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Synthesis of the C15−C35 Northern Hemisphere Subunit of the Chivosazoles

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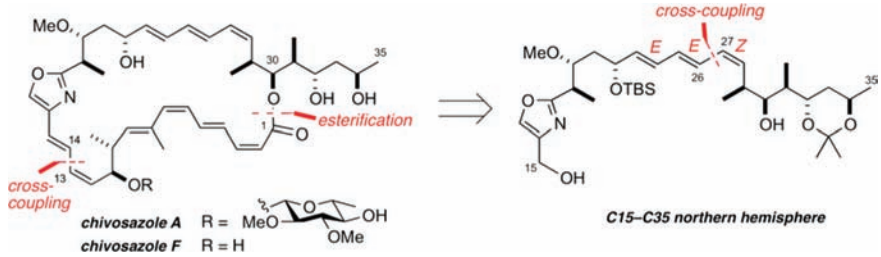
ABSTRACT



An advanced C15−C35 subunit of the chivosazole polyene macrolides was prepared in a convergent manner, exploiting boron-mediated aldol reactions for the stereocontrolled construction of the C15−C26 and C27−C35 segments, followed by their Pd/Cu-promoted Stille coupling to configure the signature (23*E*,25*E*,27*Z*)-triene motif. Correlation with a known C28−C35 degradation fragment of chivosazole A was also achieved.

Myxobacteria represent prolific sources of molecular diversity and produce a wide range of unique polyketide-derived scaffolds, which generally are associated with significant biological activities and therapeutic potential.[1] The chivosazole family of polyene macrolides, isolated from the myxobacterium *Sorangium cellulosum*,[2] displays potent antiproliferative activity against a range of human cancer cell lines (e.g., leukemia K-562, $IC_{50} = 2.9$ nM, and cervical carcinoma KB-3-1, $IC_{50} = 3.5$ nM, for chivosazole A), as well as activity against yeasts and filamentous fungi. This antimitotic activity has recently been shown to derive from selective inhibition of actin polymerization, leading to disruption of cytoskeletal dynamics in vitro.[3] However, the chivosazoles' exact mode of action appears to be distinct from other actin-binding antimicrofilament compounds, making them useful new tools for the study of the actin cytoskeleton, as well as promising leads for the development of potential chemotherapeutic agents.

From a structural perspective, these architecturally complex macrolides display a remarkable range of functionality, with some 10 stereocenters and nine alkenes associated with the aglycon. As the principal congener, chivosazole A (**1**, Scheme 1) is a 31-membered macrolactone featuring three conjugated polyene regions, with alternating *E*/*Z* alkene geometry, an oxazole ring, and three polyol sequences, together with a 6-desoxyglucopyranoside sugar at C11. A full configurational assignment for chivosazole A was proposed in 2007 by Kalesse and co-workers, which depended inter alia on detailed NMR and genetic analysis, combined with chemical degradation studies.[4] Recently, the Kalesse group validated this assignment by the first total synthesis of the aglycon, chivosazole F (**2**),[5a] with installation of most of the polyene regions using Wittig olefinations.[5b,c] As part of our interest in bioactive polyketide metabolites isolated from myxobacteria,[6] we have also embarked on the total synthesis of the chivosazoles. Recently, we described the expedient construction of the C1−C13 tetraenoate subunit **3**, corresponding to the southern hemisphere region, termi-

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(5) (a) Brodmann, T.; Janssen, D.; Kalesse, M. *J. Am. Chem. Soc.* **2010**, *132*, 13610. (b) Janssen, D.; Kalesse, M. *Synlett* **2007**, 2667. (c) This Wittig olefination strategy has also been implemented in the synthesis of chivotriene. See: Brodmann, T.; Janssen, D.; Sasse, F.; Irschik, H.; Jansen, R.; Müller, R.; Kalesse, M. *Eur. J. Org. Chem.* **2010**, 5155.

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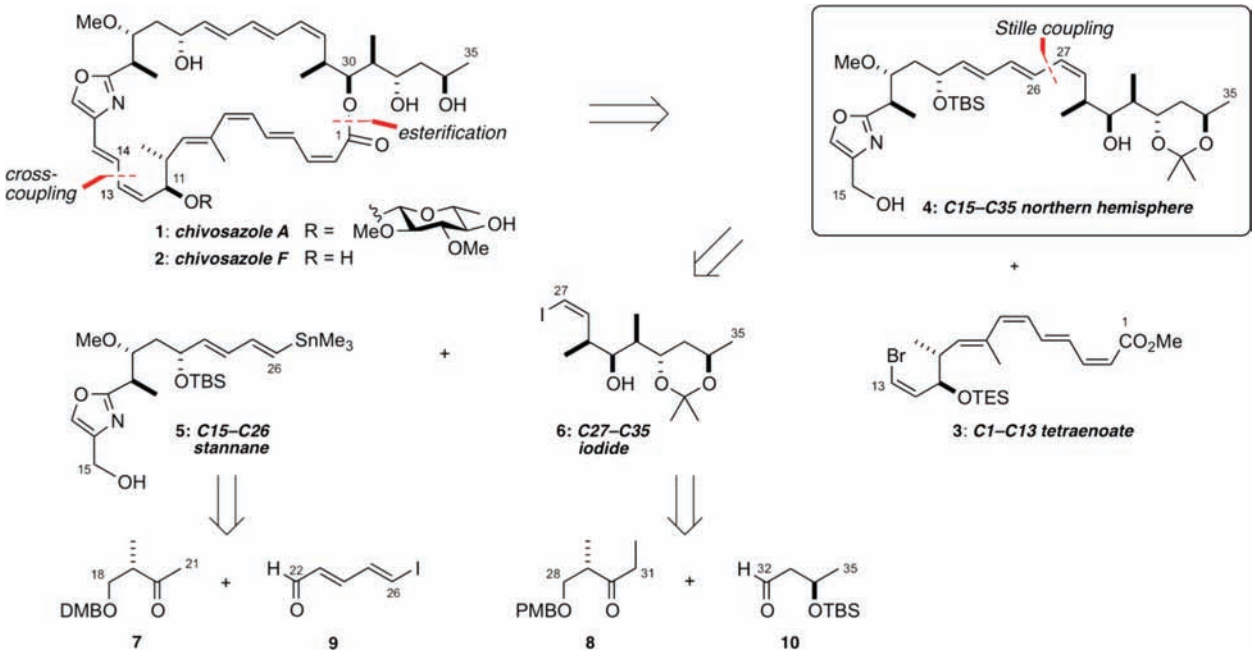
Scheme 1. Retrosynthetic Analysis



nating in a (*Z*)-vinyl bromide for planned cross-coupling to a suitable upper segment.[7] Herein, we report the stereocontrolled construction of the corresponding C15−C35 subunit **4** using our versatile boron aldol methodology and a Stille coupling reaction to efficiently introduce the signature (23*E*,25*E*,27*Z*)-triene.

Guided by the sensitivity of the chivosazole polyene regions, we targeted the preparation of three key subunits from which the aglycon could be assembled in a flexible and convergent manner using suitably mild cross-coupling protocols. As outlined in Scheme 1, the macrolactone was envisaged to arise from the cross-coupling/esterification of a suitable northern hemisphere segment **4** with the pentaene subunit **3**.[7] In turn, **4** might arise from a Stille coupling reaction between (*E*,*E*)-dienyl stannane **5** and (*Z*)-vinyl iodide **6**. On the basis of this key bond scission, the requisite C19−C22 and C29−C32 stereochemistry would be generated by the boron-mediated aldol coupling of ketones **7** and **8** with aldehydes **9** and **10** and subsequent elaboration to give coupling partners **5** and **6**, respectively.

As shown in Scheme 2, preparation of the C27−C35 iodide **6** commenced with the 1,4-*syn* boron aldol reaction[8] of (*S*)-Roche ester-derived ethyl ketone **8**[9] with *β*-silyloxy aldehyde **10**.[10] Accordingly, enolization of ketone **8** with *c*-Hex_2BCl and Et_3N, followed by addition of aldehyde **10**, afforded the desired aldol adduct **11** with a typically high level of diastereoselectivity (92%, >95:5 dr).[8]

Subsequent 1,3-*anti* reduction of *β*-hydroxy ketone **11** under Evans−Tishchenko conditions[11] also proceeded with high diastereoselectivity (>95:5 dr); methanolysis of the ensuing esters[12] then provided diol **12** (72% over 2 steps).[13] Diol differentiation by PMP acetal formation (DDQ, 4 Å MS)[14] provided alcohol **13**.[15] This key intermediate allowed us to independently verify the relative and absolute configuration of the C28−C35 fragment **14** of chivosazole A, as previously prepared by Kalesse.[4] Accordingly, TBS protection of the C32 hydroxyl in **13** and subsequent hydrogenolysis of the PMP acetal provided diol **14**, which correlated by NMR and specific rotation, $[\alpha]_D$ +7.8 (*c* 0.32, $CHCl_3$) cf. +8.3 (*c* 0.29, $CHCl_3$),[4] with the data reported for the authentic degradation fragment.

To facilitate the planned esterification onto the C30 hydroxyl, alcohol **13** was converted into acetonide **15** through desilylation (TBAF) and acetalization ($Me_2C(OMe)_2$, PPTS).

(6) (a) Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6699. (b) Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Asian J.* **2009**, *4*, 594. (c) Paterson, I.; Findlay, A. D. *Aust. J. Chem.* **2009**, *62*, 624.

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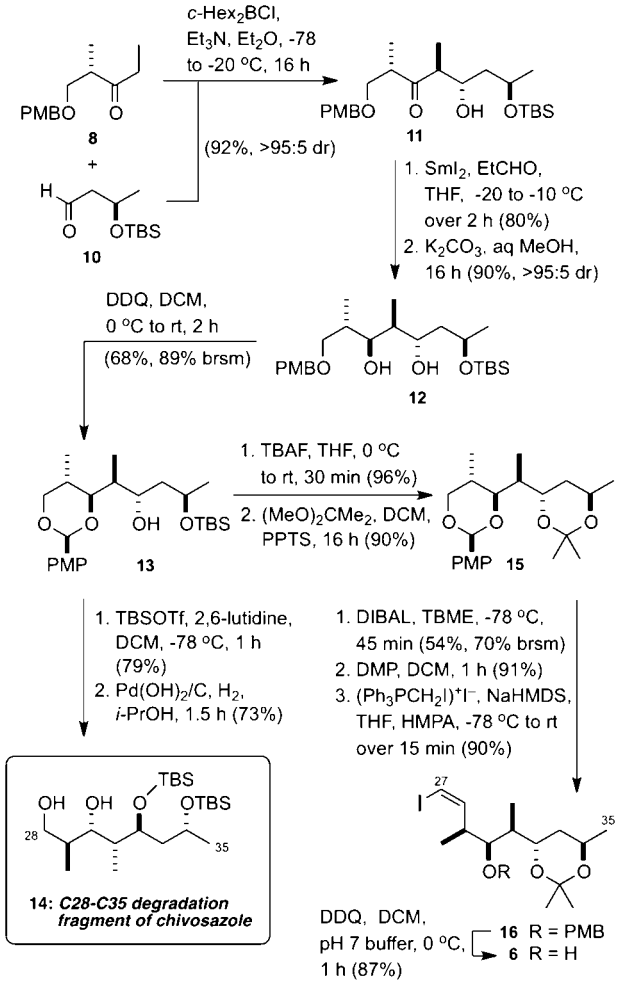
(12) Due to partial transesterification of the kinetic product, a regioisomeric hydroxy ester was sometimes formed which also gave **12** on methanolysis.

(13) The stereochemistry of this intermediate was unambiguously assigned by ^{13}C NMR analysis of the corresponding acetonide. See the Supporting Information for details.

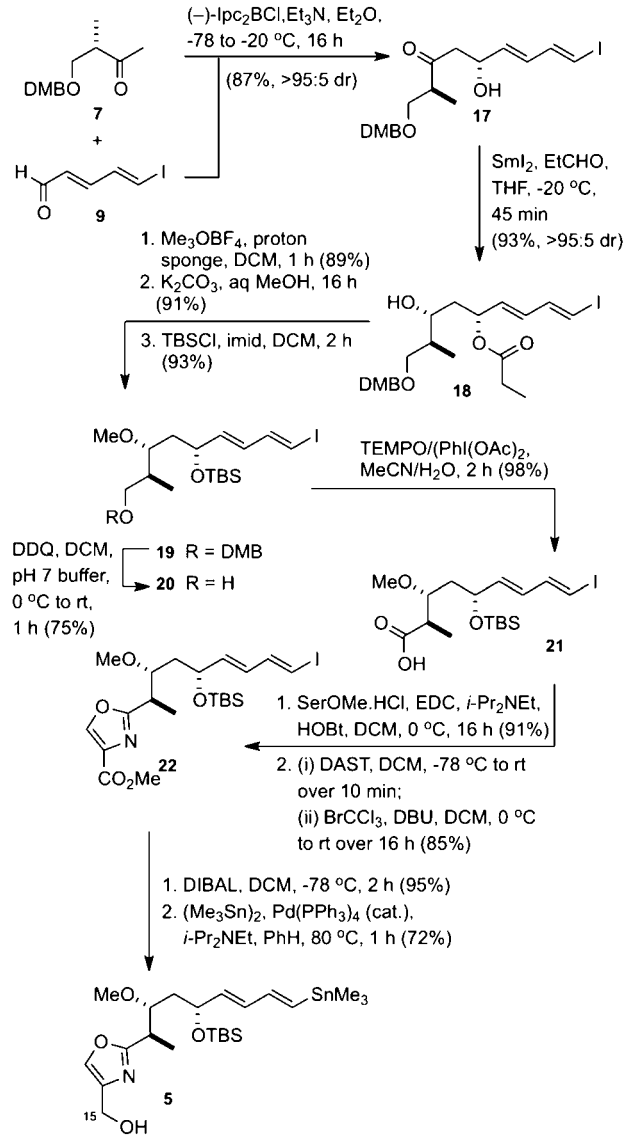
(14) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

(15) Formation of the corresponding orthoester proved problematic with prolonged reaction times.

Scheme 2. Synthesis of the C27−C35 Iodide



Scheme 3. Synthesis of the C15−C26 Stannane



To circumvent problems encountered from competing acetonide cleavage, regioselective DIBAL opening of the PMP acetal in **15** was best performed in TBME.[16,17] Dess−Martin oxidation[18] of the resulting primary alcohol then provided the corresponding α-chiral aldehyde, whose sensitivity to epimerization necessitated direct submission to Stork−Wittig olefination.[19] This afforded *Z*-vinyl iodide **16**, obtained as essentially a single geometric isomer (90%, *Z*:*E* > 20:1). Finally, DDQ-mediated oxidative cleavage of the PMB ether provided the targeted C27−C35 iodide **6** in 25% yield over the 10 steps from ketone **8**.

Preparation of the accompanying C15−C26 stannane **5** (Scheme 3) commenced with a second boron aldol reaction, in this case involving iodo dienal **9**[20] and methyl ketone **7**.[21] Under ligand-enhanced conditions,[22] treatment of ketone **7** with (−)-Ipc_2BCl and Et_3N, followed by addition of aldehyde **9** at −78 °C to the resulting enolate, afforded the desired 1,4-*syn* aldol adduct **17** with high diastereoselectivity (87%, >95:5 dr). Subsequent Evans−Tishchenko reduction[11] (SmI_2, EtCHO) proceeded smoothly to provide **18** (>95:5 dr),[13] which was advanced to **19** through a sequence of O-methylation, ester cleavage, and silylation of the ensuing alcohol.

With the full stereochemistry of the required C15−C26 subunit now in place, our attention turned to installation of the requisite oxazole ring. Accordingly, DDQ-mediated cleavage of the DMB ether in **19** provided alcohol **20**, which was oxidized to the carboxylic acid **21** in high yield (98%) using TEMPO/$PhI(OAc)_2$ in aqueous MeCN.[23] EDC-medi-

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(17) Reaction in DCM resulted in competitive opening of the acetonide at C32 in addition to PMB acetal opening at C28.

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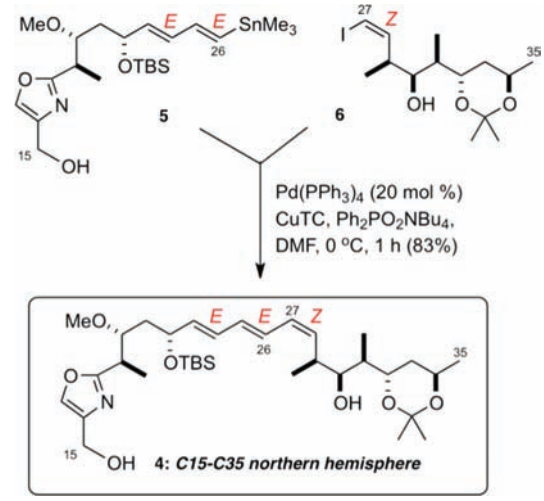
(22) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.

ated coupling[24] of **21** with serine methyl ester provided the corresponding amide, which was smoothly advanced to oxazole **22** (81%, 2 steps) via the DAST/$BrCCl_3$/DBU method of Williams and Wipf.[25] Reduction of the ester (DIBAL, 95%) and stannylation under Wulff−Stille conditions[26] ($(Me_3Sn)_2$, $Pd(PPh_3)_4$, 72%) then provided the C15−C26 stannane **5** with complete retention of the (*E*,*E*)-diene geometry.[27]

Having established effective and scalable routes to the northern hemisphere subunits, dienyl stannane **5**, and vinyl iodide **6**, their union to form the sensitive C23−C28 triene and the complete C15−C35 sequence of chivosazoles A and F could be investigated. Gratifyingly, after a degree of optimization, it was found that exposure of a slight excess of stannane **5** (1.3 equiv) and iodide **6** to a combination of $Pd(PPh_3)_4$, CuTC, and $Ph_2PO_2NBu_4$ in DMF (0 °C, 1 h)[28] resulted in the efficient union of the two coupling partners, providing the targeted northern hemisphere subunit **4** in excellent yield (83%) (Scheme 4). Comparison of the NMR data obtained for **4** with that reported for chivosazoles A[4] and F[2c,5a] allowed confirmation of the (23*E*,25*E*,27*Z*)-triene geometry.

In summary, by using a combination of our boron-mediated aldol methodology and a mild Pd/Cu-promoted Stille coupling reaction, we have prepared the full C15−C35 northern hemisphere subunit **4** of the chivosazoles with the efficient introduction of the characteristic (23*E*,25*E*,27*Z*)-triene region. Studies are now ongoing to establish the most effective means of fragment coupling with the C1−C13 tetraenoate subunit **3**, with a view to completing a convergent synthesis of the chivosazole macrolides.

Scheme 4. Completion of the C15−C35 Northern Hemisphere



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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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