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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

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S *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.
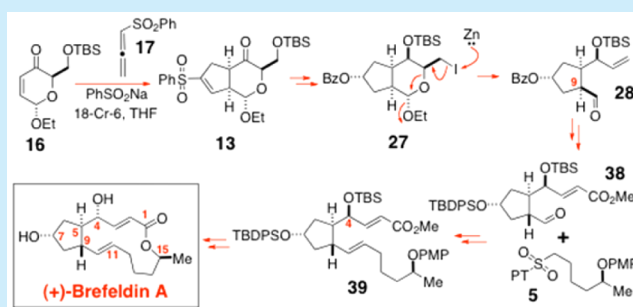
The structurally complex antitumor macrolide, (+)-brefeldin A,[1] has occupied an almost iconic position within the field of stereocontrolled natural product total synthesis,[2] due to the significant challenges it poses for complex chiral cyclopentane ring construction. In this connection, and following a recent successful deployment of the Padwa allenylsulfone anionic [3 + 2]-cycloadditive−elimination[3] in the synthesis of (−)-echino-sporin,[4] 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,[5] 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.[6] 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.[7] 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.[7−9] Despite these problems, work has continued on the synthesis of new brefeldin A analogues,[5] 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.
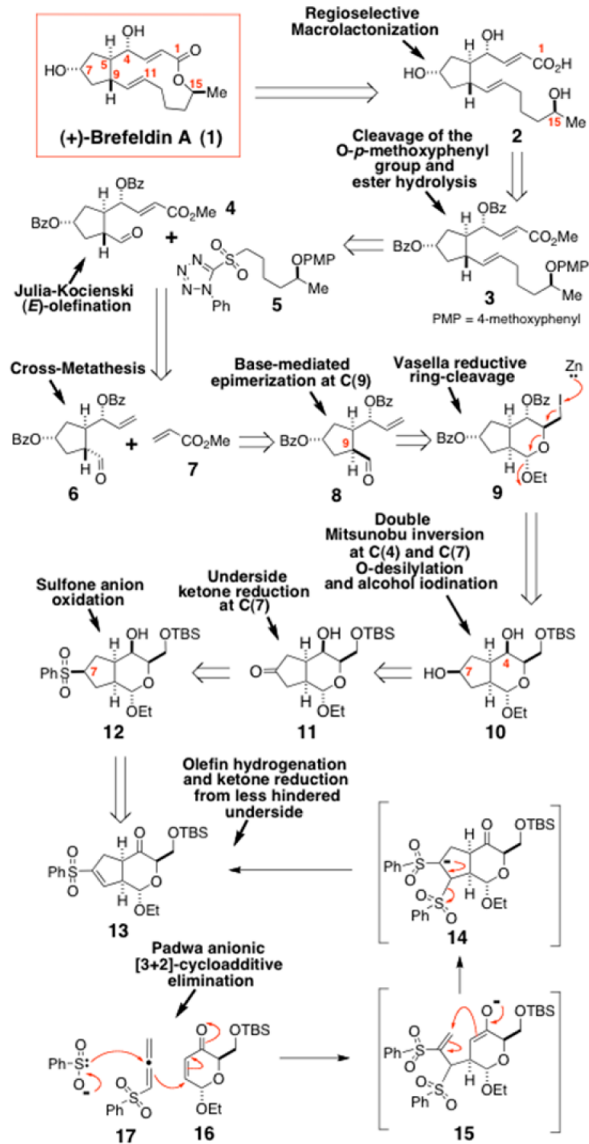
In our original retrosynthetic plan for (+)-brefeldin A (**1**) (Scheme 1), we sought to access **1** from the *seco*-acid **2** by regioselective macrolactonization. Compound **2** would emerge from **3** by cleavage of all the protecting groups, while **3** would derive from **6** by the successful implementation of *E*-olefin cross-metathesis and Julia/Kocienski olefination[10] 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.[11] 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[12] 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,[4] 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[4] to acquire cycloadduct **13** in the previously reported 56% yield (Scheme 2). The alkene in **13** was
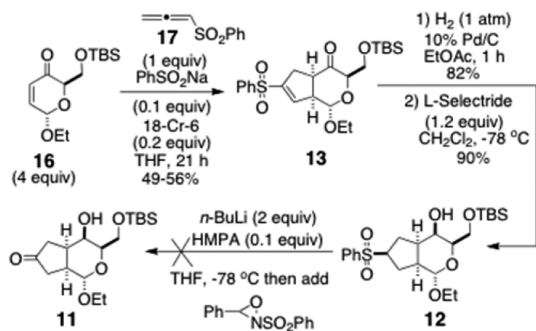
Scheme 1. Our Retrosynthetic Plan for (+)-Brefeldin A

Scheme 2. Our Attempted Synthesis of Ketone 11

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

Scheme 3. Our Attempted Early Stage Double Mitsunobu Inversion of Triol 21 at C(4) and C(7)

18, preparable from **13**.[4] On this occasion, we hoped to access **9** from triol **21** by selective iodination and double invertive Mitsunobu displacement of **25** with PhCO$_2$H,[12] 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[14] of the (8S)-O-thiocarbonylimidazolide with Bu$_3$SnH/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 Bu$_3$SnH/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[12] 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[11] 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
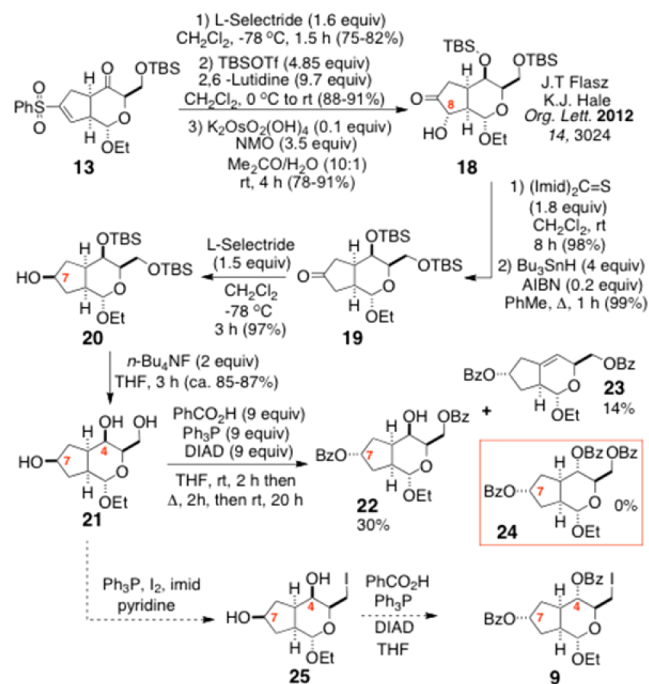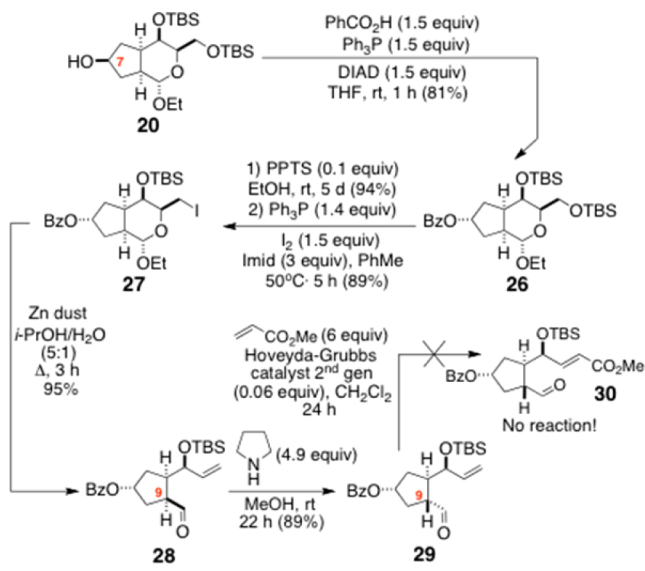
hydrogenated. The cyclopentylsulfone next had its ketone reduced from its less hindered underside with L-Selectride to provide alcohol **12** with total stereocontrol. Conversion of **12** into **11** was now attempted by forming the dianion of **12** with 2 equiv of n-BuLi in THF/HMPA at −78 °C and oxidizing this with the Davis oxaziridine.[13] Disappointingly, this reaction failed

Scheme 4. Our Synthesis of the New Alkenyl Aldehyde 29

Scheme 5. Completion of Our Syntheses of (+)-Brefeldin A (1) and 4-Epi-Brefeldin A (44) from Alkenyl Aldehyde 29


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 TBDPSCl 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 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**[2e] 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.
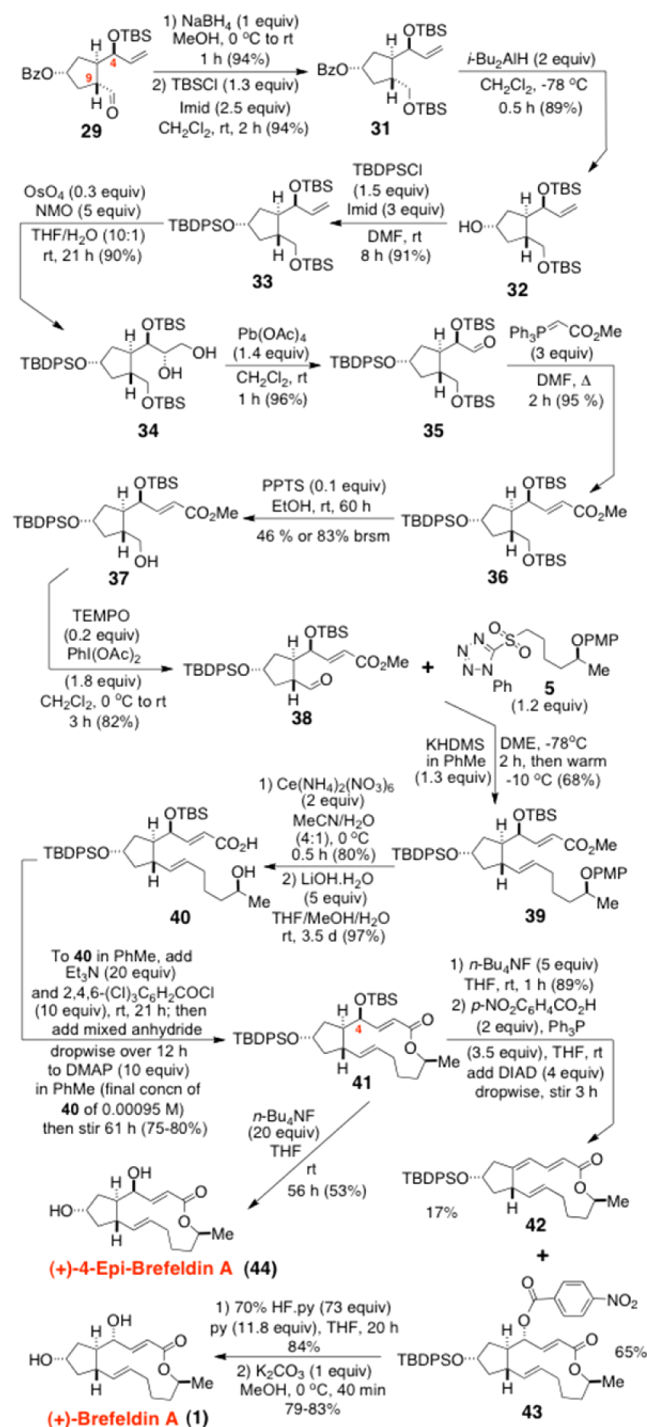
A Yamaguchi macrolactonization[19] of the *seco*-acid **40** was now accomplished at high dilution, as described in Scheme 5. Macrolactone **41** was formed in excellent yield, in what was a very clean reaction. Selective C(4) O-desilylation of **41** could subsequently be accomplished cleanly and rapidly with 5 equiv of *n*-Bu$_4$NF in THF over 1 h. The resulting alcohol was then subjected to Mitsunobu inversion with Ph$_3$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
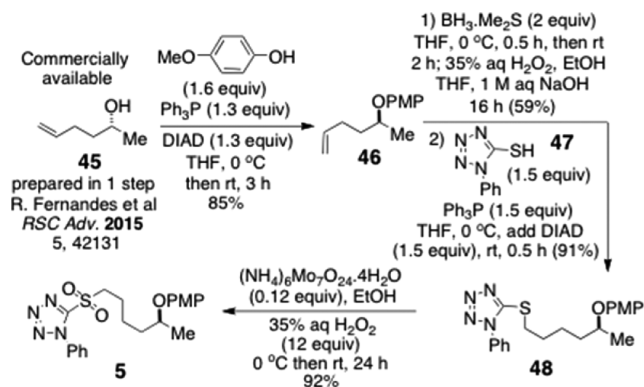
O-desilylation and brief treatment (0.5 h) with K_2CO_3 (1 equiv) in MeOH at 0 °C. Following final purification by SiO_2 flash chromatography, the natural product was obtained in 70% yield for the two steps and was spectroscopically identical with the spectra reported for (+)-brefeldin A in the literature in CD_3OD[2f] and $CDCl_3$.[20] Cleavage of the *O*-silyl protecting groups from **41** with *n*-Bu$_4$NF in THF afforded 4-epi-brefeldin A,[2h] 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 cycloaddition 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.

> Full experimental procedures for all steps, as well as copies of the IR, HMRS, and $^1H/^{13}C$ NMR spectra of every intermediate (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature* **1958**, *181*, 1072. (b) Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763.

(2) For previous (+)-brefeldin A total syntheses in reverse chronological order, see: (a) Fuchs, M.; Furstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 3978. (b) Wu, Y.; Gao, J. *Org. Lett.* **2008**, *10*, 1533. (c) Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Suh, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 6527. (d) Wu, Y.; Shen, X.; Yang, Y.-Q.; Hu, Q.; Huang, J.-H. *Tetrahedron Lett.* **2004**, *45*, 199. (e) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9328. (f) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim. *J. Org. Chem.* **2002**, *67*, 764. (g) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-H.; Shin, D.-Y.; Lee, Y.-S.; Kim, S.-H.; Park, H.-J. *J. Org. Chem.* **2002**, *67*, 4127. (h) Wang, Y.; Romo, D. *Org. Lett.* **2002**, *4*, 3231. (i) Haynes, R. K.; Lam, W. W.-L; Yeung, L.-L.; Williams, I. D.; Ridley, A. C.; Starling, S. M.; Vonwiller, S. C.; Hambley, T. W.; Lelandais, P. *J. Org. Chem.* **1997**, *62*, 4552. (j) Carnell, A. J.; Casy,

G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431. (k) Miyaoka, H.; Kajiwara, M. *J. Chem. Soc., Chem. Commun.* **1994**, 483. (l) Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555. (m) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639. (n) Nokami, J.; Ohkura, M.; Dan-Oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409. (o) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 7555. (p) Hatakeyama, S.; Sugawara, K.; Kawamura, M.; Takano, S. *Synlett* **1990**, *1990*, 691. (q) Gais, H.-J.; Lukas, K. L. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 142. (r) Le Drian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473. (s) Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Tetrahedron Lett.* **1977**, *18*, 2243.

(3) (a) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617. (b) Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386. (c) Padwa, A.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 3256. (d) Nunez, A., Jr.; Martin, M. R.; Fraile, A.; Garcia Ruano, J. L. *Chem. - Eur. J.* **2010**, *16*, 5443.

(4) Flasz, J. T.; Hale, K. J. *Org. Lett.* **2012**, *14*, 3024.

(5) (a) Anadu, N. O.; Davisson, V. J.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 3897. (b) Seehafer, K.; Rominger, F.; Helmchen, G.; Langhans, M.; Robinson, D. G.; Ozata, B.; Brugger, B.; Strating, J. R. P. M.; van Kuppeveld, F. J. N.; Klein, C. D. *J. Med. Chem.* **2013**, *56*, 5872. (c) Forster, S.; Persch, E.; Tverskoy, O.; Rominger, F.; Helmchen, G.; Klein, C.; Gonen, B.; Brugger, B. *Eur. J. Org. Chem.* **2011**, *2011*, 878.

(6) (a) Carter, C. A.; Waud, W. R.; Plowman, J. *Proc. Am. Assoc. Cancer Res.* **1995**, *36*, 386. (b) Phillips, L. R.; Wolfe, T. L.; Malspeis, L.; Supko, J. G. *J. Pharm. Biomed. Anal.* **1998**, *16*, 1301.

(7) Tosca, P.; Merrill, J.; Ryan, M.; Knostman, K.; Johnson, J.; Peggins, J.; Tomaszewski, K. *Cancer Res.* **2009**, *69*, 5102.

(8) Peyroche, A.; Antonny, B.; Robineau, S.; Acker, J.; Cherfils, J.; Jackson, C. L. *Mol. Cell* **1999**, *3*, 275. (b) Chardin, P.; McCormick, F. *Cell* **1999**, *97*, 153.

(9) Colanzi, A.; Grimaldi, G.; Catara, G.; Valente, C.; Cericola, C.; Liberali, P.; Ronci, M.; Lalioti, V. S.; Bruno, A.; Beccari, A. R.; Urbani, A.; De Flora, A.; Nardini, M.; Bolognesi, M.; Luini, A.; Corda, D. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 9794.

(10) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1998*, 26.

(11) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990.

(12) (a) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (c) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(13) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(15) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(16) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(17) Chaudhari, D. A.; Kattanguru, P.; Fernandes, R. A. *RSC Adv.* **2015**, *5*, 42131.

(18) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

(19) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(20) Glaser, R.; Shiftan, D.; Froimowitz, M. *Magn. Reson. Chem.* **2000**, *38*, 274.