Total Synthesis of the Antitumor Macrolides, (+)-Brefeldin A and 4-Epi-Brefeldin A from D-Glucose: Use of the Padwa Anionic Allenylsulfone [3+2]-Cycloadditive Elimination To Construct Trans-Configured Chiral Cyclopentane Systems


Published in:
Organic Letters

Document Version:
Publisher’s PDF, also known as Version of record

Queen’s University Belfast - Research Portal:
Link to publication record in Queen’s University Belfast Research Portal

Publisher rights
© 2016 American Chemical Society
This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

General rights
Copyright for the publications made accessible via the Queen’s University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen’s institutional repository that provides access to Queen’s research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person’s rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
Total Synthesis of the Antitumor Macrolides, (+)-Brefeldin A and 4-Epi-Brefeldin A from d-Glucose: Use of the Padwa Anionic Allenylsulfone [3 + 2]-Cycloadditive Elimination To Construct Trans-Configured Chiral Cyclopentane Systems

Ziyue Xiong and Karl J. Hale*

The School of Chemistry & Chemical Engineering and the Centre for Cancer Research and Cell Biology (CCRCB), The Queen’s University Belfast, Stranmillis Road, Belfast BT9 7AG, Northern Ireland, United Kingdom

Supporting Information

ABSTRACT: A new synthesis of (+)-brefeldin A is reported via Padwa allenylsulfone [3 + 2]-cycloadditive elimination. Cycloadduct 13 was initially elaborated into iodide 27, which, following treatment with Zn, gave aldehyde 28 whose C(9) stereocenter was epimerized. Further elaboration into enoate 38 and Julia–Kocienski olefination with 5 subsequently afforded 39, which was deprotected at C(1) and O(18). Yamaguchi macrolactonization of the seco-acid thereafter afforded a macrocycle that underwent O-desilylation and inversion at C(4) to give (+)-brefeldin A following deprotection.

The structurally complex antitumor macrolide, (+)-brefeldin A,\(^*\) has occupied an almost iconic position within the field of stereocontrolled natural product total synthesis,\(^*\) due to the significant challenges it poses for complex chiral cyclopentane ring construction. In this connection, and following a recent successful deployment of the Padwa allenylsulfone anionic [3 + 2]-cycloadditive elimination\(^5\) in the synthesis of (−)-echinosporin,\(^6\) we became interested in evaluating whether this novel cyclopentene ring-assembly method might prove useful for the stereoselective construction of chiral bicyclic cyclopentanoids with a trans-ring junction, and in this connection, (+)-brefeldin A immediately sprung to mind as a target.

(+)-Brefeldin A has elicited considerable medicinal interest over the years,\(^*\) due to the fact that its water-soluble 7-N,N-dimethylglycinate pro-drug, breflate, was reported to be a powerful inhibitor of human melanoma xenograft growth in mice.\(^*\) Despite these early exciting findings, subsequent more detailed pharmacological evaluation of breflate and other brefeldin A pro-drugs at higher dosages (20 mg/kg) did eventually reveal that they could bring about seizures in mice and cause noticeable neurodegeneration.\(^*\) Ultimately, these observations led to molecules of the brefeldin class not proceeding into human clinical development. It is now believed that much of the toxicity of (+)-brefeldin A derives from its blockade of the interaction between the adenosine diphosphate ribosylation factor 1 (Arf1)–GDP (guanosine diphosphate) complex with the Sec7 domains of various Arf–GTPase exchange factors, which interferes with their normal functioning.\(^*\) Despite these problems, work has continued on the synthesis of new brefeldin A analogues,\(^*\) with many teams retaining the hope that they might identify a structurally modified congeners that will have an improved activity/toxicity profile. It was with such thoughts in mind, that we too commenced synthetic efforts on (+)-brefeldin A, and herein, we now report a new, fully stereocontrolled, enantioselective synthesis.

In our original retrosynthetic plan for (+)-brefeldin A (1) (Scheme 1), we sought to access 1 from the seco-acid 2 by regioselective macrolactonization. Compound 2 would emerge from 3 by cleavage of all the protecting groups, while 3 would derive from 6 by the successful implementation of E-olefin cross-metathesis and Julia/Kocienski olefination tactics on 6 and 4, respectively. Aldehyde 6 would possibly emerge from 8 by pyrrolidine-induced epimerization, while 8 might be securable from the pyranoside 9 by Vasella reductive ring cleavage.\(^*\) Further retrosynthetic tracing of 9 to 12 suggested compounds 10 and 11 as intermediates, with 11 emerging from a sulfone carbanion oxidation on 12 and 10 from a ketone reduction. A double Mitsunobu inversion\(^*\) on 10 with benzoic acid and an O-desilylation and iodination would thereafter complete the route to 9. The requisite Padwa anionic [3 + 2]-cycloadduct 13 had already been prepared from 16 and 17 during our development of a new pathway to (−)-echinosporin,\(^*\) and so now we envisioned converting 13 into 12 by a simple catalytic hydrogenation reaction.

With this summary of our strategy in mind, we repeated the work of Flasz and Hale\(^*\) to acquire cycloadduct 13 in the previously reported 56% yield (Scheme 2). The alkene in 13 was...
hydrogenated. The cyclopentylsulfone next had its ketone reduced from its less hindered underside with L-Selectride to provide alcohol 12 with total stereocontrol. Conversion of 12 into 11 was now attempted by forming the dianion of 12 with 2 equiv of n-BuLi in THF/HMPA at −78 °C and oxidizing this with the Davis oxaziridine. Disappointingly, this reaction failed to give any of the desired ketone 11 even when attempted under a range of conditions.

We therefore sought to arrive at iodide 9 by a pathway (Scheme 3) that set off from the known (8S)-α-hydroxy ketone 18, preparable from 13. On this occasion, we hoped to access 9 from triol 21 by selective iodination and double invertive Mitsunobu displacement of 25 with PhCO2H but first we established whether such a double inversion would indeed be feasible on 21 to obtain 24. Hydroxy ketone 18 was thus successfully converted into 19 by Barton deoxygenation of the (8S)-O-thionocarbonylimidazolide with Bu3SnH/cat. AIBN in PhMe at reflux for 1 h. With regard to preparation of the O-thionocarbonylimidazolide, it proved essential not to add DMAP to the mix; otherwise, the epimeric (8R)-C(8)-O-thionocarbonylimidazolide would start to arise, and this would subsequently not undergo Barton deoxygenation with Bu3SnH/AIBN! With 19 in hand, l-Selectride reduction gave alcohol 20 as a single isomer, and O-desilylation led to 21. Despite many attempts, we were unsuccessful in effecting the desired double Mitsunobu inversion on 21 to obtain 24. Instead, only the di-O-benzoate 22 and elimination product 23 were formed in 30 and 14% yield, respectively. This result and those of other C(4) inversion studies that we performed on related substrates all confirmed that C(4) inversion would have to be delayed until the very final stages of the synthesis when the pyranoid ring had been fully dismantled.

Given this setback, we elected to make aldehyde 30 our new synthetic objective (Scheme 4). Alcohol 20 was thus subjected to Mitsunobu displacement to obtain 26; this reaction proceeded in high yield (81%) and gave a single product. Selective cleavage of the C(2)–OTBS group from 26 and iodination thereafter proceeded satisfactorily to deliver iodide 27 in 84% overall yield. Vasella reductive cleavage was next attempted with zinc dust in aqueous i-PrOH at reflux. It proved necessary to follow this reaction by TLC throughout to ensure that reduction of the
aldehyde also did not occur; a 3 h reaction time typically minimized this event and gave 28 in 95% yield. A variety of bases were then investigated to perform the desired epimerization of 28 into 29, but pyrrolidine soon emerged as the reagent of choice, giving a high yield of product with high stereoselectivity.

A fresh disappointment beset us when we discovered that the alkene in 29 was not a productive partner in olefin cross-metathesis with excess methyl acrylate to obtain 30 (Scheme 4). Given this undesired outcome, we decided to investigate whether a Wittig reaction might prove useful for enoate elaboration, but clearly, the adoption of this tactic would require reduction of the C(9)-aldehyde and protection of the resulting alcohol to enable the C(3)-aldehyde to be oxidatively unveiled. There was also the issue of C(4) inversion and macrolactonization to contend with much later in the synthesis. After due consideration, an orthogonal silyl ether protecting group strategy was eventually adopted, with aldehyde 29 being converted into differentially protected tri-O-silyl ether 33 (Scheme 5).

A four-step protocol accomplished this task (Scheme 5). In this, NaBH₄ reduction of 29 delivered a primary alcohol that underwent O-silylation with TBSCl and imidazole. Alkene 31 then had its O-benzoate reductively removed with i-Bu₂AlH at low temperature. The resulting alcohol 32 was then O-silylated with TBDPSCl and imidazole in CH₂Cl₂ at rt. Initially, the use of cat. OsO₄ and NaIO₄ was pursued for the oxidative cleavage of alkene 33, to obtain 35, but this gave rise to a complex reaction mixture. In the end, the alkene of 33 was best dihydroxylated under standard Upjohn conditions with cat. OsO₄ and excess N-methylmorpholine N-oxide. This afforded a single diol 34, whose stereochemistry was tentatively assigned as anti, using Kishi’s empirical rule. This diol was then oxidatively cleaved with Pb(OAc)₄ and the resulting aldehyde 35 Wittig olefinated to obtain enoate 36 as a single geometric isomer. Selective O-desilylation of 36 with cat. PPTS/EtOH at rt over 60 h cleanly gave alcohol 37, which was converted into the aldehyde 38 by TEMPO/PhI(OAc)₂ oxidation. Julia/Kocienski olefination of 38 with the N-phenyltetrazolylsulfone furnished the all (E)-alkene 39 as a single stereoisomer in 68% yield. Our new abridged synthesis of 5₂ from 45₁ from 39 then ensued; the methyl ester was likewise cleaved with aq LiOH.

Ceric ammonium nitrate cleavage of the PMP group from 39 then ensued; the methyl ester was likewise cleaved with aq LiOH.

A Yamaguchi macrolactonization of the seco-acid 40 was now accomplished at high dilution, as described in Scheme 5. Macrolactone 41 was formed in excellent yield, in what was a very clean reaction. Selective C(4) O-desilylation of 41 could subsequently be accomplished cleanly and rapidly with 5 equiv of n-Bu₄NF in THF over 1 h. The resulting alcohol was then subjected to Mitsunobu inversion with Ph₃P/DIAD and p-nitrobenzoic acid. The desired product 43 was isolated pure in 65% yield; elimination product 42 was also isolated in 17% yield by SiO₂ flash chromatography. With pure 43 in hand, (+)-brefeldin A was readily accessed after HF-pyridine-induced...
Scheme 6. Synthesis of the N-Phenyltetrazolylsulfone 5

O-desilylation and brief treatment (0.5 h) with K₂CO₃ (1 equiv) in MeOH at 0 °C. Following final purification by SiO₂ flash chromatography, the natural product was obtained in 70% yield for the two steps and was spectroscopically identical with the spectra reported for (+)-brefeldin A in the literature in CD₃OD⁴ and CDCl₃.⁵ Cleavage of the O-silyl protecting groups from 41 with n-Bu₄NF in THF afforded 4-epi-brefeldin A,⁶ as well.

In summary, a new total synthesis of (+)-brefeldin A was achieved from the Padwa [3 + 2]-cycloadduct 13. The utility of the latter cycladdition was demonstrated for the preparation of trans-configured chiral cyclopentanes. New types of brefeldin analogues should now prove accessible.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02002.

AUTHOR INFORMATION
Corresponding Author
*E-mail: k.j.hale@qub.ac.uk.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS
We thank QUB for a studentship and for funding this work.

REFERENCES