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Synthesis of the C10−C32 Core Structure of Spirangien A

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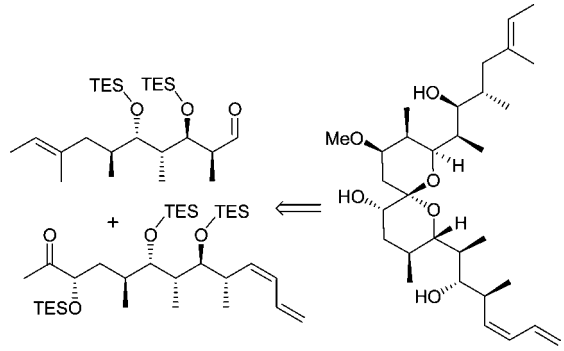
ABSTRACT



The synthesis of the C10−C32 core structure of spirangien A is reported. The pivotal aldol coupling between both key intermediates provides a synthetic challenge in the synthesis of this complex natural product.

Myxobacteria have been proven to be a valuable source for the isolation of structurally diverse and biologically active natural products. In 2005, Höfle and co-workers isolated spirangien A (**1**) and B (**2**) (Scheme 1) from *Sorangium cellulosum* (So ce 90). These unique natural products unfold remarkably high cytotoxic activity against L929 mouse fibroblast cell lines with an IC_{50} value of 0.7 ng/mL for **1**. Additionally, they exhibit antibiotic activity against yeast and fungi (diameters of inhibition zones: *Pichia membranaefaciens* 24 mm, *Rhodotorula glutins* 19 mm, *Botrytis cinerea* 11 mm).[1] The spirangiens contain a highly functionalized spiroketal core structure, a side chain bearing a pentaene chromophore, a terminal carboxyl group, and a total of 14 stereocenters. The structure elucidation was done through NMR spectroscopy and mass spectrometry. For the determination of the relative configuration of the 14 stereocenters, **1** was truncated via cross-metathesis at C10 using Grubbs second-generation catalyst and ethylene to yield **3** as the major product.

The absolute configuration was proposed by analysis of the gene cluster[2] and independently confirmed by the Paterson group through their synthesis of **3**.[3]

Despite its extraordinary activity, the mode of action and its biological targets remain unknown. Moreover, thorough investigations of the biological targets were hampered by the fact that fermentation only provides small amounts of the spirangiens which unfortunately are prone to rapid decomposition. In this context, compound **3** serves as a stable analogue which remains highly active (**3**, IC_{50} = 7 ng/mL). On the basis of its unique structure and the promising biological data, we initiated a synthesis program to provide

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(2) Frank, B.; Knauber, J.; Steinmetz, H.; Scharfe, M.; Blöcker, H.; Beyer, S.; Müller, R. *Chem. Biol.* **2007**, *14*, 221.

(3) Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6699.

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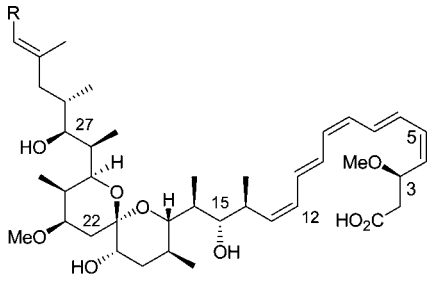
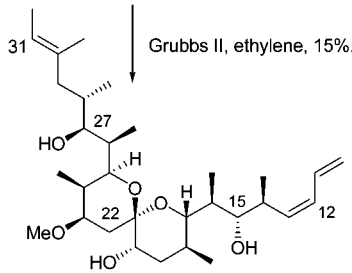
Scheme 1. Spirangiens and Their Metathesis Degradation



Spirangien A (**1**): R = CH_3
Spirangien B (**2**): R = CH_2CH_3

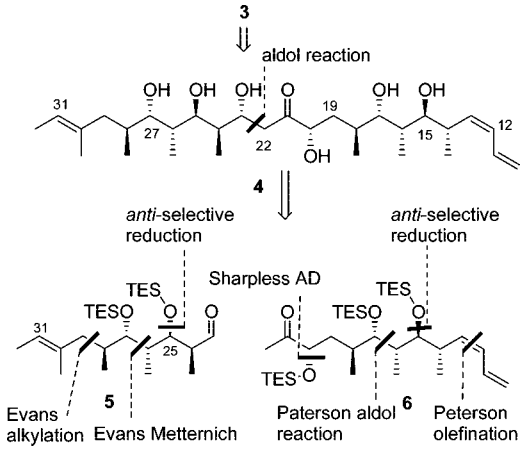


3

an efficient route to **3** and the parent natural products for providing analogues and detailed SAR studies.

As outlined in Scheme 2, our retrosynthetic analysis dissects **3** at the spiroketal moiety which we envisioned to

Scheme 2. Retrosynthetic Analysis of **3**

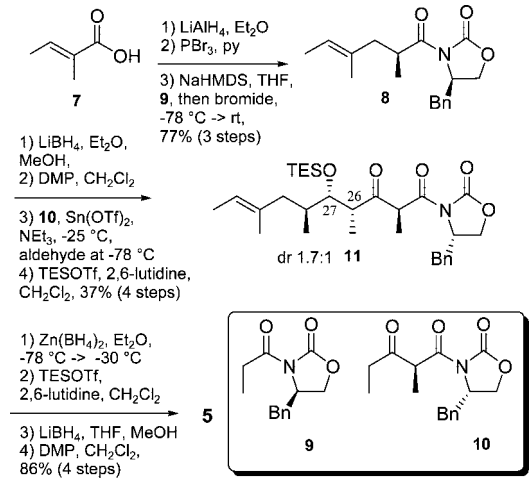


take advantage of the double anomeric effect in a synthetic direction. In turn, the resulting open chain compound **4** can be constructed through an aldol reaction using aldehyde **5** and ketone **6** (Scheme 2).

This disconnection represented a particular challenge since neither the literature precedence nor mechanistic considerations provided an obvious prediction of the selectivity in the aldol step. Finally, we proposed that with TES-protected building blocks the inherent selectivity of the methyl ketone and the *anti*-Felkin-directing effect of the β-hydroxyl group at C25 should provide the desired configuration at C23. As the key transformations for segment **5**, we selected an Evans−Metternich aldol reaction and a subsequent *anti*-selective reduction of the remaining ketone moiety. The synthesis of segment **6** features a Paterson aldol reaction and an *anti*-selective reduction as well. Finally, a Sharpless dihydroxylation of an intermediate terminal olefin was selected for the construction of the hydroxyl ketone.

Our synthesis of aldehyde **5** commenced with tiglinic acid (**7**) which is transformed to the corresponding bromide via $LiAlH_4$ reduction and reaction with PBr_3 and pyridine (Scheme 3).[4] The bromide is subsequently employed in a

Scheme 3. Synthesis of Aldehyde **5**



stereoselective alkylation of oxazolidinone **9**[5a,b] with NaHMDS as the base to obtain **8**.

Next, the auxiliary was removed reductively, and the corresponding alcohol was oxidized to the aldehyde using DMP. This aldehyde is subsequently submitted to a *syn* selective aldol reaction using Evans−Metternich conditions and **10**[5c] to yield the aldol product in a 1.7:1 ratio (analyzed by ^{1}NMR) favoring the desired stereoisomer. It has to be pointed out that the Lewis acid $Sn(OTf)_2$ has to be freshly prepared due to the changing quality of the commercially available reagent. After TES protection, the two diastereomers can be separated cleanly, and the ketone functionality of **11** is reduced highly stereoselectively (*anti*/*syn* > 95:5) with freshly prepared $Zn(BH_4)_2$ to the corresponding C25−C27 *anti*-diol. A subsequent TES protection of the alcohol functionality the auxiliary is cleaved under reductive conditions, and the corresponding alcohol is oxidized to aldehyde **5** in high yield (86% over 4 steps).

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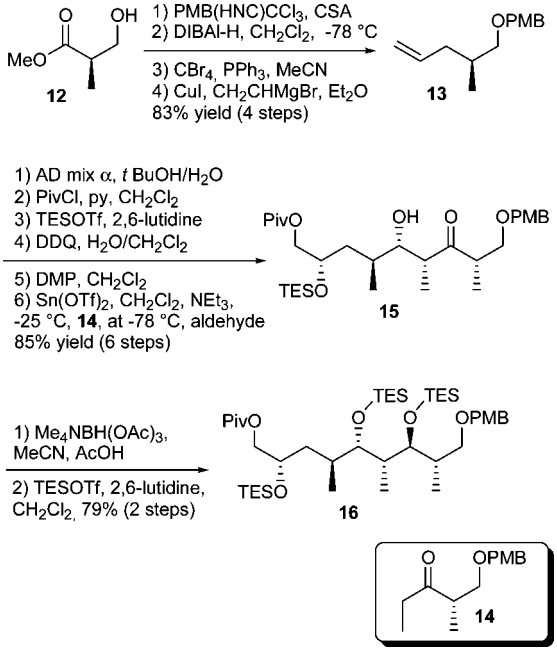
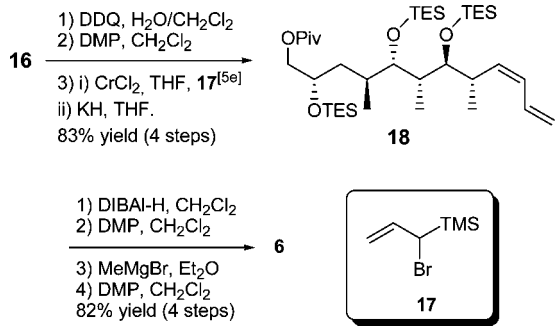
Attention was then directed to the preparation of ketone **6** (Schemes 4 and 5) which starts with Roche ester (**12**) and

Scheme 4. Synthesis of Ketone **6**



is transformed to the corresponding alcohol via PMB protection and DIBAl-H reduction. This alcohol is subsequently used in an Appel reaction to generate the bromide which in turn is displaced with vinylmagnesium cuprate to yield alkene **13**. This double bond serves in a Sharpless asymmetric dihydroxylation[6] with AD-mix α to provide the respective diol in a diastereomeric ratio of 4:1 favoring the desired stereoisomer. For selective functional group transformations, the primary alcohol is protected as a pivaloyl ester and the secondary as a TES ether. At this stage, we decided to use the Paterson aldol reaction of ketone **14**[5d] and the corrseponding aldehyde to yield **15** and a stereoselective 1,3-*anti* reduction for installing the C14−C18 *anti*−*syn*−*anti* stereopentad.[7] Thus, after PMB deprotection, the alcohol is oxidized to the aldeyhde and subjected to an

Scheme 5. Synthesis of Ketone **6**



aldol reaction with **14** and freshly prepared $Sn(OTf)_2$ to yield the desired product as a single diastereomer.[7] The reaction time varied on the reaction scale, and we realized that prolonged reaction times favor the undesired aldol condensation product. Finally, the stereoselective reduction provides the *anti*-diol, and simultaneous TES protection of both hydroxyl groups generates **16**.

For the construction of the terminal diene moiety, the primary hydroxy group was liberated and oxidized (Scheme 5) followed by a two-step Peterson olefination[8] that installs the C1−C4 diene **18** in high yields and selectivities (71%, two steps, only *cis* isomer). Gratifyingly, the two diastereomers resulting from the Sharpless asymmetric dihydroxylation can be separated after reductive cleavage of the pivaloyl group, and an oxidation−methylation sequence furnishes ketone **6**. With aldehyde **5** and ketone **6** in hand, we investigated the pivotal aldol coupling.

Careful examination of the directing effects in this aldol transformation led to the conclusion that the Felkin opposing effect of the C25 TES-ether would provide the desired selectivity.[2,9]

On the other hand, literature precedence using α-oxygenated methyl ketones did not provide a conclusive picture of the directing effects of the ketone. This prompted us to investigate this uncommon aldol connection and various reaction conditions. In particular, the observations by Paterson et al. that acetonides would provide the undesired stereoisomers (LDA 3.5:1; $c\text{Hex}_2\text{BCl}/\text{NEt}_3$ 5:1) indicate that this particular setup would be one of the key transformations in the synthesis. Paterson and his group solved this problem by using a chiral boron enolate that furnished the desired

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(7) (a) Paquette, L. A.; Konetzki, I.; Duan, M. *Tetrahedron Lett.* **1999**, *40*, 7441. (b) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (c) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023. (d) Paterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *4*, 2473. (e) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Chem.−Eur. J.* **2002**, *8*, 4272. (f) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, A. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (g) Paquette, L. A.; Konetzki, I.; Duan, M.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257.

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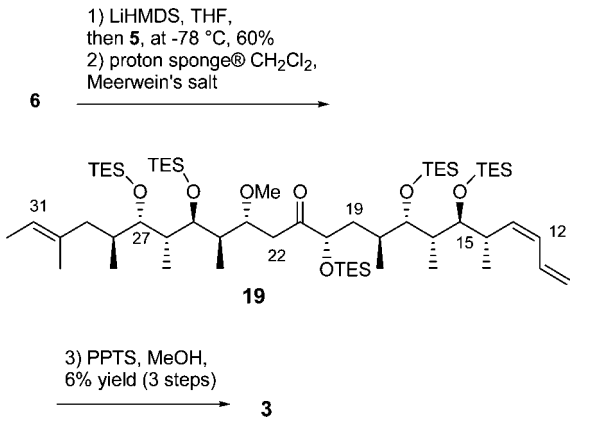
aldol product with a 2.5:1 selectivity. We examined LDA, KHMDS, and a Mukaiyama-type aldol reaction using the TMS enolate of ketone **6** and Me_2AlCl as Lewis acid, but in all cases only poor yields (less than 20%) were obtained. Finally, the use of LiHMDS as the base provided 60% of **19**[10] as a 3:1 mixture of two isomers (Scheme 6). Unfortunately, we were not able to separate these isomers and therefore decided to carry them through the remaining three steps and perform separation later.

Scheme 6. Coupling of **5** and **6**



(10) **24** was also prepared using five TBS ethers instead of TES ethers. Nevertheless, global deprotection under various mildly acidic conditions (protic and Lewis acids) and fluoride sources did not produce any defined compound.

For this reason, we proceeded with the methylation of the hydroxyl at C23, and finally global TES deprotection using PPTS provided crude **3** which allowed purification by HPLC. Gratifyingly, the spectroscopic data of synthetic compound **3** match those of the degradation product. Additionally, a second diastereomer could be detected in the course of the HPLC purification, but the minute amount did not allow for the spectroscopic characterization step. Nevertheless, the high resolution HRMS spectra strongly support that this is the minor diastereomer derived in the aldol step. On the basis of the final HPLC analysis, we can conclude that the aldol coupling proceeds in a 3:1 ratio for the desired stereoisomer.

In conclusion, a flexible and convergent synthesis of spirangien derivative **3** has been reported. This route also paves the way for preparing the spirangiens and related analogues. On the basis of the route described herein, we will focus on the pivotal aldol coupling to optimize yields and selectivities and to understand the subtle directing effects on both the methyl ketone and the aldehyde.

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Supporting Information Available: Complete procedures and ^1H and ^{13}C spectra for major compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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