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A Short and Efficient Stereoselective Synthesis of the Polyhydroxylated Macrolactone (+)-Aspicilin

Darren J. Dixon, Alison C. Foster, and Steven V. Ley*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K.

svl1000@cam.ac.uk

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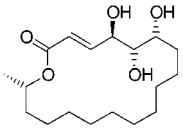
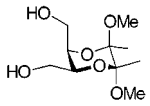
ABSTRACT



(+)-Aspicilin **1**



(R',R',R,S) **2**

A short and efficient synthesis of the polyhydroxylated macrolactone (+)-aspicilin 1 using a stereoselective lithium perchlorate mediated addition of allyltributyltin to the equatorially disposed carboxaldehyde of 3 (derived from (*R*′,*R*′,*R*,*S*) butane diacetal protected butane tetrol 2) as the key step is described. Terminal group manipulation and Masamune–Roush olefination using phosphonate ester 4 followed by macrocyclization via ring closing metathesis afforded the natural product after partial hydrogenation and global deprotection.

The abundance of polyhydroxylated natural products, ranging from relatively simple sugars to more structurally complex molecules such as polyketides which exhibit a broad range of biological properties, continues to stimulate the development of new methods for their stereoselective synthesis.

Consequently, we have recently reported the use of dimethyl tartrate derived (*R*′,*R*′,*S*,*S*)- and (*S*′,*S*′,*R*,*R*)-2,3-butanediacetal-protected butane tetrols as readily accessible building blocks for polylol production.[1] In addition, we reported the preparation and utility of isomeric (*R*′,*R*′,*R*,*S*)-2,3-butanediacetal-protected butane tetrol, derived from a C_2 symmetric dimethyl tartrate through a chiral memory protocol, as a building block for *anti*-1,2-diols through selective chemical differentiation of the spatially dissimilar hydroxyl termini.[2,3]

Here, we describe the application of these important results to the synthesis of the *anti*-1,2-diol containing polyhydroxylated macrolactone natural product aspicilin **1**. Aspicilin, an 18-membered macrolactone metabolite, was first isolated from *Lecanoraceae* lichen in 1993 by Feige and co-workers.[4] Although its biological function is yet to be determined, its structure which contains four stereogenic centers, three of which occur as an *anti*,*syn*-triol motif, makes it an ideal synthetic target to showcase the new methodology.

The synthetic plan relied on a stereoselective addition of a suitable allylic nucleophile to the equatorially disposed carboxaldehyde of **3**, itself readily derived from key building block **2**. It was believed that the sense of the addition would be governed by chelation control to the ring dioxane oxygen, mirroring our initial investigations using aldehydes derived from (*R*′,*R*′,*S*,*S*)- and (*S*′,*S*′,*R*,*R*)-2,3-butanediacetal-protected butane tetrols. Protection of the resulting secondary hydroxyl and deprotection/oxidation of the axially disposed hydroxymethyl group followed by an olefination using phosphonate ester **4**[5] should set up the desired *E*-α,*β*-unsaturated ester. Finally, macrocyclization through a ring closing metathesis reaction followed by partial hydrogenation and global deprotection should afford the natural product (Scheme 1).[6]

(1) Barlow, J. A.; Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1627−1629.
(2) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1631−1633.
(3) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635−1637.
(4) Feige, G. B.; Lumbsch, H. T.; Huneck, S.; Elix, J. A. *J. Chromatogr.* **1993**, *646*, 417−427.
(5) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121−129.

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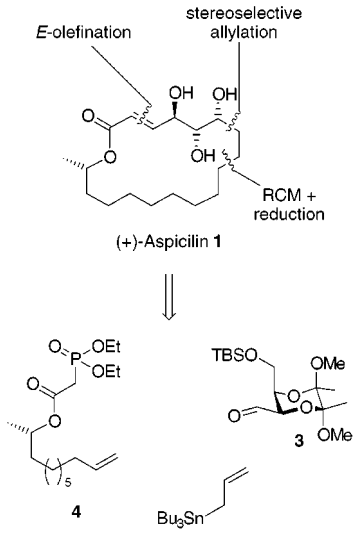
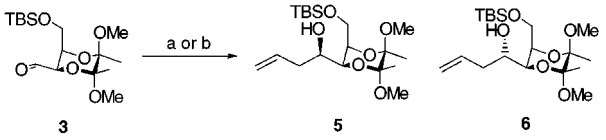
Scheme 1



The synthesis began from the readily accessible diol building block **2** which was transformed on a multigramme scale to the desired aldehyde **3** in two steps according to the previously established procedure.[3] The stereoselective addition of an allyl group to this aldehyde was indeed possible following similar conditions for the analogous addition to aldehydes derived from (*R*′,*R*′,*S*,*S*)- and (*S*′,*S*′,*R*,*R*)-2,3-butanediacetal-protected butane tetrols. Thus, **3** was dissolved in diethyl ether, and lithium perchlorate was added until the solution was saturated (~5 M). Allyltributyl tin (3 equiv) was added and the reaction left to stir overnight at room temperature. On workup, two diastereomeric products **5** and **6** were detected in a ratio of 9:1, respectively. Chromatographic purification afforded the diastereomerically pure homoallylic alcohol **5** in 70% yield (Scheme 2).

Scheme 2[a]



[a] (a) 5 M $LiClO_4$, Et_2O, allyltributyltin; 9:1 (**5**:**6**) 70% of **5**; (b) $ZnCl_2$ (3 equiv), Et_2O, allyltributyltin; 1:9 (**5**:**6**) 80% of **6**.

In the course of our investigations to increase the observed selectivity of this addition reaction, we came across an interesting result. When zinc chloride was used as the Lewis acid, the reaction proceeded to completion in a shorter time and in improved yield. However, the opposite sense of stereochemical induction was observed, giving products again in a ratio of 9:1 (Scheme 2). This extremely useful result is not easily explained but is the subject of a more detailed investigation that will be published later. The lithium perchlorate activated reaction, however, is believed to proceed via chelation control (Figure 1).

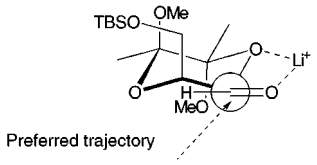
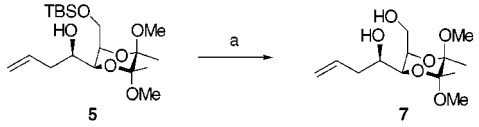


Figure 1.

Because of the hindered nature of the newly formed secondary alcohol in these reactions, Mosher analysis to confirm the stereochemistry was not possible. However, a single-crystal X-ray structure of the diol **7** derived from the major product **5** (Scheme 3) confirmed that the sense of the asymmetric induction in the lithium perchlorate mediated reaction was consistent with addition occurring through chelation control (Figure 1).

Scheme 3[a]



[a] (a) TBAF, THF, 100%.

With these results in hand, the synthesis of both natural and 6-*epi*-aspicilin was embarked upon.[7] The synthesis of both enantiomers began with protection of the homoallylic alcohol as the methoxymethyl ether. This was possible but required forcing conditions analogous to those used for the protection of tertiary alcohols.[8] Thus, alcohol **5** was treated with methoxymethyl iodide (MOMI), generated via an in situ Finkelstein reaction, and Hünigs base in refluxing DME for 13 h and afforded the desired MOM-protected material in 72% (86%)[6] yield after chromatographic purification. Standard TBS removal and oxidation following the Swern protocol afforded the axially disposed aldehyde **8** in 100% (100%) yield over two steps.

To minimize the possibility of epimerization of the axially disposed aldehyde, the Masamune−Roush conditions[9] were chosen for the subsequent olefination reaction. Accordingly, aldehyde **8** was treated with phosphonate ester **4**, lithium chloride, and Hünigs base at room temperature for 14 h and gave, on workup, a 10:1 mixture of *E*:*Z* isomers. Chromato-

(6) A similar approach was published during the course of our investigations: Nishioka, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 5597−5600.

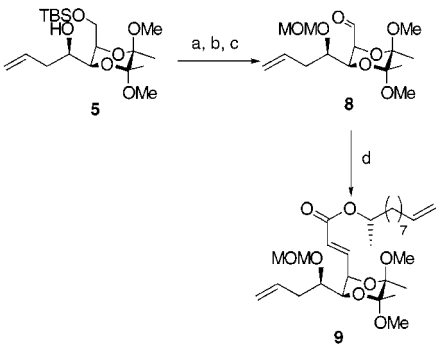
(7) Yields for the epimer synthesis given in parentheses.

(8) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Kieng, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954−2961.

(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

graphic purification afforded the isomerically pure *E* isomer **9** in 58% (71%) yield (Scheme 4).

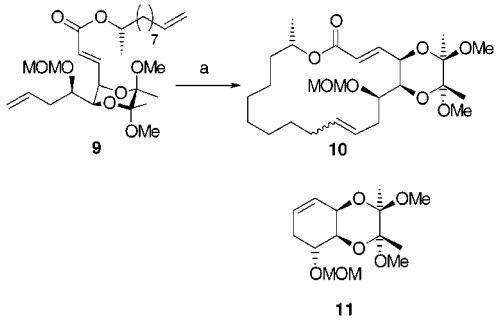
Scheme 4[a]



[a] (a) MOMCl, NaI, DME, Hünigs base, 72% (86%); (b) TBAF, THF, 100% (100%); (c) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C to rt, 100% (100%); (d) LiCl, Hünigs base, **4**, MeCN.

Macrocyclization of triene **9** was possible using standard ring closing metathesis conditions.[10] Thus, a dilute solution of **9** in dichloromethane at room temperature was treated with a catalytic quantity of Grubb's catalyst[11] (10%) for 14 h and afforded the desired material **10** in 73% (45%) yield and as a 1.5:1 mixture of *Z*:*E* isomers. The byproduct (**11**) of metathesis across the double bond of the α,β-unsaturated ester was also detected in 26% yield (Scheme 5).

Scheme 5[a]

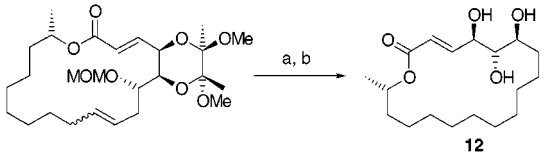


[a] (a) $(PCy_3)_2RuCl_2$ 10 mol %, DCM, 73% of **10** (45%) and 26% of **11**.

Partial hydrogenation of the isomeric mixture of alkenes **10** occurred smoothly using palladium on barium sulfate in ethyl acetate under an atmosphere of hydrogen for 40 min to give the fully protected aspicilin in 100% (100%)[6] yield. Global deprotection using the standard conditions for BDA removal, namely treatment with a 90% aqueous solution of trifluoroacetic acid followed by removal of volatiles in vacuo, proceeded smoothly on fully protected 6-*epi*-aspicilin to give the triol product **12** in 44% yield.

(10) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.
(11) Purchased from Strem Chemicals.

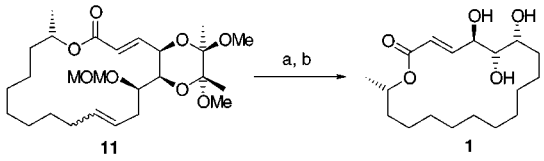
Scheme 6[a]



[a] (a) Pd−$BaSO_4$, EtOAc, 40 min, 100%; (b) TFA/H_2O 9:1, 44%.

When these conditions were applied to the deprotection of the natural diastereoisomer, the reaction gave only an unidentifiable byproduct. However, treatment with ethanedithiol and boron trifluoride etherate afforded (+)-aspicilin **1** in 73% yield. The ^1H NMR, ^{13}C NMR, IR, melting point, MS, and specific rotation $[\alpha]^{28}_D$ +35.0 (*c* 0.20, $CHCl_3$) [lit. $[\alpha]^{23}_D$ +37.5 (*c* 0.55, $CHCl_3$)][12] of the synthesized material were in excellent agreement with the reported data[4] and that of an authentic sample (Scheme 7).[13]

Scheme 7[a]



[a] (a) Pd−$BaSO_4$, EtOAc, 40 min, 100%; (b) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, DCM, 73%.

In summary, a short and efficient stereoselective synthesis of the polyhydroxylated natural product (+)-aspicilin **1** and the C-6 epimer has been achieved using (*R*′,*R*′,*R*,*S*)-2,3-butanediacetal-protected butane tetrol as the starting material. The key step relied on the stereoselective allylation of the equatorially disposed aldehyde in **3**. Terminal group manipulation and olefination using phosphonate ester **4** followed by macrocyclization via ring closing metathesis afforded, after partial hydrogenation and global deprotection, the target compounds. Both diastereoisomers of aspicilin have been submitted for biological screening.

Acknowledgment. We thank the EPSRC (to D.J.D. and A.C.F.), Zeneca Agrochemicals (to A.C.F.), and the Novartis Research Fellowship (to S.V.L.) for financial support and Dr. Mike Turnbull of Zeneca Agrochemicals for useful discussions.

Supporting Information Available: Characterization data for aspicilin and 6-*epi*-aspicilin. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991214S

(12) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505−7515.
(13) Kindly donated by Professor Hatakeyama.