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Total Synthesis of Chivosazole F

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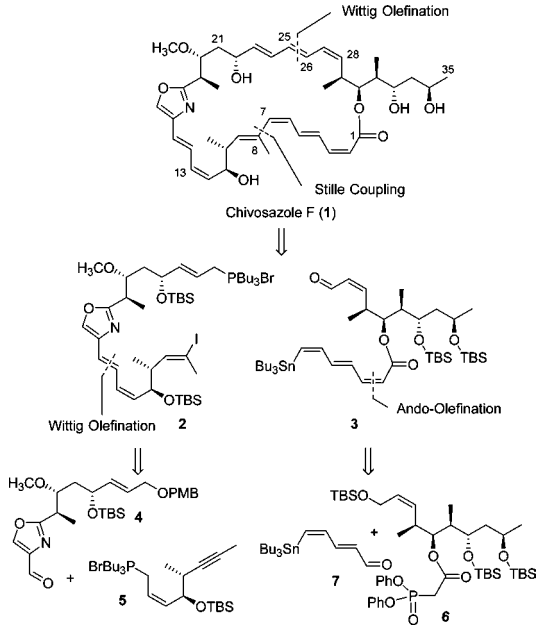
Abstract: The first synthesis of the highly biologically active chivosazole F is described. It features an intramolecular Stille coupling for the macrolactone formation and thereby circumvents the problem of isomerization associated with the tetraene segment. Additionally, the synthesis confirms the structure which has been proposed based solely on a combination of NMR/computational methods and genetic analysis.

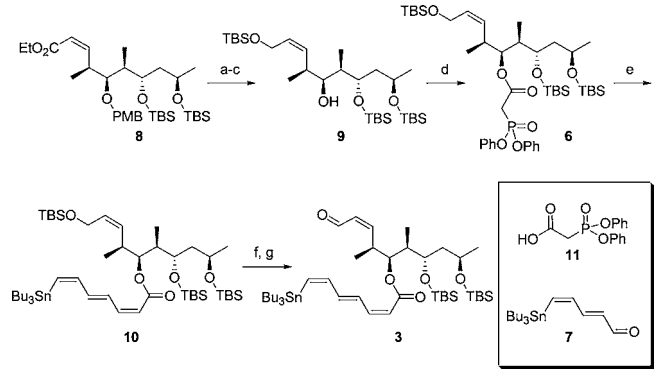
The family of the chivosazoles contains seven 31-membered macrolides which possess a remarkable biological profile.[1] They exhibit antifungal and cytotoxic activity against mouse fibroblasts (L-929) and HeLa cells (IC_{50} 9 ng/mL for both cell lines)[1a] and reduce actin polymerization.[2] In these studies it became apparent that the chivosazoles act on F-actin differently than proposed for cytochalasin D, chondramide, or rhizopodin.[3] Structurally, chivosazole F differs from the other members of this family by lacking the 6-deoxyglucose derivative (chivose) at C11.

Scheme 1



At the outset of our investigations we proposed the unknown configurations of the 10 stereogenic centers through a combination of NOE experiments and computational methods.[4] The configurations at the secondary alcohols were confirmed by genetic analysis put forward by Reid and Caffrey.[4,5] Even with this state of knowledge total synthesis was required to confirm the configurations of the 10 stereocenters. As a consequence of the lability of polyenes, in particular when *Z*-configured double bonds are involved, we embarked on a strategy that established the two sensitive polyene segments in the last steps of the macrolactone formation. Additionally, the recently published synthesis on the southern hemisphere of chivosazole F by Paterson et al. confirmed the sensitive nature of the tetraenoate subunit.[6] We proposed the final connections to be made between C25 and C26 by a Wittig olefination and between C7 and C8 by an intramolecular Stille coupling. During our studies on the synthesis of chivotriene we realized that the best selectivities were observed when segment **2** serves as the Wittig reagent and segment **3** as the corresponding aldehyde (Scheme 1).[7] The assembly of segment **3** started from unsaturated ester **8**.[8] Removal of the PMB group, DiBAl-H reduction, and protection of the primary alcohol as the TBS ether was followed by esterification with phosphonate **11**.[9] Finally, olefination of **6** with aldehyde **7**[10] provided triene **10** in 80% yield as a 1:1 mixture of the *Z* and *E* isomers (Scheme 2). Gratifyingly, the mixture of isomers could be separated by simple column chromatography and the desired olefin was used for the subsequent transformations.

Scheme 2[a]



[a] Reagents and conditions: (a) DDQ, CH_2Cl_2/H_2O, 70%; (b) DiBAl-H; (c) TBSCl, imidazole, 78% (over 2 steps); (d) **11**, DMAP, Et_3N, 2,4,6-trichlorobenzoyl chloride, toluene, 87%; (e) **7**, NaH, THF, 80%, *Z*/*E* = 1:1; (f) HF-pyridine, pyridine, 51%; (g) MnO_2, CH_2Cl_2, 85%.

For the construction of the western hemisphere, we aimed to establish the *anti* relationship in segment **5** through a Marshall−Tamaru reaction. In order to circumvent the modest selectivities of the Marshall reaction in transformations with unsaturated aldehydes,[11] we employed aldehyde **12** with a triethyl silyl group in the α-position to enhance the diastereoselectivity in this reaction.

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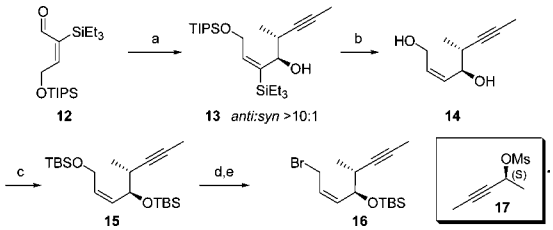
Using the indium protocol developed by Marshall et al.[11a] and *S*-configured propargylic mesylate **17**, the reaction was performed with high selectivities (*anti*/*syn* > 10:1) and provided **13** in good yields (68%) (Scheme 3). The subsequent standard transformations established allyl bromide **16**.

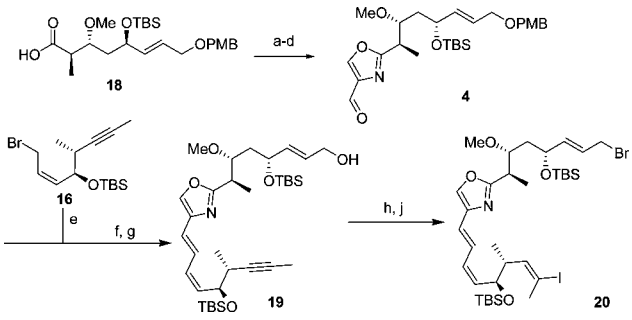
Scheme 3[a]



[a] Reagents and conditions: (a) **17**, $Pd(OAc)_2$, $\cdot PPh_3$, InI, THF-HMPA, 68%; (b) TBAF (5% H_2O), 83%; (c) TBSOTf, 2,6-lutidine, 99%; (d) PPTS, MeOH, 65%; (e) CBr_4, PPh_3, 99%.

Aldehyde **4** was derived from acid **18** through a sequence of esterification and standard oxazole formation.[12] DiBAl-H reduction established the aldehyde functionality required for the Wittig olefination with **5**.[13] The subsequent olefination installed the new double bond with high selectivity (*E*/*Z* > 10:1). At that stage it proved beneficial to remove the PMB protecting group prior to the functionalization of the alkyne. For this transformation the palladium-catalyzed hydrostannylation provided the highest yields and regioselectivities. Finally, the allylic alcohol was converted to the corresponding allyl bromide **20** (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (a) SerOMe•HCl, EDC•HCl, HOBT, *i*-Pr_2NEt, 78%; (b) DAST, CH_2Cl_2; (c) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C; (d) DiBAl-H, toluene, 70% 3 steps; (e) PBu_3, MeCN; (f) KO*t*Bu, toluene, 91% (over 2 steps); (g) DDQ, CH_2Cl_2/H_2O, 63%; (h) (i) Bu_3SnH, $(PPh_3)_2PdCl_2$; (ii) I_2, THF, 67%; (j) (i) MsCl, Et_3N; (ii) LiBr, THF, 82%.

With both hemispheres in hand we continued to establish the *E*-configured double bond between C25 and C26 using a Wittig reaction. Without further functional group transformations the intramolecular Stille[14] reaction followed to establish the carbon framework of chivosazole. The final global deprotection using buffered HF then completed the total synthesis of chivosazole F (Scheme 5). The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS, optical rotation) were in all respect identical to the data originally reported by Höfle and co-workers thus confirming the previously made configurational assignment.

In summary, the first total synthesis of (−)-chivosazole F has been achieved through a strategy that establishes the delicate polyene systems using late-stage Wittig reactions and an intramolecular Stille coupling as the pivotal transformations for their constructions.

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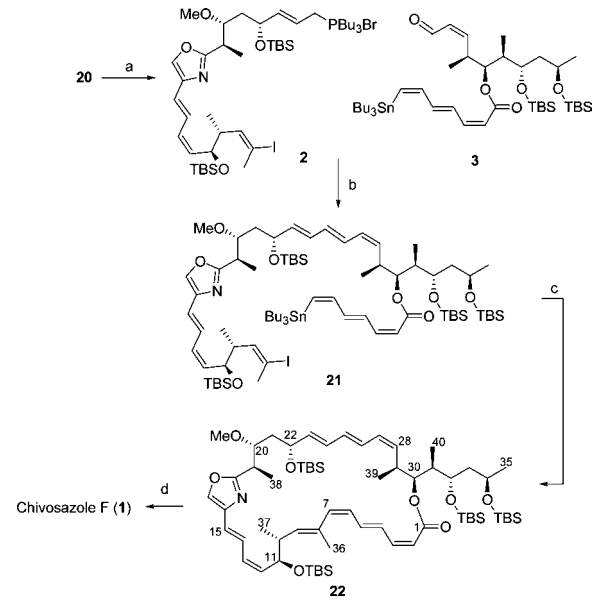
Scheme 5[a]



[a] Reagents and conditions: (a) PBu_3, MeCN; (b) KO*t*Bu, toluene, 48% (over 2 steps); (c) $PdCl_2(PhCN)_2$, DMF; (d) HF-pyridine, pyridine, 18% (over 2 steps).

Supporting Information Available: Spectroscopic and analytical data as well as experimental procedures for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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