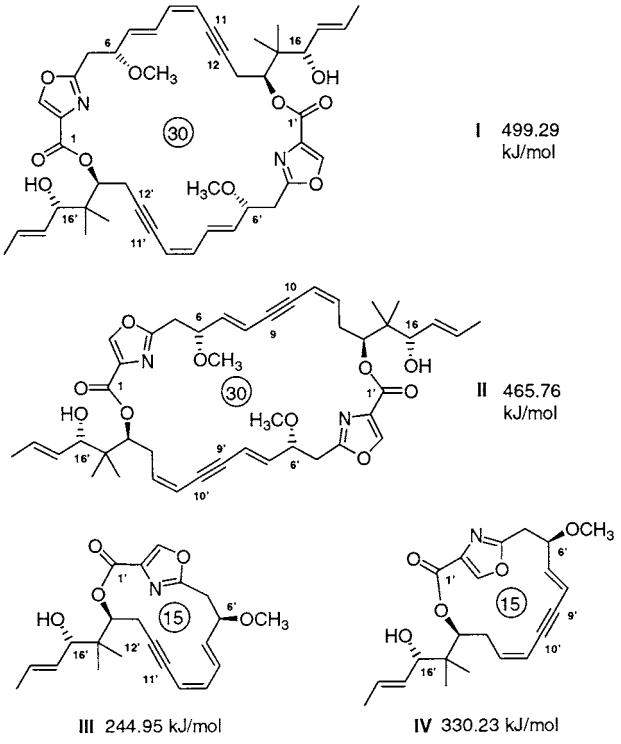


Figure 1.

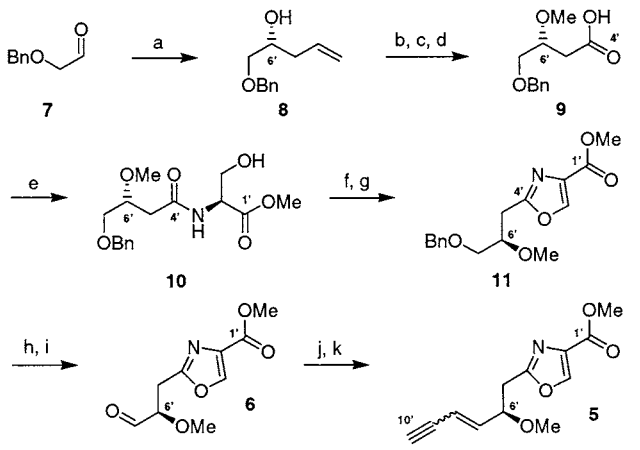
(7) Late-stage transformation of alkynes to *Z*-olefins has been used in a variety of natural product synthesis. For recent examples, see: (a) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956−4957. (b) Nazaré, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363−3376. (c) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **2000**, *56*, 327−331. See also [18]annulene: Stöckel, K.; Sondheimer, F. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 68−75.

(8) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490−512.

seems to be unperturbed by the presence of the C9′−C10′ triple bond (465.76 kJ/mol for **II** vs 463.30 kJ/mol for disorazole C_1, **1**). Therefore, the C9′−C10′ *Z*-olefin was chosen to be masked as an alkyne.[11]

The synthesis of the C1′−C10′ fragment **5** starts from commercially available 2-benzyloxy acetaldehyde **7** (Scheme 2). Keck allylation[12] using (*R*)-BINOL leads in 84% yield

Scheme 2[a]



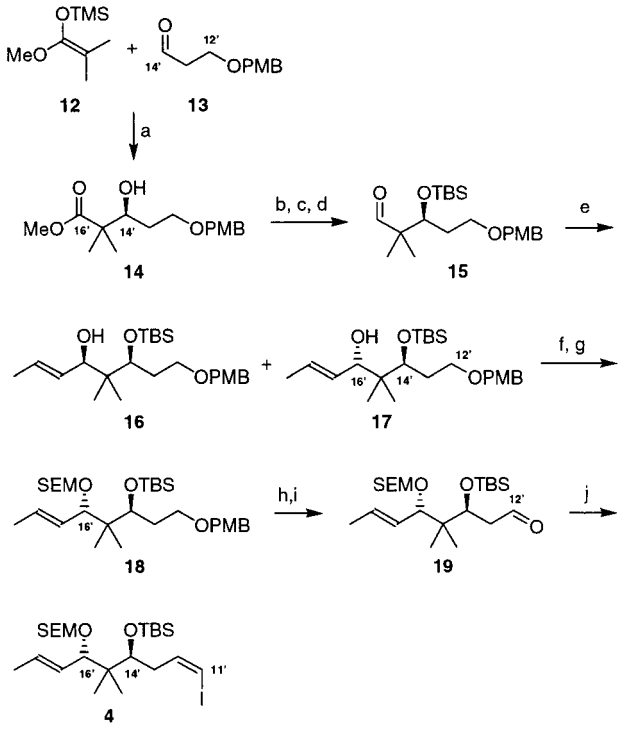
[a] Reaction conditions: (a) (*R*)-BINOL, $Ti(OiPr)_4$, MS 4 Å, allyltributylstannane, CH_2Cl_2, −20 °C, 84%; (b) NaH, MeI, THF, rt, 94%; (c) O_3, CH_2Cl_2, −78 °C; PPh_3, rt, 86%; (d) $NaClO_2$, KH_2PO_4, H_2O_2, CH_3CN/MeOH/H_2O 1:1:2, 10 °C, 98%; (e) L-SerOMe·HCl, IBCF, NMM, THF, −25 °C → rt, 71%; (f) DAST, K_2CO_3, CH_2Cl_2, −78°C; (g) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C → rt, 79% from **10**; (h) H_2, Pd/C, EtOH, rt, 97%; (i) SO_3·pyr, Et_3N, CH_2Cl_2/DMSO 4:1, 0 °C, 75%; (j) $Br^-Ph_3P^+CH_2C{=}CTMS$, *n*-BuLi, THF, −78 to 0 °C, 49% (*E*:*Z* = 2.5:1); (k) K_2CO_3, MeOH, rt, 77%. IBCF = isobutyl chloroformate; NMM = *N*-methylmorpholine; DAST = diethylaminosulfuryl trifluoride.

to homoallylic alcohol **8** with the desired (*R*)-configuration at C6′.[13] O-Methylation followed by ozonolysis and subsequent oxidation[14] of the resulting aldehyde provides carboxylic acid **9** (79% from **8**).

The elaboration of carboxylic acid **9** into oxazole ester **11** is achieved employing a three-step sequence consisting of amide formation with L-serine methyl ester hydrochloride, cyclodehydration using DAST,[15] and oxidation of the oxazoline to oxazole **11** by DBU/$BrCCl_3$.[16] After removal of the benzyl protecting group by hydrogenation, oxidation of the primary alcohol leads to α-methoxy aldehyde **6**. The synthesis of enyne **5** is completed by a three-carbon chain elongation involving Wittig olefination of aldehyde **6** with TMS-protected propargyl triphenylphosphonium bromide (2.5:1 *E*/*Z* selectivity) and removal of the terminal TMS group.

The synthesis of vinyl iodide **4** is summarized in Scheme 3. Starting from readily available PMB-protected 3-hydroxy-

Scheme 3[a]



[a] Reaction conditions: (a) *N*-Tos-D-valine, BH_3·THF, CH_2Cl_2, −78 °C; K_2CO_3, MeOH, 96%; (b) TBSOTf, 2,6-lutidine, DMAP, CH_2Cl_2, rt, 99%; (c) DIBAH, toluene, −78 °C, 94%; (d) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, 83%; (e) *trans*-1-bromopropene, *t*-BuLi, Et_2O/THF 1:1, −95 °C, 99% (**16**:**17** = 1.1:1); (f) separation of diastereomers; (g) SEMCl, Hünig's base, Bu_4NI, CH_2Cl_2; (h) DDQ, CH_2Cl_2/H_2O 10:1, 0 °C, 98% from **17**; (i) SO_3·pyr, Et_3N, CH_2Cl_2/DMSO 6:1, 0 °C, 80%; (j) $I^-Ph_3P^+CH_2I$, NaHMDS, THF/HMPA 10:1, −78 °C, 82%.

propanal **13**,[17] asymmetric Mukaiyama-aldol addition of silyl ketene acetal **12** under Kiyooka's conditions (in situ formation of the chiral oxazaborolidine promotor from *N*-Tos-D-valine and BH_3·THF)[18] gives β-hydroxy ester **14** in 96% yield and 88% ee.[19] After protection of the secondary

(9) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(10) All minimizations are calculated without a solvent model to complete convergence. Monte Carlo searches are run until the global minimum is found more than once. Goodmann, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110−1117.

(11) In the meantime Meyers et al. have reported that the direct dimerization of the southern half of disorazole A_1 containing a C11′−C12′ alkyne leads preferentially to the 15-membered macrolactone: Hillier, M. C.; Price, A. T.; Meyers, A. I. *J. Org. Chem.* **2001**, *66*, 6037−6045.

(12) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12−18.

(13) The enantiomeric excess is estimated to be higher than 94% by two independent methods (chiral GC, Mosher ester analysis).

(14) Dalcanale, E. *J. Org. Chem.* **1986**, *51*, 567−569.

(15) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947−958.

(16) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331−334.

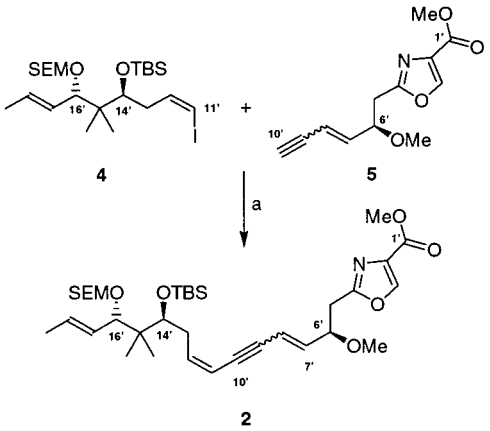
(17) PMB-protected 3-hydroxypropanal **13** is prepared from 1,3-propandiol by mono PMB protection and Parikh−Doering oxidation in 77% overall yield.

(18) (a) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278. (b) Kiyooka, S.-i.; Kaneko, Y.; Kume, K.-i. *Tetrahedron Lett.* **1992**, *33*, 4927−4930. (c) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511−5523.

hydroxy group as the TBS ether, aldehyde **15** is formed via reduction with DIBAH and Dess−Martin oxidation.[20] Addition of lithiated *trans*-bromopropene (*t*-BuLi, −95°C)[21] leads to a mixture of *syn* and *anti* alcohols **16** and **17** with slight preference for the *syn* diastereomer (**16**:**17** = 1.1:1).[22]

The epimeric alcohols are easily separated by column chromatography; the undesired *syn* diastereomer **16** can be recycled to *anti* epimer **17** by oxidation to the enone and diastereoselective reduction with Corey's Me-(*R*)-oxazaborolidine reagent.[23] The C16′ hydroxy group is protected as 2-trimethylsilylethoxymethyl (SEM) ether. PMB cleavage with DDQ in wet dichloromethane[24] is followed by Parikh−Doering oxidation[25] of the primary alcohol to aldehyde **19**. Finally, the vinyl iodide **4** is generated with freshly prepared $I^-Ph_3P^+CH_2I$ applying the Stork−Zhao procedure.[26] With both fragments in hand, the crucial Sonogashira coupling[27] is approached. Using the combination of $PdCl_2(PPh_3)_2$/CuI/Et_3N, coupling of vinyl iodide **4** and enyne **5** (1:1.2 ratio) furnishes the masked southern segment of disorazole A_1 and C_1 **2** (58% yield; 97% yield based on recovered vinyl iodide **4**) (Scheme 4). The C7′−C8′ *Z*/*E* isomers are easily separated by column chromatography. At −20°C both isomers are stable for months. In addition, *syn* alcohol **16** is independently converted into a masked nonnatural southern hemisphere of disorazole A_1. By using a slightly modified procedure (degassed DMF instead of CH_3CN as solvent; addition of the more labile enyne **5** after premixing catalyst, vinyl iodide, and base) a satisfying yield of 75% for the final Sonogashira coupling is achieved.

Scheme 4[a]



[a] Reaction conditions: (a) $PdCl_2(PPh_3)_2$ (10 mol %), CuI (30 mol %), Et_3N, CH_3CN, −20 °C to rt, 58% (97% based on recovered **4**).

In conclusion, a masked and fully resolved southern segment of disorazole A_1 and C_1 has been synthesized in a highly convergent manner in 12 linear steps. The synthesis of the northern segment **3** and a cyclization sequence are currently under investigation in our laboratories.

Acknowledgment. We thank Dr. Jonathan Goodman (University of Cambridge, U.K.) for an introduction to computational chemistry (L.O.H.) and Dr. Christian B. W. Stark and Ulrike Eggert for helpful discussions. We are grateful to the Innovation Campaign of the University of Hannover and the Fonds der Chemischen Industrie for support.

Supporting Information Available: Physical and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The enantiomeric excess is quantified by ^{1}H NMR shift measurement with europium tris[heptafluoropropyl-hydroxymethylene]-(+) camphorate $Eu(hfc)_3$. The measured enantiomeric excess of 88% is in agreement with comparable literature results: Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456−7467.

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(23) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. As in similar cases with sterically very demanding ketones, the Me-CBS reagent has to be used in excess: Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9449−9450.

(24) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021−3028.

(25) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

(26) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.

(27) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley VCH: Weinheim, Germany, 1998; pp 203−229.