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


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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 5AG, 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(15). 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 in the synthesis of (−)-echinosporin, we became interested in evaluating whether this novel cyclopentene ring-assembly method might prove useful for the stereocontrolled 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 congener 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 alkenes in 13 was

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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. Unfortunately, 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 PhCO2H12 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 deoxygenation14 of the (8S)-O-thiocarbonylimidazolide 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)-O(8)-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 displacement12 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 cleavage11 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

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*Scheme 1. Our Retrosynthetic Plan for (+)-Brefeldin A*

*Scheme 2. Our Attempted Synthesis of Ketone 11*

*Scheme 3. Our Attempted Early Stage Double Mitsunobu Inversion of Triol 21 at C(4) and C(7)***
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, NaBH\(_4\) 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 \(i\)-Bu\(_2\)AlH at low temperature. The resulting alcohol \(32\) was then O-silylated with TBDPSCI and imidazole in CH\(_2\)Cl\(_2\) at rt. Initially, the use of cat. OsO\(_4\) and NaIO\(_4\) 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. OsO\(_4\) and excess \(N\)-methylmorpholine \(N\)-oxide\(^{15}\). This afforded a single diol \(34\), whose stereochemistry was tentatively assigned as anti, using Kishi’s empirical rule\(^{16}\). This diol was then oxidatively cleaved with \(\text{Pb(OAc)}_4\) 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\(^{10}\) of \(38\) with the \(N\)-phenyltetrazolylsulfone \(5\) furnished the all (\(E\))-alkene \(39\) as a single stereoisomer in 68% yield. Our new abridged synthesis of \(5\) from \(45\)\(^{17}\) is presented in Scheme 6.

Ceric ammonium nitrate cleavage of the PMP group\(^{18}\) from \(39\) then ensued; the methyl ester was likewise cleaved with aq LiOH. A Yamaguchi macrolactonization\(^{19}\) 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 \(n\)-Bu\(_4\)NF in THF over 1 h. The resulting alcohol was then subjected to Mitsunobu inversion with \(\text{Ph}_3\text{P/DIAD and }p\)-nitrobenzoic acid\(^{12c}\). The desired product \(43\) was isolated pure in 65% yield; elimination product \(42\) was also isolated in 17% yield by SiO\(_2\) 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 K$_2$CO$_3$ (1 equiv) in MeOH at 0 °C. Following final purification by SiO$_2$ flash chromatography, the natural product was obtained in 70% yield for the two steps and was spectroscopically identical with the achieved from the Padwa [3 + 2]-cycloadduct.

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Notes

Corresponding Author

*E-mail: k.j.hale@qub.ac.uk.

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