A Short Synthesis of (+)-Brefeldin C *via* Enantioselective Radical Hydroalkynylation

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Abstract: A very concise total synthesis of (+)-brefeldin C starting from 2-furanylcyclopentene is described. This approach is based on an unprecedented enantioselective radical hydroalkynylation process to introduce the two cyclopentane stereocenters in a single step. The use of a furan substituent allows to achieve a high *trans* diastereoselectivity during the radical process and it contains the four carbon atoms C1–C4 of the natural product in an oxidation state closely related to the one of the target molecule. The eight-step synthesis require six product purifications and it provides (+)-brefeldin C in 18% overall yield.

In 1958, the group of Singleton isolated a new compound called decumbin from *Penicillium decumbens,* which showed toxicity properties against rats and goldfish.[1] Four years later, Betina et al. isolated a compound called cyanein from *Penicillium cyaneum*, which displayed antibiotic properties against pathogenic and non-pathogenic fungi and demonstrated significant inhibition of HeLa cell multiplication.[2,3] Later, Härri isolated and characterized two new compounds from *Penicillium brefeldianum*, named brefeldin A and brefeldin C.[4] Sigg later confirmed the equivalence of decumbin, cyanein and brefeldin A (Figure 1).[5] Few compounds have triggered so much the interest of the scientific community. Indeed, brefeldin A has been investigated as a lead molecule for drug development due to its promising biological activities in the antitumor,[6] antifungal,[4] and antiviral[7] fields. Its ability to disrupt the Golgi apparatus acted as a magnet for biochemists and chemical biologists interested in intracellular protein trafficking.[8,9] However, these promises have not yet led to clinical applications.
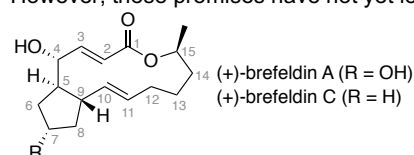
Figure 1. Structures of (+)-brefeldin A and C

The unique biological profile of brefeldin A, C, and analogues[10] has attracted a lot of interest in the synthetic organic chemistry community. The first synthesis of the racemic brefeldin A was reported by Corey and Wollenberg[11] in 1976 followed by around 40 total and formal syntheses.[11–51] Brefeldin C was prepared for the first time by total synthesis in 1988 by Schreiber and Meyers[52] followed by Takano,[25] Guingant (along with aspects of the biological properties of BFA)[48,53] and Tsunoda.[54] Following the pioneer work of Corey and Wollenberg,[11] the majority of the syntheses of brefeldin A and C accessed the 13-membered ring

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lactone in high yields by macrolactonization.[55] On the other hand, the preparation of the polysubstituted 5-membered ring has been achieved using very diverse strategies. Among them, the one reported by Kobayashi which used a furan moiety to introduce the C(1)–C(4) carbon atoms retained all our attention due to its conciseness.[35]

Recently, our group reported a method for enantioselective hydroazidation of trisubstituted nonactivated alkenes.[56] This reaction was extended to other enantioselective hydrofunctionalization processes such as hydrobromination,[56] hydrofluroination,[57] hydrosulfurization[56], and hydroallylation.[56] Brown et al. have pioneered the enantioselective hydralkynylation of alkenes.[58] However, their multistep approach was lengthy and required severe reaction conditions to convert alkylboronates to thexyl(alkyl)boranes before treatment with lithium acetylide and iodine under Zweifel type conditions.[59–62] Due to its obvious synthetic interest, the enantioselective hydroalkynylation of unactivated alkenes has been recently reinvestigated[63] but its scope remains so far limited to electron rich[64,65] and electron poor alkenes.[66,66] The only unactivated alkenes that were enantioselectively hydroalkynylated were strained system such as cyclopropene[67] and norbornene derivatives[68–70] and aryl substituted conjugated dienes.[71] The simple enantio-random hydroalkynylation of non-activated alkenes with Markovnikov regioselectivity has been described in 2017 by Cui and co-workers using iron catalysis.[72] Before that, we had developed the enantio-random hydroalkynylation of unactivated alkenes using a hydroboration radical alkynylation process.[73]

Herein, we report a concise synthesis of (+)-brefeldin C based on an unprecedented enantioselective version of our radical mediated hydroalkynylation. The conciseness of the reaction could be achieved by using a furan ring to introduce the first four carbon of the macrolactone with the desired oxidation state in a particularly straightforward manner.
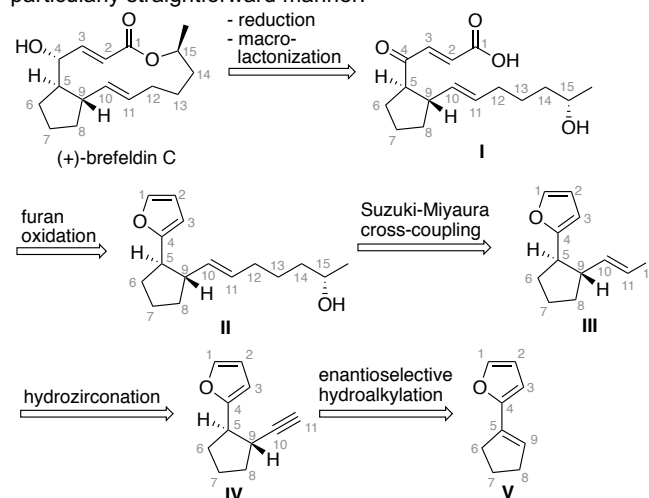
Scheme 1.Retrosynthesis of (+)-befeldin C

The retrosynthetic analysis of the synthesis is depicted in Scheme 1. Brefeldin C will be prepared from the corresponding seco acid I *via* Yamaguchi macrolactonization and stereoselective reduction
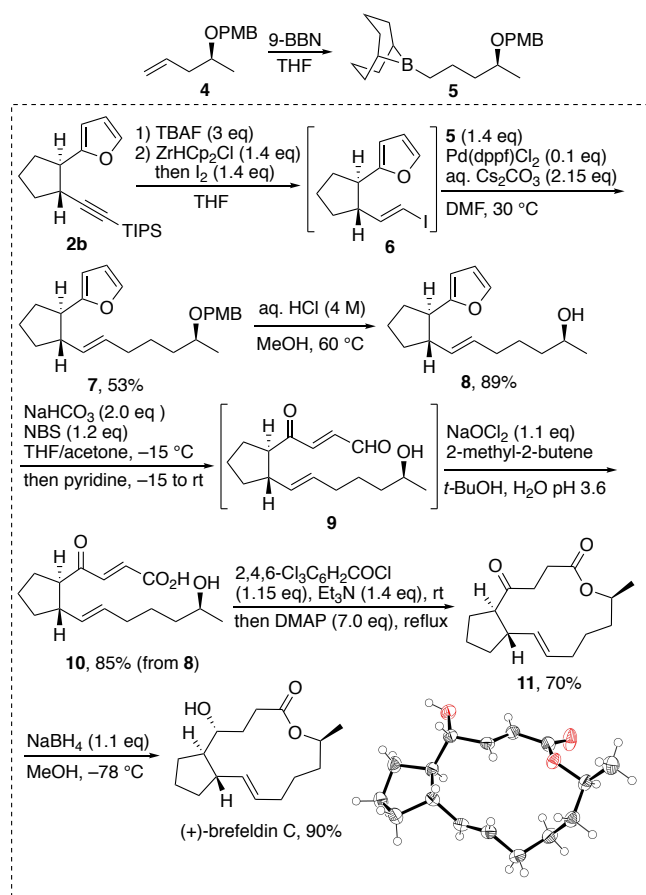
of the resulting α-β unsaturated ketone according to the seminal work of Corey and Wollenberg.[11] In analogy to the work of Kobayashi in his syntheses of brefeldin A[35] and of macrosphelides A and B,[74,75] the 3-carboxyacryloyl chain (carbon C1–C4) will be prepared via oxidative opening of the furan ring of **II**. The pentan-4-ol-1-yl side chain (carbon C12–C16) will be inserted via a Suzuki-Miyaura cross-coupling process starting from iodide **III** in analogy to the work of Guingant.[48,53] The (E)-iodide **III** will be obtained from the alkyne **IV** via a hydrozirconation-iodination process.[76] The planed key reaction of our approach is the enantioselective and diastereoselective hydroalkynylation of 1-furanylcyclopentene **V** that has to be designed based on our previous work.[73,56]

The enantioselective hydroalkynylation of 1-furanylcyclopentene **1** was investigated first since this substrate was already used in our hydroazidation study[56] and we knew that it can be hydroborated using (+)-monisopinocampheylbroane in high enantiomeric excess according to Brown's procedure.[77,78] Hydroboration of **1** with (+)-monoisocampheylborane was directly followed by conversion of the B-catecholborane upon successive treatment with acetaldehyde and catechol according to the procedure developed for the enantioselective hydroazidation reaction.[56] The in situ generated B-alkylcatecholborane was treated with trimethylsilylethynyl phenyl sulfone in the presence of di-tert-butyl hyponitrite as a radical precursor (Scheme 2). Satisfyingly, the desired hydroethynylated product **2a** was obtained as a single diastereomer (trans/cis ≥98:2) in 10–40% yield depending on the run. The resulting TMS-protected alkyne **2a** was immediately desilylated to give the terminal alkyne **3** in nearly quantitative yield. However, compounds **2a** and **3** were found to be unstable when heated. The irreproducibility of the yield of the hydroalkynylation was attributed to partial decomposition of **2a** during the radical process in refluxing dichloromethane (about 60 °C). Therefore, we decided to use the triisopropylsilyl (TIPS) protected ethynyl sulfone as radical trap to introduce the ethynyl moiety. Gratifyingly and in contrast to the TMS-protected sulfone, the preparation of the triisopropylethynyl phenyl sulfone was achieved in 98% yield from TIPS-acetylene and the corresponding product **2b** is bench stable. Running the hydroalkynylation reaction with this reagent afforded the TIPS-protected alkyne trans-**2b** in 43% yield when run with di-tertbutyl hyponitrite[79] (DTBHN) as an initiator. By initiating the reaction with to di-tert-butyl peroxyoxalate[80,81] (DTBPO), the reaction time could be decreased from 1 day (DTBHN) down to 40 min which resulted in an increased yield of 70% (up to 85% on small scale). An enantiomeric purity of 95:5 was determined after desilylation to **3** by HPLC. This enantiomeric purity is identical within experimental error to the one measured for 2-furanylcyclopentanol obtained upon oxidation of the organoborane intermediate with NaOH/H$_2$O$_2$ (see supporting information) demonstrating that the radical process is taking place without epimerization.
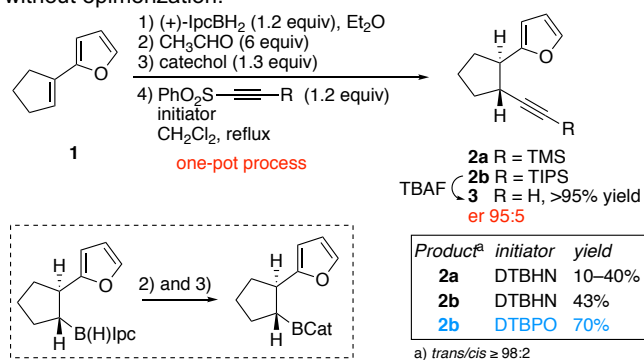
With the TIPS-protected alkyne **2b** in hand, we next focussed on the introduction of C12-C16 chain via Suzuki-Miyaura coupling in analogy to work of Guingant (Scheme 3).[48] The p-methoxybenzyl (PMB) protected alkenol **4** was conveniently accessible in two steps from (S)-propylene epoxide[48,82] and it was converted to **5** by hydroboration with 9-BBN. Due to its volatility and instability, the deprotected alkyne **3** obtained by treatment of **2b** with TBAF was immediately converted into the vinyl iodide **6** via hydrozirconation using the Schwartz reagent followed by treatment with iodine.[76,83] The Suzuki-Miyaura cross-coupling process delivered **7** in good 53% yield over 3 steps. At this stage, compound **7** contains all the C-atoms present in (+)-brefeldin C and the remaining steps are dealing with functional group interconversion. Oxidation of the furan to the access the trans-4-oxo-2-alkenoic acid was attempted next. The oxidation method reported by Salomon was tried first since it should deliver directly the desired acid upon simple treatment with sodium chlorite under acidic conditions. The reaction conditions were optimized on 2-cyclopentylfuran (see supporting material) to give the desired acid in 74% yield. However, all attempts to oxidize **7** failed to give the desired product. Moreover, it was observed that Salomon's conditions were partly deprotecting PMB ethers. Therefore, it was decided to deprotect first the PMB ether. This deprotection turned out to more difficult than expected since most standard conditions (DDQ, trifluoroacetic acid, triflic acid, cerium ammonium nitrate, etc.) were either degrading **7** or led to the desired free alcohol **8** contaminated with impurities difficult to remove by chromatographic purification. Gratifyingly, treatment of **7** in methanol with 4 M aqueous HCl afforded the clean deprotected alcohol **8** in 89% yield. After another extensive screening of furan oxidation conditions, we used a two-step one-pot procedure inspired by the work of Jørgensen[84], Kobayashi[35,75] and Blair.[85] Furan **8** was first treated with NBS in H$_2$O/acetone in the presence of NaHCO$_3$ followed by treatment with pyridine to obtain the ring opened 4-oxo-2-alken1-al intermediate **9** that was rapidly filtered through a pad of silica gel. Pinnick oxidation of the aldehyde **9** afforded the acid **10** in 85% yield overall yield from furan **8**. Yamaguchi type lactonization provided **11** that was stereoselectively reduced to (+)-brefeldin C upon treatment with NaBH$_4$ in analogy to the work of Corey and Wollenberg.[11] The structure of (+)-Brefeldin C was confirmed by X-ray crystallography (Scheme 3).[aaa 86 xxx]

Product[a]	initiator	yield
2a	DTBHN	10–40%
2b	DTBHN	43%
2b	DTBPO	70%

a) trans/cis ≥ 98:2

Scheme 2. Enantioselective hydroalkynylation of **1**

Scheme 3. Conversion of alkyne 2b into (+)-brefeldin C. X-ray single crystal structure of (+)-brefeldin C (50% probability ellipsoids).

In conclusion, we have reported a very concise total synthesis of (+)-brefeldin C starting from 2-furanylcyclopentene using an unprecedented enantioselective radical hydroalkynylation process to introduce the two cyclopentane stereocenters in a single step. To achieve efficiently this key transformation, a TIPS protected alkynyl sulfone was used together with radical initiation with DTPBO at 40 °C. The use of the furan substituent was crucial for the success of this synthesis. Indeed, it allows to achieve a high *trans* diastereoselectivity during the radical process and it contains the four carbon atoms C1–C4 of the natural product in an oxidation state closely related to the one of the target molecule. The longest linear sequence of the synthesis involves eight steps, six product purifications and it provides (+)-brefeldin C in 18% overall yield.

Acknowledgements

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[86] CCDC 1937167 Contain the Supplementary Crystallographic Data for This Paper. These Data Are Provided Free of Charge by The Cambridge Crystallographic Data Centre.