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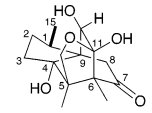
The Total Synthesis of (±)-11-*O*-Debenzoyltashironin

Silas P. Cook,[†] Alessandra Polara,[†] and Samuel J. Danishefsky*[,†,‡]

Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021

Received September 30, 2006; E-mail: s-danishefsky@ski.mskcc.org

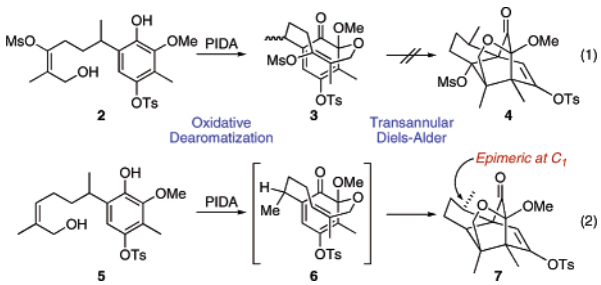
Our laboratory is engaged in a program devoted to the total synthesis and evaluation of small molecule natural products exhibiting neurotrophic activity. 11-*O*-Debenzoyltashironin (**1**), isolated from the pericaps of *Illicium merrillianum*,[1] has been shown to induce neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1 μM. The reported neurotrophic activity, in addition to the rich functionalization and complex architecture of the molecule, renders **1** a particularly compelling target for synthetic endeavors. We report herein the inaugural total synthesis of 11-*O*-debenzoyltashironin (**1**).



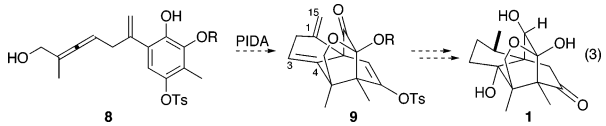
11-O-Debenzoyltashironin (**1**)

We had originally conceived of a biomimetic cascade strategy toward **1**, wherein a substrate of the type **2** (Scheme 1, eq 1) would, upon exposure to a hypervalent iodine source (such as phenyliodine-(III) diacetate, or PIDA), undergo oxidative dearomatization to afford an intermediate of the type **3**. It was our hope that this intermediate would subsequently suffer transannular Diels−Alder cyclization to provide an advanced compound, **4**, possessing the tetracyclic carbon framework of **1**. In the event, although we were pleased to find that oxidative dearomatization did indeed proceed in the desired regiochemical sense, the subsequent Diels−Alder reaction could not be achieved. We tentatively ascribed the failure of the projected cyclization to electronic and possibly steric constraints posed by the mesyl enol ether in the tetrasubstituted dienophilic component. Indeed, the simple trisubstituted congener (**5**) was found to readily undergo the cascade sequence to provide cycloadduct **7** (eq 2). Unfortunately, the transformation cleanly yielded the diastereomer in which the relative stereochemistry of the C_1 methyl group would be opposite to that required for **1**.[2]

Scheme 1. Original Synthetic Strategy toward **1**

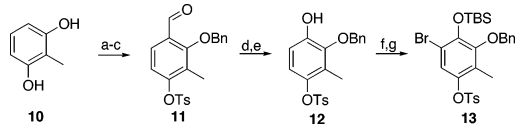


On the basis of these early experiments, we sought to design a modified oxidative cyclization substrate that would incorporate appropriate functional handles to allow for the eventual installation of the C_1 methyl group in the correct orientation, as well as for the placement of the requisite C_4 hydroxyl group. We thus set as a target an allenic phenol of the type **8** (eq 3), which might undergo oxidative dearomatization followed by transannular Diels−Alder reaction, to provide a tetracyclic compound such as **9**. From this intermediate, the C_1-C_{15} exocyclic olefin could hopefully be selectively reduced to provide the C_1 methyl group in the required stereochemical sense. Additionally, we anticipated that the C_3-C_4 olefin could be susceptible to a stereo- and regioselective epoxidation/epoxide opening sequence, allowing for the installation of the C_4 hydroxyl group.



The synthesis of the allenic substrate (**8**, R = Bn) commenced with the preparation of aromatic bromide **13** from 2-methylresorcinol (**10**), as shown (Scheme 2). Thus, formylation of **10**, as previously described,[3] followed by sequential phenolic tosylation and benzylation, provided intermediate **11**. The latter was subjected to Baeyer−Villiger oxidation, and hydrolysis of the resultant formate afforded phenol **12** in nearly quantitative yield. As expected, NBS-mediated bromination occurred exclusively *ortho* to the phenol functionality. Subsequent TBS protection yielded the requisite aromatic bromide **13**.

Scheme 2. Synthesis of Aromatic Bromide **13**



[a] Key: (a) $Zn(CN)_2$, HCl, ether, rt (>99%); (b) TsCl, DCM, −10 °C (57%); (c) BnBr, K_2CO_3, TBAI, acetone, reflux (97%); (d) *m*CPBA, DCM, rt then; (e) TEA, MeOH/DCM (1:1), rt (98% over two steps); (f) NBS, DCM, 0 °C (85%); (g) TBSCl, DCM, TEA (87%).

With **13** in hand, we turned to the venerable Stille reaction as a means of installing the required allene side chain. Initial attempts at coupling the allene moiety in its entirety, using a vinyl tin species, proved unsuccessful. However, the previously described[4a,b] vinyl stannane **14** was found to be an excellent participant in the Stille coupling using Fu's conditions[5] (Scheme 3). The product of the coupling, alcohol **15**, was converted to the corresponding aldehyde in nearly quantitative yield, through exposure to Dess-Martin periodinane.[6] Alkyne addition to the aldehyde provided propargyl alcohol (**16**). Although this addition could be accomplished in low yield with a simple lithium alkynyl anion, significant substrate

[†] Columbia University.
[‡] Sloan-Kettering Institute for Cancer Research.

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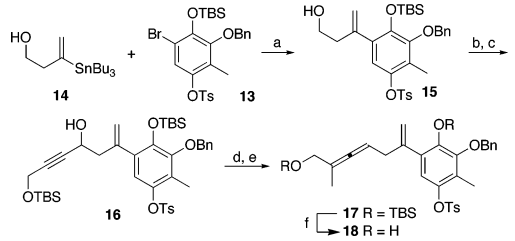
Scheme 3. Synthesis of Oxidative Dearomatization Precursor **18**

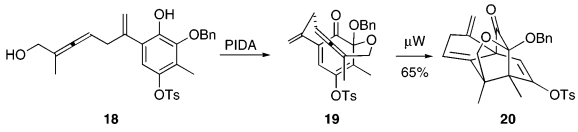


[a] Key: (a) $Pd_2(dba)_3$, tBu_3P, DMF, 80 °C, (77%); (b) DMP, DCM, 0 °C, (98%); (c) 2-propargyloxyTBS 4eq, Et_2Zn, $Ti(OiPr)_4$, rt, (91%); (d) MsCl, TEA, rt, then; (e) $Me_2Cu(CN)Li_2$, −78 °C, (88% over two steps); (f) TBAF, AcOH, rt, (95%).

polymerization and other side reactions severely compromised the efficiency of the reaction, presumably due to the sensitivity of the β,γ-unsaturated aldehyde. Examination of a variety of known alkyne addition conditions revealed the $Et_2Zn/Ti(i\text{PrO})_4$ (without BINOL) system, developed by Pu et al., to be highly effective, providing the desired product (**16**) in consistently high yield.[7] Mesylation of propargyl alcohol **16** under standard conditions, followed by S_N2' nucleophilic methylation using the higher-order Lipshutz dimethylcyano cuprate,[4c] provided **17** in 60% yield over five steps. Although removal of the silyl protecting groups was initially problematic due to the sensitivity of the allene-containing skipped diene, high yields of **18** were ultimately obtained through the use of excess tetrabutylammonium fluoride (TBAF), buffered in acetic acid.

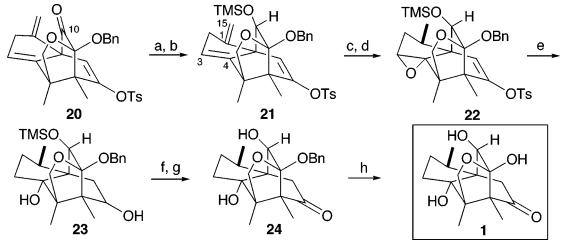
With substrate **18** in hand, we were able to examine the key biomimetic oxidative dearomatization/transannular Diels−Alder sequence. In the event, upon exposure of **18** to PIDA, a mixture of oxidized quinone monoketal intermediate (**19**) and Diels−Alder adduct (**20**) was observed (Scheme 4). Subsequent heating of this mixture for 4 min under microwave irradiation produced Diels−Alder adduct **20** as the only isolable compound in 65% yield. In short, this remarkable transformation had produced all four rings of 11-*O*-debenzoyltashironin in a single transannular Diels−Alder reaction of a tetrasubstituted diene with a trisubstituted allenic dienophile.

Scheme 4. Oxidative Dearomatization/Transannular Diels−Alder



Having assembled the entire carbon skeleton of **1**, we could now focus on completing the synthesis through a series of deprotections and substrate-controlled diastereoselective oxidation state adjustments. Thus, adduct **20** was found to undergo $NaBH_4$-mediated reduction of the ketone at C_{10} in good yield and diastereoselectivity (>9:1) (Scheme 5). Although protection of the newly formed secondary alcohol proved difficult (presumably due to the highly hindered nature of the alcohol), silylation could be achieved by stirring the substrate in neat trimethylsilyl-imidazole to afford **21**.[8] Differentiation of the olefins in triene **21** proved to be a formidable challenge. The Prilezhaev reaction[9] led to selective epoxidation at the less hindered α-face of the trisubstituted (C_3-C_4) olefin after brief exposure of **21** to *m*CPBA in cold CH_2Cl_2. The short reaction time resulted in low conversions but prevented significant overoxidation. The exomethylene group (C_1-C_{15}) was then reduced with Wilkinson's catalyst under a hydrogen atmosphere at 100 psi to provide compound **22**.[10,11] The reductive opening of the epoxide of **22** was accomplished in modest yield with $LiEt_3BH$ (Superhydride) in a sealed tube at 100 °C.[12] The harsh conditions required to open the epoxide also resulted in the reductive cleavage of the tosyl enol ether to provide **23**. Interestingly, the hindered TMS ether survived the reaction conditions, at least to the extent of being present on the isolated product (*vide* **23**). Dess−Martin mediated oxidation of the secondary alcohol, followed by TMS deprotection afforded **24** in high yield. Exposure of **24** to 10% Pd/C under a hydrogen atmosphere afforded 11-*O*-debenzoyltashironin (**1**), whose spectral data were identical to those derived from natural sources.[1]

Scheme 5. Synthesis of (±)-11-*O*-Debenzoyltashironin **1**



[a] Key: (a) $NaBH_4$, DCM/MeOH (3:1), −78 °C (83%); (b) TMS-imidazole, neat, rt (>99%); (c) *m*CPBA 1.9eq, DCM, 0 °C (39%; 71% BORSM); (d) $(PPh_3)_3RhCl$, H_2, benzene, 100 psi (74%); (e) $LiEt_3BH$ 52eq, THF, 100 °C (32%); (f) DMP, DCM, rt (96%); (g) HF-pyr. TBAF, THF, rt (87%); (h) H_2, Pd/C 10%, EtOAc (91%).

In summary, we have developed a concise synthesis of 11-*O*-debenzoyltashironin (**1**). The key transformation in our sequence involved a remarkable oxidative dearomatization/ transannular Diels−Alder cascade, which allowed for the rapid assembly of the tetracyclic carbon skeleton of the natural product. We are currently investigating an asymmetric version of this synthesis and applying our sequence to the synthesis of analog structures with the aim of identifying optimal therapeutic agents. Results of these studies will be forthcoming.[13]

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Supporting Information Available: Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The results described herein are part of a much larger study of the tashironin problem, described in the PhD thesis of Silas Cook (Columbia University, 2006). This thesis contains confirmatory crystallographic studies of related compounds, which will be disclosed as part of a full paper.

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