Synthesis of the C15–C35 Segment of Chivosazole A

Dominic Janssen, Markus Kalesse*

Institut für Organische Chemie, Leibniz-Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
Fax +49(511)7623011; E-mail: Markus.Kalesse@oci.uni-hannover.de

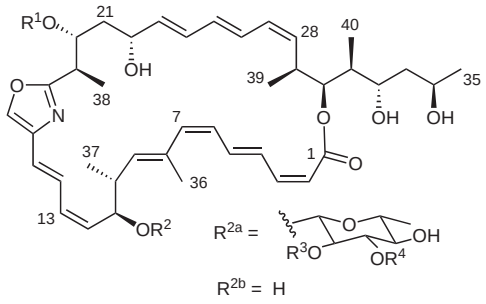
Received 21 August 2007

Abstract: The synthesis of the C15–C35 segment of chivosazole A is reported using a convergent approach that incorporates an *E*-selective Wittig olefination for joining both subunits of this fragment.

Key words: chivosazole, natural product, antibiotic, myxobacteria

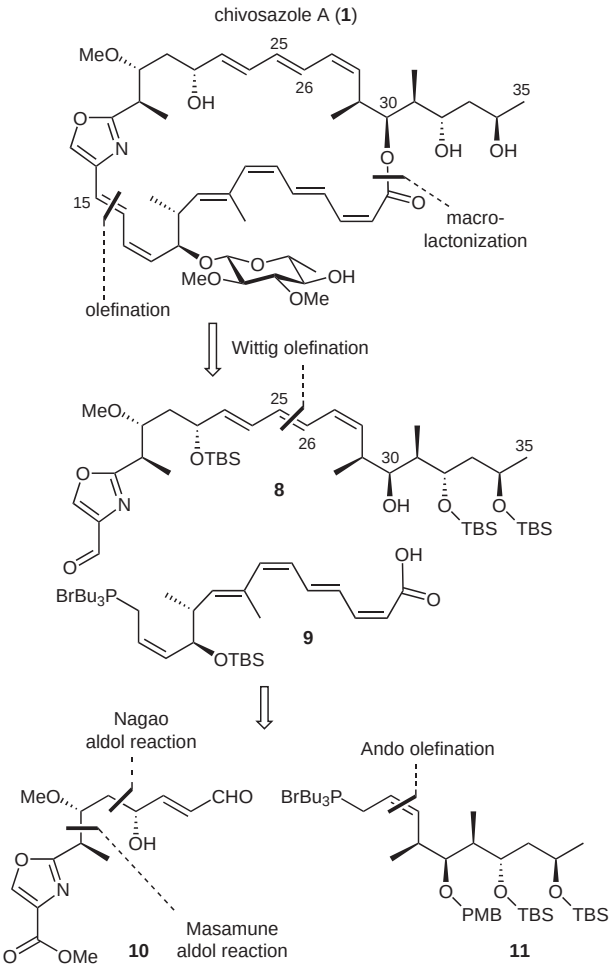
Chivosazole A (Table 1) belongs to a family of 31-membered macrolide glycosides isolated at the Helmholtz Centre for Infection Research (HZI, formerly GBF) in 1997 from *S. cellulosum* So ce12.[1] They are active against yeasts and filamentous fungi and they are highly cytotoxic against mammalian cell cultures (IC50 9 ng/mL L 929 and HeLa). Except for chivosazole F (**7**), all natural variants possess a 6-desoxyglucopyranose (chinovose) at C11.

Table 1 Chivosazoles



	Chivosazoles	R^1	R^2	R^3	R^4
1	A	Me	R^{2a}	Me	Me
2	A_1 (6,7-*E*)	Me	R^{2a}	Me	Me
3	B	H	R^{2a}	Me	Me
4	C	Me	R^{2a}	H	H
5	D	H	R^{2a}	H	Me
6	E	H	R^{2a}	H	H
7	F	Me	R^{2b}	–	–

The stereochemistry of chivosazole A (**1**) was solved by chemical degradation, NMR studies, and analysis of the polyketide reductase gene cluster.[2] Finally, an additional confirmation of the configurational assignment of the segment obtained from ozonolysis was obtained by re-synthesizing this segment. In order to independently confirm the proposed stereochemistry of the remaining structural motifs and to access derivatives for structure–activity investigations we initiated a program that aims at the synthesis of chivosazole A (**1**).

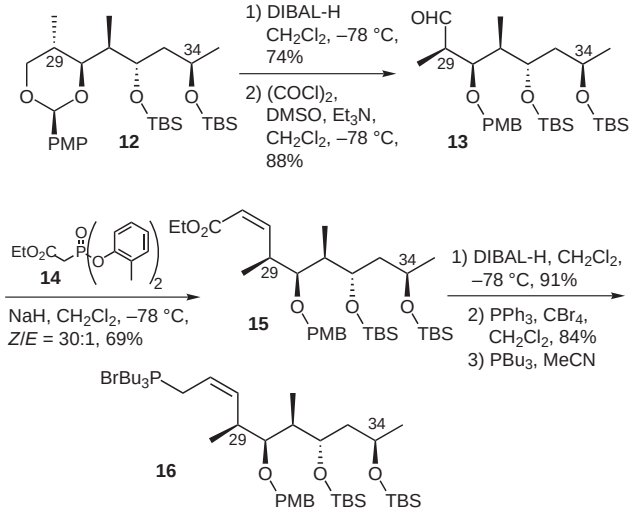


Scheme 1 Retrosynthetic disconnection of chivosazole

We envisioned constructing chivosazole A (**1**) from the two equally complex fragments **8** and **9** via olefination at carbons C14 and C15 followed by macrolactone formation (Scheme 1). In synthetic direction the northern hemisphere **8** can be constructed from aldehyde **10** and Wittig reagent **11**. This segment contains already eight out of the ten stereocenters of the aglycon of chivosazole A (**1**). The synthesis of **11** commenced with the construction of the C28–C35 segment **12** which was synthesized according to our strategy used for the structural elucidation. An *anti*-

SYNLETT 2007, No. 17, pp 2667–2670
Advanced online publication: 25.09.2007
DOI: 10.1055/s-2007-991049; Art ID: G27407ST

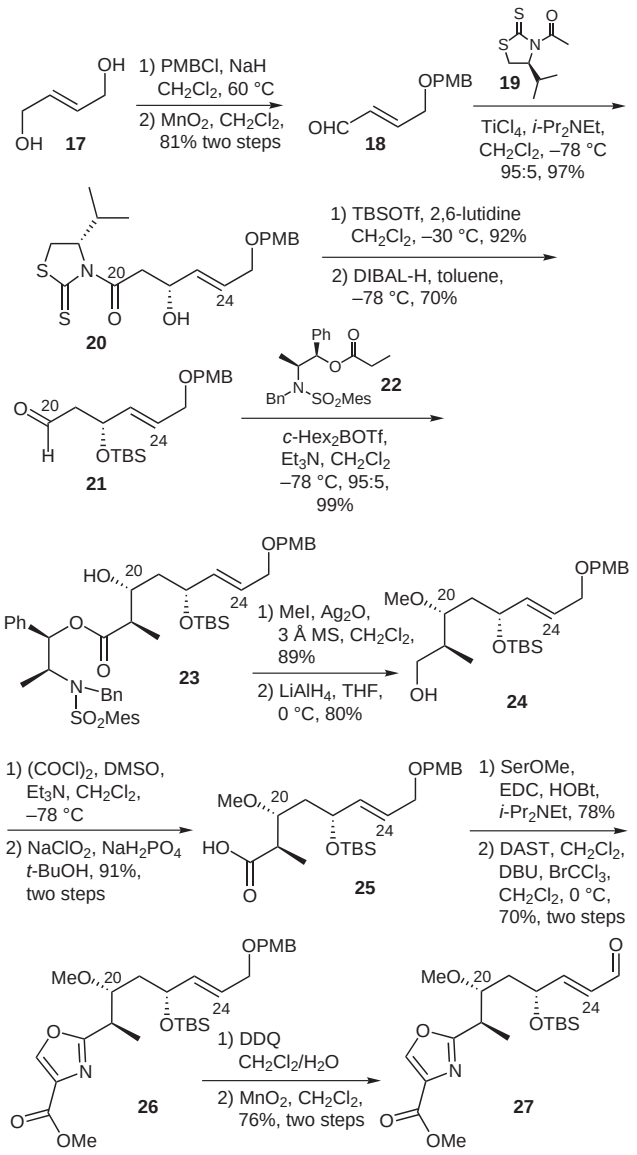
Felkin selective Mukaiyama aldol reaction and an *anti*-selective reduction of the so-obtained hydroxyl ketone were used as the pivotal transformations for this segment.[2] Reductive opening of the PMP acetal and subsequent Swern oxidation provided compound **13**. In the subsequent olefination the Ando protocol[3] installing the *Z*-configured double bond provided higher yields and selectivities compared to the Still–Gennari[4] reaction (*Z*/*E* = 20:1, 58%). The so-obtained ester **15** was reduced and transformed to the corresponding bromide,[5] which was subsequently reacted with PBu_3 to generate Wittig salt **16**[6] (Scheme 2).



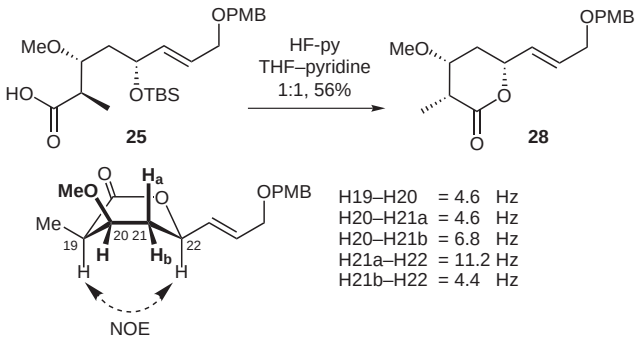
Scheme 2 Synthesis of segment **16**

The synthesis of the C15–C25 segment **10** began with PMB protection and oxidation of diol **17**. For the required enantioselective aldol reaction the Nagao protocol[7] provided high yields and selectivity (90% ee, 97%). After TBS protection and transformation of the amide to the corresponding aldehyde the *anti*-aldol reaction according to Masamune[8] gave superior results compared to the Evans or Paterson *anti*-aldol reactions and provided aldol product **23** with three configurations established. Methylation of the so-generated secondary alcohol was achieved by treatment with MeI and Ag_2O[9] and for cleaving the chiral auxiliary reduction with $LiAlH_4$ was mandatory. Re-oxidation to acid **25** was accomplished via a two-step Swern[10] and Pinnick[11] oxidation sequence. Finally, the oxazole moiety was introduced under standard conditions.[12] In order to liberate the aldehyde carbonyl group necessary for coupling, the PMB group was removed using DDQ and the alcohol oxidized with MnO_2 to provide segment **27** (Scheme 3).

Even though the Nagao and Masamune protocols are known as reliable and widely applicable methods in aldol chemistry we independently confirmed the relative configuration of compound **25** through analyzing the H–H coupling constants of lactone **28**, obtained by treatment of **25** with HF in pyridine (Scheme 4).[13]



Scheme 3 Synthesis of segment **27**

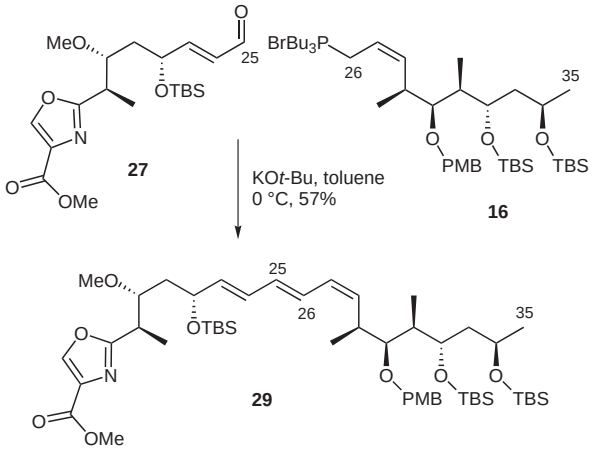


Scheme 4 Configurational assignment of lactone **28**

The observed NOE contacts and the coupling constants clearly support the configurations expected from these aldol reactions. The boat conformation on which the configurational analysis was performed was deduced from coupling constants and computational analysis of the lactone.

The final coupling of both segments could then be obtained in toluene at 0 °C with KO*t*-Bu as the base with gratifying yields and the *E*-configured double bond as the only detectable isomer (Scheme 5).[14] Even though the ^{1}H NMR spectrum of the C24–C28 segment was of higher order and confirmation of the *E*-configuration was therefore not accessible through analysis of the coupling constants, a Win-Dyna simulation clearly confirmed the expected *E*-configured double bond.

With a reliable and efficient route for the northern hemisphere in hand we now aim for the construction of the aglycon of chivosazole A (**1**).



Scheme 5 Coupling of segments **27** and **16** via Wittig reaction

Acknowledgment

We gratefully acknowledge Dr. R. Jansen (HZI) for support in the isolation of natural chivosazole A.

References and Notes

(1) Jansen, R.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann./Recl.* **1997**, 1725.
(2) Janssen, D.; Albert, D.; Jansen, R.; Müller, R.; Kalesse, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4898; *Angew. Chem.* **2007**, *119*, 4985.
(3) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
(4) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(5) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *87*, 801.
(6) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4364; *Angew. Chem.* **2000**, *112*, 4535.
(7) (a) Nagao, Y.; Yamada, S.; Kumagi, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418. (b) Nagao, Y.; Hagiwara, Y.; Kumagi, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.
(8) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) Inoue, T.; Liu, J. F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5286.
(9) Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *22*, 8349.
(10) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(11) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(12) (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (b) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.
(13) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.
(14) **Synthesis of Alkene 15**
Reagent **14** (14 mg, 44 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. Then, NaH (2.5 mg, 62 μmol, 60% dispersion on mineral oil) was added, the solution stirred for 15 min at 0 °C, and then cooled to –78 °C. Aldehyde **13** (27 mg, 49 μmol) was added and the mixture was warmed over 2 h to 0 °C and then quenched with sat. NH_4Cl solution (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 × 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified via flash chromatography. The reaction yielded 21 mg of the *Z*-olefin (0.03 mmol, 69%). R_f = 0.29 (EtOAc–hexane, 1:30); $[\alpha]_D^{23}$ +6.5 (*c* 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 6.40 (dd, *J* = 11.6, 10.2 Hz, 1 H), 5.82 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 10.6 Hz, 1 H), 4.52 (d, *J* = 10.6 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.95–3.90 (m, 1 H), 3.88–3.83 (m, 1 H), 3.80 (s, 3 H), 3.23 (dd, *J* = 5.8, 3.8 Hz, 1 H), 1.77–1.73 (m, 2 H), 1.57 (ddd, *J* = 14.0, 8.0, 1.9 Hz, 1 H), 1.41 (ddd, *J* = 13.7, 9.1, 4.1 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.02 (s, 3 H), –0.01 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 166.1, 159.1, 156.3, 152.4, 131.4, 129.4, 119.8, 113.8, 83.8, 74.3, 72.2, 66.9, 59.8, 55.4, 43.7, 37.1, 26.2, 26.1, 25.4, 18.2, 17.7, 14.4, 9.5, –3.6, –3.8, –4.3, –4.3. ESI-HRMS: *m/z* calcd for $C_{33}H_{62}O_6NaSi_2$: 645.3983 [M + Na^+]; found: 645.3975.
Synthesis of Lactone 28
Acid **25** (10 mg, 22.1 μmol) was dissolved in THF (0.25 mL) and treated with pyridine (0.25 mL). A HF–pyridine complex (ca. 70% HF, ca. 30% pyridine, 0.4 mL, 15.3 mmol) was added. The reaction mixture was stirred for 16 h at r.t. and then poured into sat. $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (5 × 5 mL). The combined organic layers were washed with sat. NH_4Cl solution (5 mL) and brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified via flash chromatography. The reaction yielded 4 mg of lactone **28** (12.5 μmol, 56%). R_f = (EtOAc–hexane, 1:4); $[\alpha]_D^{23}$ –14.2 (*c* 0.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.91 (dt, *J* = 15.5, 5.2 Hz, 1 H), 5.82 (dd, *J* = 15.7, 6.0 Hz, 1 H), 4.75 (ddd, *J* = 10.6, 5.3, 5.3 Hz, 1 H), 4.46 (s, 2 H), 4.02 (d, *J* = 5.0 Hz, 2 H), 3.81 (s, 3 H), 3.73 (ddd, *J* = 6.8, 4.6, 4.6 Hz, 1 H), 3.31 (s, 3 H), 2.75 (dq, *J* = 6.8, 4.6 Hz, 1 H), 2.25 (ddd, *J* = 14.5, 6.9, 4.4 Hz, 1 H), 1.87 (ddd, *J* = 14.6, 11.2, 4.6 Hz, 1 H), 1.28 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 159.4, 130.2, 130.1, 129.6, 129.5, 114.0, 76.2, 75.9, 72.3, 69.4, 56.8, 55.4, 39.6, 34.0, 11.5. ESI-HRMS: *m/z* calcd for $C_{18}H_{24}O_5Na$: 343.1521 [M + Na^+]; found: 343.1533.
Synthesis of the C15–C35 Segment (29)
Wittig salt **16** (17 mg, 20 μmol) was dissolved in toluene (1 mL) and cooled to 0 °C. A solution of the aldehyde **27** (10 mg, 24 μmol) in toluene (0.2 mL) was added to the mixture. The reaction mixture was then treated with a KO*t*-Bu solution (18 μL, 28 μmol, 1 M solution in THF). After 30 min H_2O (2 mL) was added, the layers separated, and the

aqueous layer was extracted with MTBE (2 × 5 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified via flash chromatography. The reaction yielded 11 mg of compound **29** (15 μmol, 57%). R_f = 0.32 (EtOAc–hexane, 1:10); $[\alpha]_D^{23}$ +3.9 (*c* 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.9 Hz, 2 H), 6.42–6.36 (m, 1 H), 6.18–6.09 (m, 2 H), 6.04 (t, *J* = 11.1 Hz, 1 H), 5.62 (t, *J* = 10.4 Hz, 1 H), 5.59 (dd, *J* = 14.0, 8.2 Hz, 1 H), 5.32–5.54 (m, 2 H), 4.51 (s, 2 H), 4.32–4.27 (m, 1 H), 3.97–3.92 (m, 1 H), 3.91 (s, 3 H), 3.84–3.81 (m, 1 H), 3.79 (s, 3 H), 3.78–3.76 (m, 1 H), 3.42 (dq, *J* = 6.8, 5.0 Hz, 1 H), 3.37 (s, 3 H), 3.12 (dd, *J* = 6.5, 3.8 Hz, 1 H), 2.93–2.84 (m, 1 H), 1.86–1.79 (m, 1 H), 1.43–1.37 (m, 4 H), 1.34 (d, *J* = 6.8 Hz, 3 H), 1.16 (d, *J* = 5.8 Hz), 1.06 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.10 (s, 6 H), 0.04 (s, 3 H), –0.01 (s, 3 H), –0.02 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 162.0, 159.1, 144.1, 137.2, 134.6, 133.2, 132.6, 131.3, 130.0, 129.5, 128.9, 128.4, 113.8, 84.7, 79.1, 74.6, 71.7, 70.3, 66.7, 57.6, 55.4, 52.3, 43.1, 40.3, 36.2, 32.1, 29.9, 26.2, 26.1, 26.0, 25.6, 22.9, 18.8, 18.2, 14.3, 11.5, 9.2, 7.5, 1.2, –3.3, –3.5, –3.8, –4.1, –4.3, –4.8. ESI-HRMS: *m/z* calcd for $C_{52}H_{91}NO_9Si_3Na$: 980.5899 [M + Na^+]; found: 980.5900.