## Toward the Total Synthesis of **Disorazole A**<sub>1</sub> and C<sub>1</sub>: 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 A1 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.<sup>1</sup> Disorazole  $A_1$  is by far the major component, being isolated in 17.2% from the crude extraction residue. While the structure of disorazole A1 was reported in 1994, the correct absolute configuration of all seven stereocenters had not been assigned unambiguously until 2000.<sup>2</sup> Disorazole A<sub>1</sub> 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<sub>1</sub> 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.<sup>3</sup> With an IC<sub>50</sub> value of 3 pg/mL (cell line L

(3) Elnakady, Y. A. Ph.D. Thesis, TU Braunschweig, 2001.

929, mouse fibroblasts)<sup>4</sup> 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.

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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.

<sup>(1)</sup> Jansen, R.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. Liebigs Ann. Chem. 1994, 759-773.

<sup>(2)</sup> Höfle, G. GBF Annual Report 1999/2000, 102-103.

<sup>(4)</sup> Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. J. Antibiot. 1995, 48, 31-35.

<sup>(5)</sup> Hillier, M. C.; Park, D. H.; Price, A. T.; Ng, R.; Meyers, A. I. Tetrahedron Lett. 2000, 41, 2821-2824.

<sup>(6)</sup> Vakalopoulos, A.; Smits, R.; Hoffmann, H. M. R. Eur. J. Org. Chem. 2002, 5, 1538-1545.



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).<sup>7</sup> 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<sup>8</sup> within MacroModel 7.2.<sup>9</sup> These minimized

conformations were used as input for a Monte Carlo search to find the global minimum.<sup>10</sup> Our calculations imply a more strained 15-membered macrolactone in the case of the C9'-C10' alkyne, while the relative energy of the macrodiolide





<sup>(7)</sup> 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.

<sup>(8)</sup> 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<sub>1</sub>, 1). Therefore, the C9'-C10' Z-olefin was chosen to be masked as an alkyne.<sup>11</sup>

The synthesis of the C1'-C10' fragment **5** starts from commercially available 2-benzyloxy acetaldehyde **7** (Scheme 2). Keck allylation<sup>12</sup> using (*R*)-BINOL leads in 84% yield



<sup>*a*</sup> Reaction conditions: (a) (*R*)-BINOL, Ti(O*i*Pr)<sub>4</sub>, MS 4 Å, allyltributylstannane, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 84%; (b) NaH, MeI, THF, rt, 94%; (c) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; PPh<sub>3</sub>, rt, 86%; (d) NaClO<sub>2</sub>, KH<sub>2</sub>PO<sub>4</sub>, H<sub>2</sub>O<sub>2</sub>, CH<sub>3</sub>CN/MeOH/H<sub>2</sub>O 1:1:2, 10 °C, 98%; (e) L-SerOMe•HCl, IBCF, NMM, THF, -25 °C → rt, 71%; (f) DAST, K<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C; (g) DBU, BrCCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → rt, 79% from **10**; (h) H<sub>2</sub>, Pd/C, EtOH, rt, 97%; (i) SO<sub>3</sub>•pyr, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>/DMSO 4:1, 0 °C, 75%; (j) Br<sup>-</sup>Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>C=CTMS, *n*-BuLi, THF, -78 to 0 °C, 49% (*E*:*Z* = 2.5:1); (k) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 77%. IBCF = isobutyl chloroformate; NMM = *N*-methylmorpholine; DAST = diethylaminosulfuryl trifluoride.

to homoallylic alcohol **8** with the desired (*R*)-configuration at C6'.<sup>13</sup> O-Methylation followed by ozonolysis and subsequent oxidation<sup>14</sup> 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,<sup>15</sup> and oxidation of the oxazoline to oxazole **11** by DBU/BrCCl<sub>3</sub>.<sup>16</sup> After removal of

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

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

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

the benzyl protecting group by hydrogenation, oxidation of the primary alcohol leads to  $\alpha$ -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-



<sup>*a*</sup> Reaction conditions: (a) *N*-Tos-D-valine, BH<sub>3</sub>·THF, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; K<sub>2</sub>CO<sub>3</sub>, MeOH, 96%; (b) TBSOTf, 2,6-lutidine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 99%; (c) DIBAH, toluene, -78 °C, 94%; (d) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 83%; (e) *trans*-1bromopropene, *t*-BuLi, Et<sub>2</sub>O/THF 1:1, -95 °C, 99% (**16**:17 = 1.1: 1); (f) separation of diastereomers; (g) SEMCl, Hünig's base, Bu<sub>4</sub>NI, CH<sub>2</sub>Cl<sub>2</sub>; (h) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O 10:1, 0 °C, 98% from **17**; (i) SO<sub>3</sub>·pyr, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>/DMSO 6:1, 0 °C, 80%; (j) I<sup>-</sup>Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>I, NaHMDS, THF/HMPA 10:1, -78 °C, 82%.

propanal **13**,<sup>17</sup> 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<sub>3</sub>·THF)<sup>18</sup> gives  $\beta$ -hydroxy ester **14** in 96% yield and 88% ee.<sup>19</sup> After protection of the secondary

<sup>(9)</sup> 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.

<sup>(10)</sup> 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.

<sup>(11)</sup> 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.

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

<sup>(16)</sup> Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. Tetrahedron Lett. 1997, 38, 331-334.

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

<sup>(18) (</sup>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.<sup>20</sup> Addition of lithiated *trans*-bromopropene (*t*-BuLi,  $-95^{\circ}C)^{21}$  leads to a mixture of *syn* and *anti* alcohols **16** and **17** with slight preference for the *syn* diastereomer (**16**:**17** = 1.1:1).<sup>22</sup>

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.<sup>23</sup> The C16' hydroxy group is protected as 2-trimethylsilylethoxymethyl (SEM) ether. PMB cleavage with DDQ in wet dichloromethane<sup>24</sup> is followed by Parikh-Doering oxidation<sup>25</sup> of the primary alcohol to aldehyde **19**. Finally, the vinyl iodide 4 is generated with freshly prepared I<sup>-</sup>Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>I applying the Stork–Zhao procedure.<sup>26</sup> With both fragments in hand, the crucial Sonogashira coupling<sup>27</sup> is approached. Using the combination of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/CuI/ Et<sub>3</sub>N, coupling of vinyl iodide **4** and enyne **5** (1:1.2 ratio) furnishes the masked southern segment of disorazole A1 and C<sub>1</sub> 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  $-20^{\circ}$ C both isomers are stable for months. In addition, syn alcohol 16 is independently converted into a masked nonnatural southern hemi-

(22) The *syn* and *trans* relationship is assigned by Rychnovsky's acetonide method: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. J. Org. Chem. **1993**, *58*, 3511–3515.

(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.

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



<sup>*a*</sup> Reaction conditions: (a)  $PdCl_2(PPh_3)_2$  (10 mol %), CuI (30 mol %), Et<sub>3</sub>N, CH<sub>3</sub>CN, -20 °C to rt, 58% (97% based on recovered **4**).

sphere of disorazole  $A_1$ . By using a slightly modified procedure (degassed DMF instead of CH<sub>3</sub>CN 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.

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.

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**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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<sup>(19)</sup> The enantiomeric excess is quantified by <sup>1</sup>H NMR shift measurement with europium tris[heptafluoropropyl-hydroxymethylene]-(+) camphorate Eu(hfc)<sub>3</sub>. 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.

<sup>(20) (</sup>a) Dess, D. B.; Martin, J. C. J. Org. Chem. 1983, 48, 4155-4156.
(b) Dess, D. B.; Martin, J. C. J. Am. Chem. Soc. 1991, 113, 7277-7287.
(c) Frigerio, M.; Santagostino, M.; Sputore, S. J. Org. Chem. 1999, 64, 4537-4538.

<sup>(21)</sup> Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. J. Am. Chem. Soc. 2001, 123, 4851–4852.