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Synthesis of the C1−C13 Tetraenoate Subunit of the Chivosazoles

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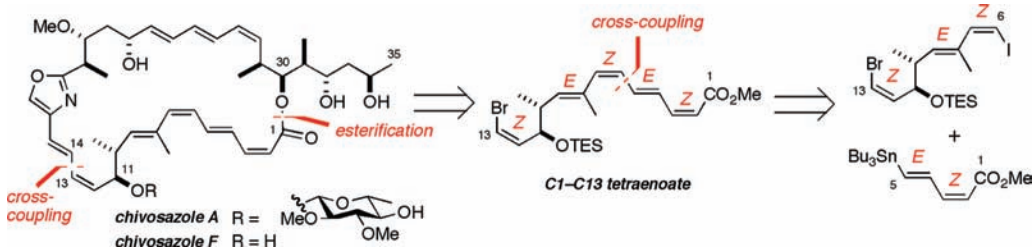
ABSTRACT



Using a combination of asymmetric vinylogous Mukaiyama aldol and Stille cross-coupling reactions, an advanced polyene fragment of the chivosazoles was prepared in a highly stereocontrolled manner. This key C1−C13 pentaene subunit, featuring the conjugated (2*E*,4*Z*,6*E*,8*Z*)-tetraenoate motif and *anti*-configured C10 and C11 stereocenters of the chivosazoles, terminates in a (*Z*)-vinyl bromide for the planned cross-coupling to a northern hemisphere fragment.

The chivosazoles are a unique family of polyene macrolides, isolated initially by the Höfle and Reichenbach group from the myxobacterium *Sorangium cellulosum* (strain So ce12),[1] that show potent antiproliferative activity against a range of human cancer cell lines, as well as activity against yeasts and filamentous fungi. The chivosazoles function through specific binding to G-actin, leading to disruption of cytoskeletal dynamics in vitro. Importantly, their exact mode of action appears to be distinct from other microfilament-disrupting compounds such as rhizopodin and cytochalasin D,[1c] making them promising leads for the development of new chemotherapeutic agents, as well as tools for study of the actin cytoskeleton.

The chivosazoles are also structurally intriguing and synthetically enticing polyketides[2] possessing an elaborate 31-membered macrolactone ring, featuring an oxazole, 10 stereocenters, and, most notably, three distinctive polyene arrays (Scheme 1). Members of the chivosazole family (A−F) are distinguished by variation in the C20 oxygenation and C11 glycosylation patterns, with chivosazole F (**1**) corresponding to the aglycon of chivosazole A (**2**). The stereochemistry of chivosazole A has only recently been elucidated, using a combination of NMR methods, chemical degradation, partial synthesis, molecular modeling, and analysis of the ketoreductase domains of the biosynthetic gene cluster.[3]

There has been limited synthetic work reported on this important family of bioactive macrolides, with Kalesse's synthesis of a C15−C35 northern segment representing the only published effort to date.[4] As part of our interest in antimitotic polyketide metabolites from myxobacteria,[5,6] we have also identified the chivosazoles as testing targets for total synthesis. Herein, we outline our strategy and report

(1) (a) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 962. (b) Jansen, R.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1997**, 1725. (c) Diestel, R.; Irschik, H.; Jansen, R.; Mohammed, W. K.; Reichenbach, H.; Sasse, R. *ChemBioChem* **2009**, *10*, 2900.

(2) For identification and analysis of the chivosazole biosynthetic gene cluster, see: Perlova, O.; Gerth, K.; Kaiser, O.; Hans, A.; Müller, R. *J. Biotechnol.* **2006**, *121*, 174.

(3) Jansen, D.; Albert, D.; Jansen, R.; Müller, R.; Kalesse, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4898.

(4) Jansen, D.; Kalesse, M. *Synlett* **2007**, 2667.

(5) (a) Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Asian J.* **2009**, *4*, 594. (b) Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6699.

(6) (a) Wenzel, S. C.; Müller, R. *Nat. Prod. Rep.* **2007**, *24*, 1211. (b) Weissman, K. J.; Müller, R. *Nat. Prod. Rep.* **2010**, *27*, DOI: 10.1039/c001260m.

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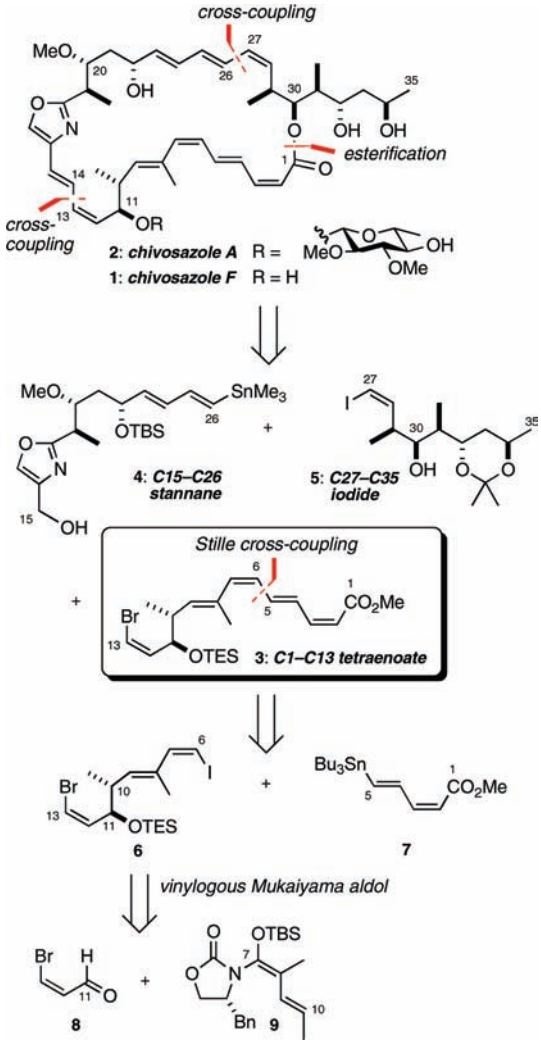
Scheme 1. Retrosynthetic Analysis



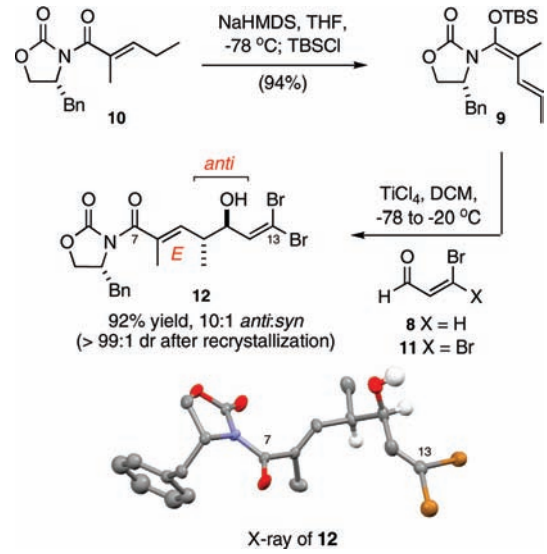
progress toward the synthesis of the chivosazoles, culminating in the highly stereocontrolled construction of the advanced C1−C13 pentaene subunit **3** for planned cross-coupling to a suitable C14−C35 fragment.

The potential sensitivity of the polyene regions of the chivosazoles, in particular the conjugated (2*Z*,4*E*,6*Z*,8*E*)-tetraenoate moiety, should clearly be a prime consideration for any synthetic approach. Guided by this, and the fact that the configuration has not yet been assigned with full confidence, we sought to prepare each stereocluster in isolation and construct the chivosazole aglycon through the flexible and convergent assembly of the appropriate fragments. As outlined retrosynthetically in Scheme 1, we initially anticipated integrating the tetraenoate motif into the nascent chivosazole macrocycle through the late-stage union of the key C1−C13 subunit **3** with a suitable northern hemisphere fragment, arising from the cross-coupling of stannane **4** and iodide **5**.

Simplification of tetraenoate **3** to give two (*Z*,*E*)-dienes **6** and **7** was planned through a Stille coupling reaction, in which we aimed to exploit the relative vinyl halide reactivity of the bidirectional coupling partner **6**. Bishalide linker **6** might then be derived from (*Z*)-bromoacrolein **8** and silyl ketene *N*,*O*-acetal **9** through an asymmetric vinylogous Mukaiyama aldol reaction to define the trisubstituted olefin geometry, and the C10 and C11 stereogenic centers, in a single operation.

Our synthetic efforts commenced with the preparation of silyl dienolate **9** (Scheme 2).[7] Enolization of imide **10** with

Scheme 2. Synthesis of the C7−C13 Region via an Asymmetric Vinylogous Mukaiyama Aldol Reaction



NaHMDS followed by silylation with TBSCl afforded (*E*,*E*)-**9** cleanly. Following the Kobayashi protocol,[8] reaction of **9** with aldehyde **8**[9] in the presence of $TiCl_4$ proceeded to give the *anti* aldol adduct as a *Z*/*E* mixture of vinyl bromides under all attempted conditions. This is likely due to Lewis acid-mediated isomerization of the starting (*Z*)-enal **8** prior to aldol coupling.[10] With a view to performing a selective *trans*-debromination at a later stage, we then examined the use of dibromoacrolein **11**.[9] Pleasingly, the vinylogous Mukaiyama aldol reaction with **9** using $TiCl_4$ now afforded the desired adduct **12** in high yield and diastereoselectivity (92%, 10:1 *anti*:*syn*). The dr could be upgraded to >99:1 by recrystallization, which also enabled us to obtain the X-ray crystal structure, confirming the trisubstituted (*E*)-olefin geometry and also the requisite 10,11-*anti* configuration.[11]

(7) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633.

(8) (a) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604. (b) Shinoyama, M.; Shirokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277.

(9) See the Supporting Information for the synthesis of aldehydes **8** and **11**.

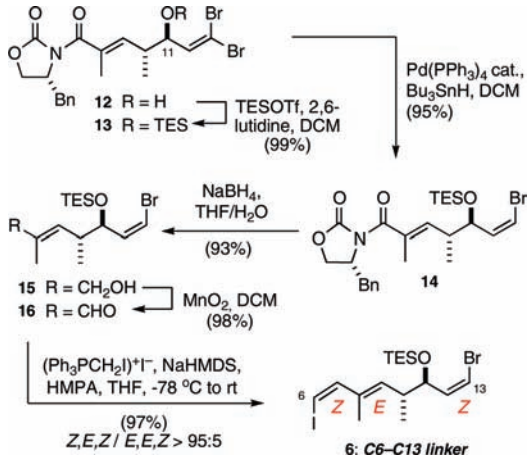
(10) The Kobayashi vinylogous aldol reaction using the corresponding (*Z*)-iodoacrolein gave only the isomerized (*E*)-vinyl iodide adduct in low yield.

(11) CCDC 782548 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Notably, this aldol addition provides an expedient and versatile entry to the C7−C13 region of the chivosazoles, where, if required, all four C10/C11 stereoisomers could be prepared selectively, starting with *ent*-**9** and/or followed by a Mitsunobu inversion at the C11 hydroxyl.[7,12]

Elaboration of aldol adduct **12** to cross-coupling linker **6** began with TES protection of the newly installed C11 hydroxyl group (TESOTf, 2,6-lutidine, 99%, Scheme 3).

Scheme 3. Synthesis of C6−C13 Cross-Coupling Linker

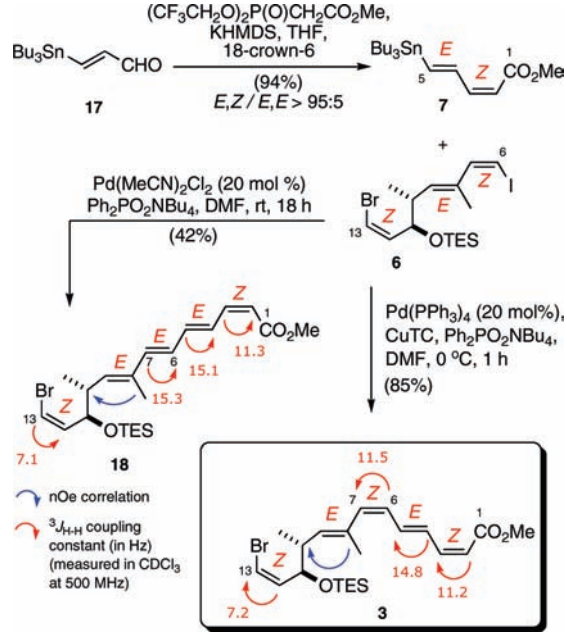


Selective (*E*)-debromination of dibromoalkene **13** was then achieved, using Bu_3SnH and catalytic $Pd(PPh_3)_4$,[13] to afford (*Z*)-vinylbromide **14** in 95% yield. Reductive cleavage of the imide with $NaBH_4$ and subsequent MnO_2-mediated allylic oxidation of **15** generated aldehyde **16** (91% over 2 steps), which was submitted to a range of Stork−Wittig olefination conditions.[14] Optimally, addition of **16** to a mixture of $(Ph_3PCH_3I)^+I^-$ and NaHMDS in THF/HMPA (88:1) at −78 °C, followed by slow warming to room temperature, afforded the requisite (*Z*,*E*)-iododiene **6** with excellent selectivity (97%, >95:5 *Z*,*E*:*E*,*E*). This delicate building block is light sensitive and prone to isomerization, requiring careful handling, and was best used without purification.

At this stage, we required access to the Stille coupling partner (2*Z*,4*E*)-dienoate **7**. This was conveniently prepared from known stannylenal **17**[15] through a Still−Gennari olefination[16] (94%, >95:5 *Z*,*E*:*E*,*E*),[17] setting the stage for the critical task of generating the full C1−C13 tetraenoate fragment with the required chivosazole alkene stereochemistry. When iododiene **6** and stannane **7** were subjected to catalytic $Pd(MeCN)_2Cl_2$ in DMF, in the presence of $Ph_2PO_2NBu_4$ as a tin halide scavenger,[18] cross-coupled product **18** was obtained as the major product (42%), which was inseparable from other isomeric products by flash chromatography. Detailed NMR analysis indicated a (2*Z*,4*E*,6*E*,8*E*)-tetraenoate had been generated.[19] Although this initial study failed to establish the required (6*Z*)-alkene geometry, it succeeded in demonstrating that electron-deficient stannyldienoate **7** was a competent coupling partner and that the greater reactivity of the iodide over the bromide termini in linker **6** permitted a chemoselective monocoupling reaction.

The preferential formation of the (6*E*)-olefin in **18** was attributed to isomerization of the starting vinyl iodide **6**. To circumvent this problem, the known ability of copper salts to accelerate Stille cross-coupling reactions might be exploited to achieve a more rapid fragment union with **6**.[20] Following this reasoning, a Stille cross-coupling reaction of **6** and **7**, using a combination of $Pd(PPh_3)_4$, CuTC, and $Ph_2PO_2NBu_4$ in DMF, was then performed (Scheme 4).

Scheme 4. Completion of the C1−C13 (2*Z*,4*E*,6*Z*,8*E*)-Tetraenoate Subunit



Under these Fürstner-type conditions,[21] the reaction proceeded cleanly even at 0 °C, providing the desired coupled product **3**, isolated as a single (2*Z*,4*E*,6*Z*,8*E*)-stereoisomer

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(14) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.
(15) (a) Beaudet, I.; Parrain, J.-L.; Quintard, J. P. *Tetrahedron Lett.* **1991**, *32*, 6333. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.
(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(17) Franci, X.; Martina, S. L. X.; McGrady, J. E.; Webb, M. R.; Donald, C.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7735.
(18) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.
(19) Interestingly, the congeneric chivosazole A_1 is reported to have this configuration of the tetraenoate, i.e., with the (6*E*)-geometry.
(20) For leading references, see: (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (c) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
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in 85% yield.[22] Gratifyingly, the diagnostic ^{1}H NMR coupling constants measured for **3** agreed with those reported for the corresponding tetraenoate region of chivosazole A,[3] indicating that the (6*Z*)-olefin had now been installed correctly.

In summary, by using a combination of asymmetric vinylogous Mukaiyama aldol and Stille cross-coupling reactions, we have prepared the fully elaborated C1−C13 tetraenoate subunit **3** of the chivosazoles with high stereochemical fidelity and efficiency. This key C1−C13 pentaene subunit, featuring the characteristic conjugated (2*E*,4*Z*,6*E*,8*Z*)-tetraenoate motif and *anti*-configured C10 and C11 stereocenters, terminates in a (*Z*)-vinyl bromide in readiness for union with a suitable northern hemisphere fragment. Studies toward the remaining C15−C26 and C27−C35 subunits **4** and **5**, respectively, and their controlled assembly incorporating building block **3** to give the chivosazoles are ongoing.

(22) This pentaene product was purified on Et_3N-washed silica gel and is stable upon storage at −20 °C under an inert atmosphere with the exclusion of light.

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

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