Natural Product Synthesis

DOI: 10.1002/anie.200801900

Synthesis and Reactions of the Pestalotiopsin Skeleton**

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The pestalotiopsins and taedolidols are caryophyllene-type sesquiterpenes isolated from *Pestalotiopsis sp.*, an endophytic fungus of *Taxus brevifolia*.[1,2] Taedolidol and its epimer, 6-*epi*-taedolidol, possess intricate cage structures consisting of a pentacyclic framework housing nine stereocentres. Pestalotiopsin A (**1**) also has a unique oxatricyclic structure (Figure 1) and has been shown to display cytotoxicity and

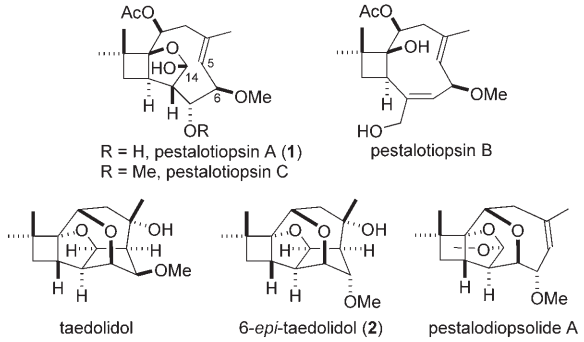

Figure 1. The pestalotiopsins and taedolidols.

immunosuppressive activity in preliminary assays.[1a] We reported the first synthesis of the fully-functionalized oxabicyclic core of pestalotiopsin A (**1**)[3] employing a stereoselective SmI_2-mediated[4] 4-*exo*-trig cyclization of a γ,δ-unsaturated aldehyde.[5] Studies by Paquette et al.[6,7] and Tadano et al.[8] have recently culminated in the first total synthesis of (−)-pestalotiopsin A by the Tadano group.[8b] Herein we report the synthesis of (−)-14-*O*-methyl-pestalotiopsin A by using a diastereoselective Nozaki–Hiyama–Kishi cyclization to construct the C5–C6 bond and the nine-membered ring of the target, and describe the first synthetic entry into the previously unexplored taedolidol family of natural products through the acid-mediated cyclization of the pestalotiopsin skeleton.

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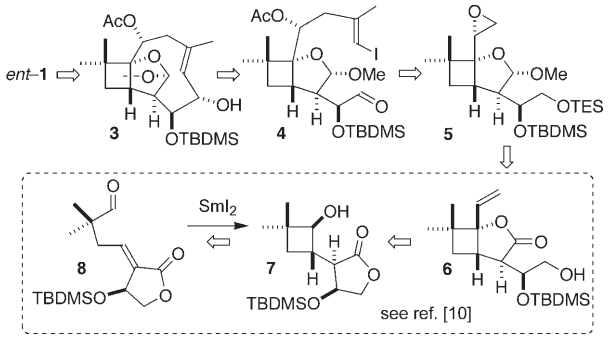
[**] This work was supported by EPSRC, Leverhulme Trust, University of Manchester, University of Glasgow, Merck Sharp & Dohme, AstraZeneca, and Pfizer.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801900.

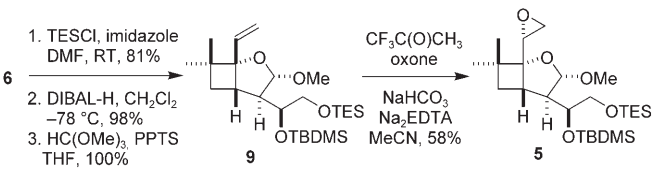
We envisaged the construction of the cyclononene ring of the target could be achieved by using a Nozaki–Hiyama–Kishi cyclization[9] of vinyl iodide-aldehyde **4** (Scheme 1). This



Scheme 1. Retrosynthetic analysis of *ent*-**1**. TES = triethylsilyl; TBDMS = *tert*-butyl dimethylsilyl.

approach is attractive as it potentially allows a stereocontrolled synthesis of the C4–C5 olefin. Epoxide **5** should be a suitable precursor of **4**, that in turn will derive from the bicyclic lactone intermediate **6**. We have previously reported the synthesis of bicyclic lactone **6** from cyclobutanol **7** that in turn was prepared by SmI_2-mediated 4-*exo*-trig cyclization[5] of unsaturated aldehyde **8**.[10] We have since carried out the preparation of **8** on a 20 g (64 mmol) scale.

Protection of the primary hydroxy group in **6**, reduction of the lactone, and formation of the methyl acetal gave **9** as a single diastereoisomer in excellent yield (Scheme 2). Epox-

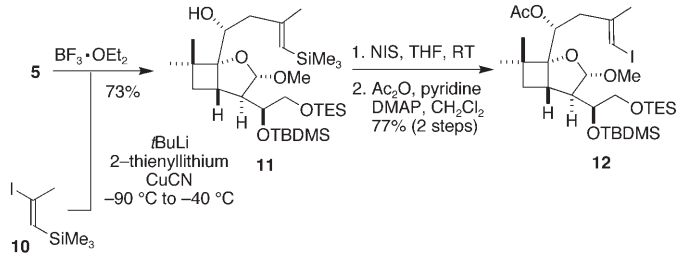


Scheme 2. Synthesis of epoxide **5**. DIBAL-H = diisobutylaluminum hydride; PPTS = pyridinium tosylate; EDTA = ethylenediaminetetraacetic acid.

idation of the alkene in **9** proved to be challenging, however, the trifluoroacetone–oxone reagent system[11] was found to give **5** with moderate diastereoselectivity (3.2:1 by ^{1}H NMR spectroscopy; **5** isolated in 58% yield).

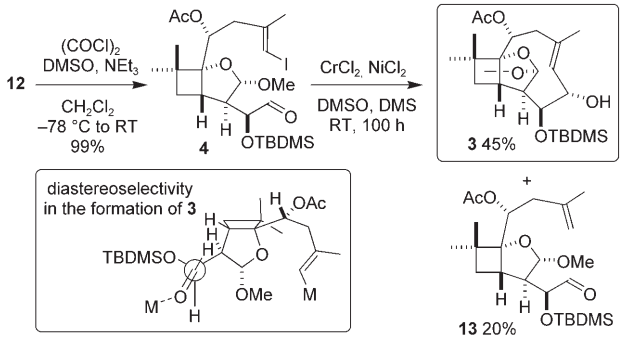
Installation of the requisite vinyliodide group began with the synthesis of iodo-vinylsilane **10** according to the procedure of Nicolaou et al.[12] Conversion of **10** into the corresponding heterocuprate and Lewis acid mediated opening of

epoxide **5** gave **11** in 73% yield (Scheme 3). Subsequent silicon–iodine exchange[12] and acetylation of the secondary alcohol at C2 gave **12**.



Scheme 3. Installation of the vinyliodide group. NIS = *N*-iodosuccinimide; DMAP = 4-dimethylaminopyridine.

Vinyliodide **12** was then converted into the aldehyde cyclization substrate **4** by one-pot deprotection–oxidation of the TES-protected primary alcohol under Swern conditions (Scheme 4).[13] Treatment of aldehyde **4** with $CrCl_2$ and

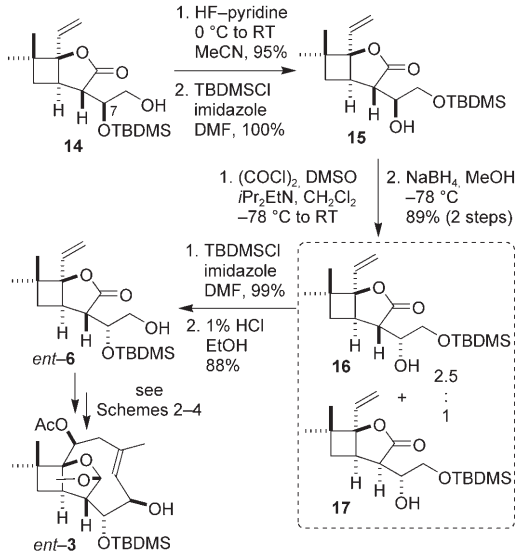


Scheme 4. Nozaki–Hiyama–Kishi cyclization to form **3**.

$NiCl_2$[14] at room temperature for 80–120 h gave **3** in 45% yield as a single diastereoisomer. Byproduct **13**, resulting from the protonation of the alkenylmetal intermediate, was also formed in 20% yield. The diastereoselectivity of the cyclization appears to arise from the preference of C6 of the aldehyde for a conformation in which the metal-complexed carbonyl oxygen atom is orientated away from the crowded bicyclic core of **4** (Scheme 4).

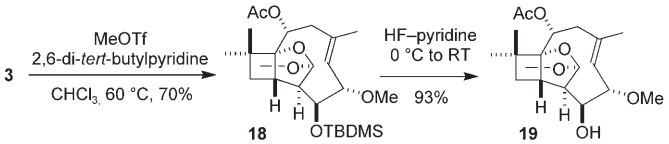
The stereochemical course of the cyclization was confirmed by conversion of **3** into the corresponding 3,5-dinitrobenzoate (3,5-nitrobenzoyl chloride, pyridine, DMAP, CH_2Cl_2, 64%) and X-ray crystallographic analysis.[15]

Our approach to bicyclic lactone **6** also provides access to diastereoisomer **14**,[10] thus potentially allowing the synthesis of the natural enantiomer of pestalotiopsin A (**1**) provided inversion of the C7 configuration in **14** can be achieved. Conversion of **14** into secondary alcohol **15** followed by an oxidation/reduction sequence[16] gave **16** as the major product. Byproduct diastereoisomer **17** could be recycled by epimerization to **16** by using lithium diisopropylamide (LDA). Protection of the secondary hydroxy group in **16** and selective removal of the primary TBDMS ether gave *ent*-**6** in high yield (Scheme 5). Bicyclic lactone *ent*-**6** was then converted into *ent*-**3** by using the route described in Schemes 2–4.



Scheme 5. Synthesis of *ent*-**3**: epimerization of the C7 hydroxy group in **14**.

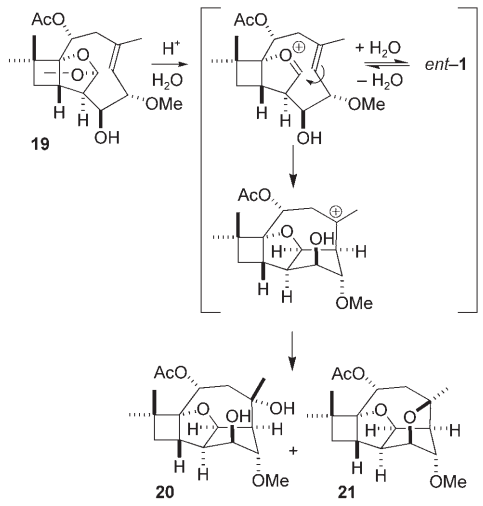
Having established a route to the carbon framework of both enantiomers of pestalotiopsin A (**1**), **3** was used in further studies towards the target. Treatment of **3** with MeOTf and 2,6-di-*tert*-butylpyridine gave **18** in 70% yield (Scheme 6). Deprotection of the TBDMS-protected secondary alcohol was achieved in excellent yield by treatment with HF-pyridine to give (−)-14-*O*-methyl pestalotiopsin A (**19**) (Scheme 6).



Scheme 6. Synthesis of (−)-14-*O*-methyl pestalotiopsin A (**19**).

Hydrolysis of the acetal in **19**, to reveal the lactol motif found in pestalotiopsin A (**1**), by using protic or Lewis acid conditions instead led to a completely diastereoselective, transannular cyclization and the isolation of **20** and **21** possessing four of the five rings of the taedolidol natural products (Scheme 7).

When protic acids were used to trigger the cyclization (examples include aq. HCl and phenylsulfinic acid) intramolecular trapping of the resultant tertiary carbocation was the dominant pathway and pentacyclic structure **21** was isolated as the major product (75% when $PhSO_2H$ was used). When Lewis acids, such as $BF_3{\cdot}2H_2O$, were employed, the major product of the cyclization was **20** (isolated in 67% yield). Attempts to convert **19** into *ent*-**1** by using the



Scheme 7. Acid-promoted cyclization of the pestalotiopsin framework.

conditions employed by Tadano et al. to hydrolyze a C14 acetate in the final step of their synthesis of the nonnatural enantiomer of pestalotiopsin A (1:1:1 AcOH/THF/H_2O, 3 h),[8b] gave only a trace of the natural product in a mixture otherwise containing starting material, and **20** and **21**, after 24 hours. The configuration of **20** and **21** was confirmed by NOE studies (Figure 2).

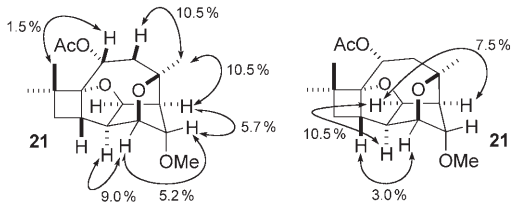


Figure 2. NOE correlations for **21**.

While the acid conditions required for the hydrolysis of **19** appear to limit its use in an efficient synthesis of pestalotiopsin A (**1**), cyclizations of the pestalotiopsin skeleton in **19** provide stereocontrolled access to more complex compounds. It is interesting to speculate that these compounds may be natural products that have yet to be discovered.

In summary, we have developed an approach to the pestalotiopsin framework employing a SmI_2-mediated cyclization and a Nozaki–Hiyama–Kishi coupling to form the four- and nine-membered rings, respectively. We have also shown that the C4=C5 double bond in pestalotiopsin A (**1**) is predisposed to undergo addition to a C14 oxonium ion, suggesting a biosynthetic link between the pestalotiopsin and taedolidol families. We are currently developing a second-generation approach to the pestalotiopsins and taedolidols.

Received: April 23, 2008
Published online: June 23, 2008

Keywords: natural products · pestalotiopsins · samarium · taedolidols · total synthesis

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[15] See Supporting Information for X-ray structure. CCDC 684818 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.
[16] Attempts to invert the configuration at C7 by using Mitsunobu conditions led to elimination of the secondary hydroxy group.

