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Samarium(II)-Mediated 4-*exo*-trig Cyclization. A Stereocontrolled Approach to the Core of Pestalotiopsin A

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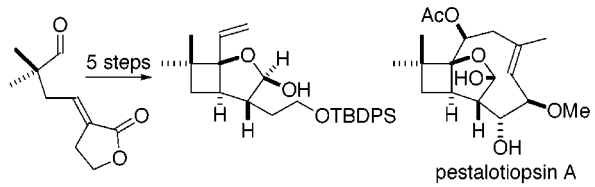
ABSTRACT



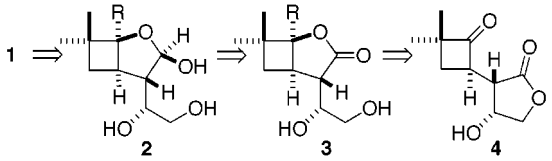
Pestalotiopsin A is a structurally unique caryophyllene-type sesquiterpene which has shown immunosuppressive activity and cytotoxicity in preliminary assays. A stereocontrolled approach to the functionalized 2-oxabicyclo[3.2.0]heptane core of pestalotiopsin A is described. The approach includes a samarium(II)-mediated 4-*exo*-trig cyclization and a trans-lactonization process triggered by the addition of alkylytterbium reagents to a cyclobutanone intermediate.

The pestalotiopsins are caryophyllene-type sesquiterpenes isolated from an endophytic fungus of *Taxus brevifolia*, the Pacific yew.[1,2] Pestalotiopsin A **1** is of particular interest as it possesses an oxatricylic structure unique among natural products[3] and has shown immunosuppressive activity and cytotoxicity in preliminary assays.[1] It would appear to be possible that the activity of this compound originates from the 2-oxabicyclo[3.2.0]heptan-3-ol core, since pestalotiopsin B, which lacks this structural feature, has no reported activity.

We recently developed a stereoselective approach to functionalized cyclobutanols using a samarium(II)-mediated[4] 4-*exo*-trig cyclization of unsaturated aldehydes.[5,6] We now report the application of this chemistry to the successful synthesis of the functionalized 2-oxabicyclo[3.2.0]heptane system found in pestalotiopsin A. The second part of our approach draws on observations made by Kende in his approach to punctaporonin B[7a] and involves an efficient trans-lactonization process triggered by the addition of an alkylytterbium reagent to a cyclobutanone intermediate.

Retrosynthetic analysis of pestalotiopsin A (Scheme 1) reveals possible disconnections of the nine-membered ring at several points between C1 and C6 (pestalotiopsin A numbering scheme, Figure 1). Disconnections between C3 and C4, or across the C4−C5 double-bond, appear to be particularly attractive. Bicyclic lactones **3**, therefore, are key

Scheme 1. Retrosynthetic Analysis of Pestalotiopsin A



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(1) Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshida, S.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 2122.

(2) Pulici, M.; Sugawara, F.; Koshino, H.; Okada, G.; Esumi, Y.; Uzawa, J.; Yoshida, S. *Phytochemistry* **1997**, *46*, 313.

(3) Kende has reported a synthetic intermediate with a related structure in his approach to Punctaporonin B. See ref 7a.

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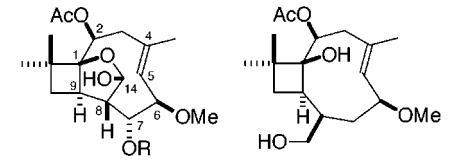


Figure 1. The pestalotiopsin natural products.

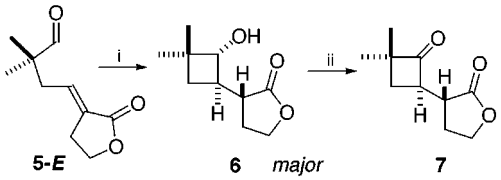
intermediates in our approach to pestalotiopsin A. Importantly, flexibility in the nature of the R group is crucial for the examination of several future approaches to the final, nine-membered ring.

We envisaged that the addition of alkylmetal reagents to cyclobutanone **4** would proceed selectively from the opposite face to the lactone substituent,[7] triggering trans-lactonization and releasing the hydroxyethyl side chain necessary for the construction of the final ring. We felt that cyclobutanones such as **4** would be accessible using our previously reported samarium(II) cyclization chemistry. A feature of our strategy is that stereocenters at C8 and C9 can be established directly in the samarium(II) cyclization step and carried intact through the addition/trans-lactonization sequence.

Here we report studies which illustrate the feasibility of our approach and represent the first synthetic approach to the core of pestalotiopsin A.

We have previously reported the cyclization of unsaturated aldehyde **5-*E*** to give *anti*-cyclobutanol **6** in good yield and as a 4:1 mixture at the center α to the lactone carbonyl.[6b] In this reaction three contiguous stereocenters are established in a single step with significant control. We felt that cyclobutanol **6** would be an excellent model compound for our studies. Oxidation of **6** with tetrapropylammonium perrhuthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) gave cyclobutanone **7** in quantitative yield (Scheme 2).

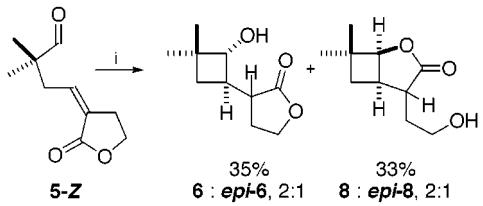
Scheme 2[a]



[a] Reagents and conditions: (i) SmI_2, THF−MeOH (4:1), 0 °C, 79%, 4:1 mixture of diastereoisomers; (ii) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 100%.

To assess the effect of the initial double bond geometry on the stereochemistry α to the lactone carbonyl group in the cyclobutanol products, we next examined the cyclization of **5-*Z*** (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (i) SmI_2, THF−MeOH (4:1), 0 °C.

Interestingly, cyclization of **5-*Z*** gave a complex mixture of products. In stark contrast to the complete *anti*-selectivity observed in the cyclization of **5-*E***, a 1:1 mixture of *syn* and *anti* cyclization products was obtained, with the *syn* products undergoing spontaneous lactonization to give lactones **8**. In addition, 2:1 mixtures at the center α to the lactone carbonyl group were also obtained. It is therefore clear that the initial double bond stereochemistry has a profound effect on the relative stereochemistry across the newly formed ring junction but has a less dramatic effect on the stereochemistry α to the lactone carbonyl group. Enholm first observed a marked dependence of diastereoselectivity on the olefin geometry in samarium(II)-mediated reductive cyclizations to form five-membered carbocycles.[8] Identification of the products from the cyclization was facilitated by the preparation of lactones **8** and ***epi*-8** independently (vide infra).

We next turned our attention to the sequential nucleophilic addition/trans-lactonization step. We began by examining the addition of simple alkylmetal reagents to cyclobutanone **7**.

Initial attempts to add MeMgBr and MeLi to **7** led to substantial epimerization of the starting material, giving cyclobutanone **10**, although pleasingly the desired bicyclic lactone **9a** was also obtained in low yield (29% and 15%, respectively).[9] We next investigated the use of less basic organocerium reagents. Although less epimerization was observed using this approach, the yields obtained from the addition were still unsatisfactory. Molander has reported that organoytterbium reagents, prepared by the addition of alkyllithium or Grignard reagents to ytterbium(III) triflate,[10] exist as brightly colored, homogeneous solutions in THF and

(4) For reviews on the use of samarium(II) iodide in organic synthesis, see: (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (f) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745.

(5) Prior to our work, a single example of such a cyclization had been described by Weinges: Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305.

(6) (a) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. (b) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 681.

(7) (a) Kende, A. S.; Káldor, I.; Aslanian, R. *J. Am. Chem. Soc.* **1988**, *110*, 6265. (b) Kende, A. S.; Káldor, I. *Tetrahedron Lett.* **1989**, *30*, 7329.

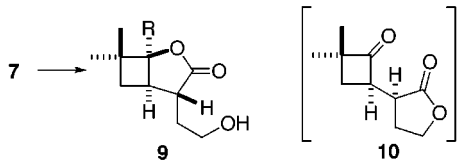
(8) (a) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. (b) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (c) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841.

(9) Cyclobutanone **10** was prepared independently from the minor diastereoisomer formed in the samarium(II)-mediated 4-*exo*-trig cyclization.

(10) Commercially available "anhydrous" ytterbium triflate was dried thoroughly before use (140 °C/0.1 mmHg/20 h).

are attractive alternatives to organocerium reagents.[11] Such reagents have also been shown to give enhanced diastereoselectivities, when compared to the parent organolithium and magnesium reagents in additions to simple carbonyl compounds.[11] Using Molander's approach, alkylytterbium reagents derived from MeLi and vinylmagnesium bromide added smoothly to cyclobutanone **7** to give **9a** and **9b**, respectively, in good yields and with no trace of epimerized byproducts (Table 1).[11b] Results from the additions of other

Table 1. Alkylytterbium Additions to Cyclobutanone **7**



alkylmetal	product	yield[a]
MeLi	**9a** R= Me	68%
MgBr	**9b** R= vinyl	67%
Me, MgBr	**9c** R= Me	78%
MgBr, Me	**9d** R= Me	85%
Li, BnO	**9e** R= BnO	50%[b]

[a] See the Supporting Information for general procedure. [b] Unoptimized.

alkylmetal reagents are also shown in Table 1. Clearly, by varying the alkylmetal reagent employed, a variety of approaches to the final nine-membered ring can be accommodated.

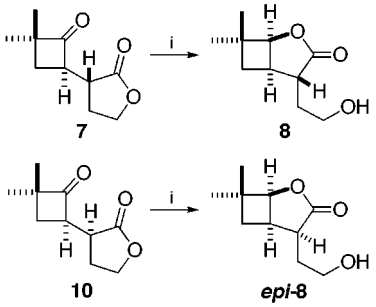
To confirm the stereochemistry of the bicylic lactone products, **9a** was converted to the corresponding *p*-nitrobenzoate **11** (p-$O_2NC_6H_4COCl$, pyridine, rt, 88%) and its structure determined by X-ray crystallography.[12]

(11) (a) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990. (b) During the course of our studies, Molander described a similar diastereoselective, sequential addition/lactonization process triggered by the addition of an organoytterbium to a functionalized cyclopentanone and a cyclohexanone: Molander, G. A.; Köllner, C. *J. Org. Chem.* **2000**, *65*, 8333.

(12) See Supporting Information. Crystal data for **11**: $C_{18}H_{21}NO_6$, M = 347.36, triclinic, a = 6.569(1), b = 7.667(1), and c = 19.936(2) Å, α = 85.81(1), β = 81.75(1), and γ = 62.17(1)°, U = 878.7(2) Å^3, T = 293 K, space group P-1 (No. 2), Z = 2, μ(Mo Kα) 0.10 mm^{-1}, 6176 reflections measured, 5116 unique F^2 values used in refinement (R_{int} = 0.044). R_1-[2504 with $I > 2\sigma(I)$] = 0.051, wR_2(all data) = 0.16, $|\Delta\rho|$ < 0.23 e Å^{-3}. The orientations of the three methyl groups were determined from difference maps and then refined. CCDC reference number 164157. Programs used: SHELX97 − Programs for Crystal Structure Analysis (Release 97-2). G. M. Sheldrick, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998. WinGX − A Windows Program for Crystal Structure Analysis. L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837. CAD4EXPRESS Diffractometer Control Program, Nonius B.V., 2600 AV Delft, The Netherlands, 1994.

In a related addition/trans-lactonization process, the reduction of cyclobutanones **7** and **10** with L-Selectride at −78 °C was found to give lactones **8** and ***epi*-8**, respectively, in 59% and 88% yields (Scheme 4). This confirmed our assignment of the products from the cyclization of **5-*Z***.

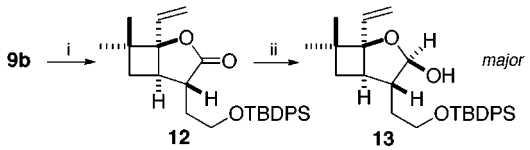
Scheme 4[a]



[a] Reagents and conditions: (i) L-Selectride, THF, −78 °C, 59% for **8**, and 88% for ***epi*-8**.

To complete our approach to the pestalotiopsin A core, the primary hydroxyl group of **9b** was protected and the lactone **12** reduced to the lactol **13**. Treatment of the lactone with DIBAL-H gave a 2:1 mixture of lactols (Scheme 5).

Scheme 5[a]



[a] Reagents and conditions: (i) TBDPSCl, imidazole, DMF, rt, 73%; (ii) DIBALH, CH_2Cl_2, −78 °C, 86% [2:1 mixture of diastereoisomers].

We envisaged that the major product would arise from reduction from the "outside" of the bicyclic system. NOE studies on the lactols did indeed reveal that **13** was the major product from the reduction (Figure 2).[13]

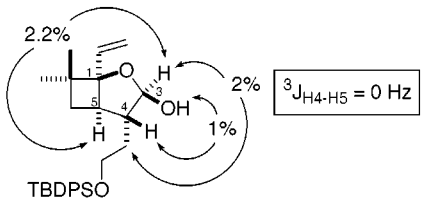


Figure 2. NOE study on lactol **13**.

The retention of the desired stereochemistry at C4 was clear from the lack of coupling between H4 and H5, with

the dihedral angle between the two protons being virtually 90° in the correct C4 epimer (see Figure 2 for numbering).

In conclusion, the functionalized 2-oxabicyclo[3.2.0]-heptane core of pestalotiopsin A has been prepared with stereocontrol at four contiguous stereocenters using an approach based on a samarium(II)-mediated 4-*exo*-trig cyclization and a trans-lactonization process triggered by the addition of alkylytterbium reagents. Importantly, our approach is sufficiently versatile to allow for disconnections at a number of positions around the final nine-membered ring.

We are currently preparing the fully functionalized core of pestalotiopsin A using this approach and are developing strategies for the closure of the final ring.

(13) The stereochemistry at C3 in the major lactol isomer was determined by comparison of NOE values for both isomers. For example, in the minor isomer an NOE of 5.6% between H3 and H4 was observed, while a 2.3% NOE was observed between the two protons in the major isomer.

Acknowledgment. We thank the EPSRC (D.J., Grant GR/M13572) and the Carnegie Trust (Summer studentship to D.J.E.) for financial support. We also thank Dr. Kenneth Muir for obtaining X-ray crystal data for compound **11** and Mr. J. Gall from the NMR Spectroscopy Laboratory at the University of Glasgow for technical assistance.

Supporting Information Available: X-ray crystal structure and crystallographic data for **11** and experimental procedures and full characterization data for compounds **7**, **9a**−**e**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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