Tetrahedron Letters 51 (2010) 4942–4946

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient and enantioselective total synthesis of naturally occurring L-783277

Hwan Geun Choi [†], Jung Beom Son [†], Dong-Sik Park, Young Jin Ham, Jung-Mi Hah, Taebo Sim [*]

Life/Health Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea

ARTICLE INFO

Article history:
Received 25 May 2010
Revised 20 July 2010
Accepted 22 July 2010
Available online 29 July 2010

ABSTRACT

Naturally occurring L-783277 which belongs to 14-membered resorcylic acid lactones (RALs) turned out to be a potent kinase inhibitor against MEK (MAP kinase kinase). We successfully accomplished efficient and enantioselective total synthesis of L-783277 based on convergent assembly of one aromatic unit and two chiral building blocks with efficient orthogonal protection-deprotection strategy. Three key steps composed of olefin cross metathesis, addition of acetylene derivative to aldehyde, and Yamaguchi macrolactonization were subsequently employed to construct the framework of L-783277. The optical rotation value of L-783277 is for the first time presented in this Letter.

1. Introduction

Naturally occurring resorcylic acid lactones (RALs)[1] have been known with the first isolation of radicicol[2] (monorden) in 1953 followed by zearalenone,[3] LL-Z1640-2,[4] hypothemycin,[5] L-783277,[6] and aigialomycin D[7] (Fig. 1). As for biological activity of RALs, zearalenone has been shown to possess estrogen agonistic properties. Zhao et al.[6] have revealed that RALs bearing cis-enone functionality such as hypothemycin and L-783277 have kinase inhibitory activities. Especially, L-783277 isolated from fruitbody of *Helvella acetabulum* has turned out to be highly potent against MEK (IC_{50} of 4 nM). L-783290 that is the corresponding C7′–C8′ trans-enone analog of L-783277 was found to be much less (IC_{50} of 300 nM) active against MEK.

All of kinase inhibitors could be classified into four categories based on their binding sites (ATP- and/or allosteric binding site on kinase) and reversibility (covalent or non-covalent binding to kinase). The fourth class of kinase inhibitors categorized by Gray's proposal[8] is capable of forming an irreversible bond to kinase protein.[9] The RALs containing cis-enone functionality, hypothemycin, and L-783277 undergo Michael addition reaction with a cysteine residue located in kinase activation loop and belong to the fourth class of kinase inhibitors. These findings have recently been corroborated in a more comprehensive study by Schirmer et al. on the mode of action and on the kinase specificity of hypothemycin.[10] In accordance with this Schirmer's publication, other groups have more recently reported that RALs containing cis-enone such as L-783277 and 5-(*Z*)-7-oxozeaenol inhibit not only MEK but also other kinases such as VEGFR2/3, PDGFR-α, and FLT3 with submicromolar IC_{50} values.[11]

The first total synthesis of L-783277 was disclosed by Hofmann and Altmann in 2008.[12] In this Letter, a macrolactone substrate bearing unprotected four hydroxyl groups was submitted to the final synthetic step, oxidation reaction of C6′ hydroxyl group using polymer-bound IBX, which resulted in L-783277 with a concomitant second oxidation by-product presumably derived from other unprotected secondary hydroxyl groups. This by-product could not be separated by thin layer chromatography or flash chromatography and L-783277 was purified with HPLC. The second total synthesis of L-783277 was reported[13] by Dakas et al. in 2009. Homologation between C1′ and C2′ using benzylic sulfide intermediate and macrolactonization under Mitsunobu conditions were adopted in order to construct molecular framework in this Letter. In the meanwhile, the synthesis of 7′-fluoro L-783277 was most recently reported.[14] It was anticipated that a fluorine substituent at the α-position of enone might accentuate the Michael addition reaction. As a part of expanding our MEK kinase program, we aimed to make a further assessment of biological activities of L-783277 and to conduct SAR study with L-783277 analogs. We first embarked to explore an efficient synthetic route toward L-783277 to meet these goals. Hence, we report herein an effective synthetic route with efficient orthogonal protection/deprotection strategy which differs from the synthetic approach reported in precedent literature[12,13] and enables to obtain L-783277 in the range of tens of milligrams with simple purification method using flash silica chromatography.

2. Results and discussion

The retrosynthetic analysis of L-783277 (**1**) outlined in Figure 2 involves in the construction of three key fragments (compounds **6**, **13**, and **22**) and two successive assemblies of these fragments followed by macrolactonization. We envisioned that the first assembly between fragment I and II, C1′–C2′ bond formation could be accomplished by an olefin cross metathesis using Grubbs 2nd generation catalyst. It was hoped that the incorporation of fragment III to form

* Corresponding author. Tel.: +82 2 958 6347; fax: +82 2 958 5189.
E-mail address: tbsim@kist.re.kr (T. Sim).
† These authors contributed equally to this work.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.122

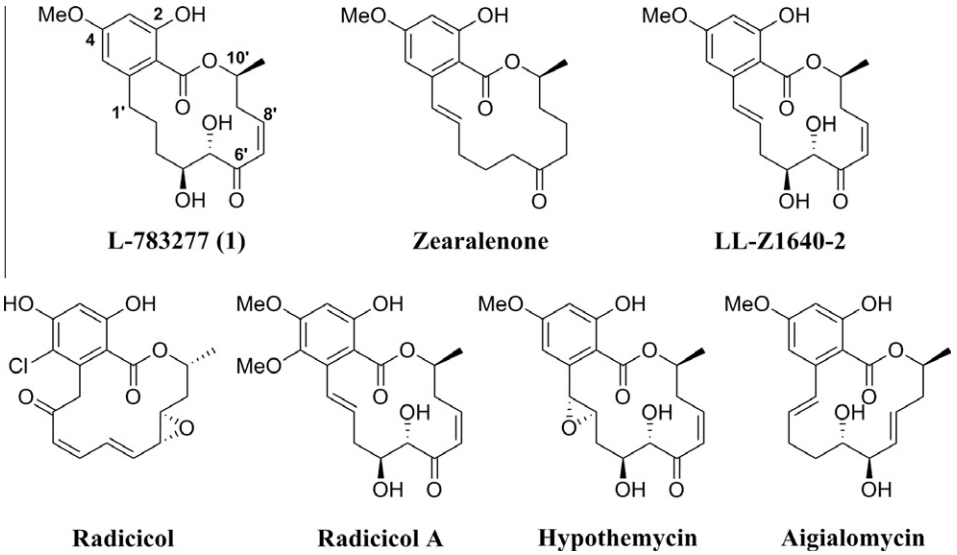


Figure 1. Naturally occurring resorcylic acid lactone polyketides.

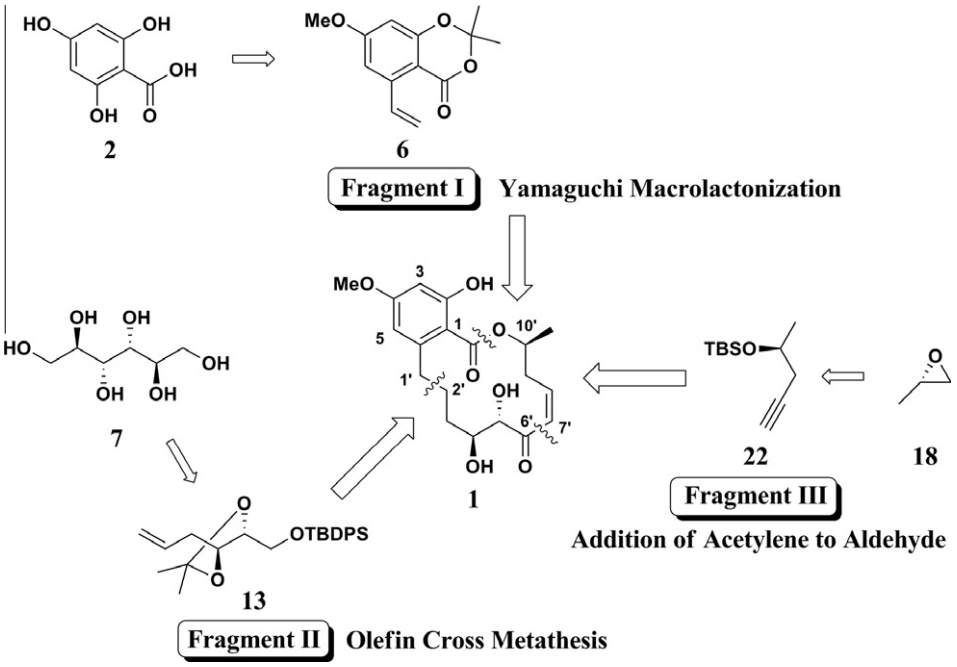
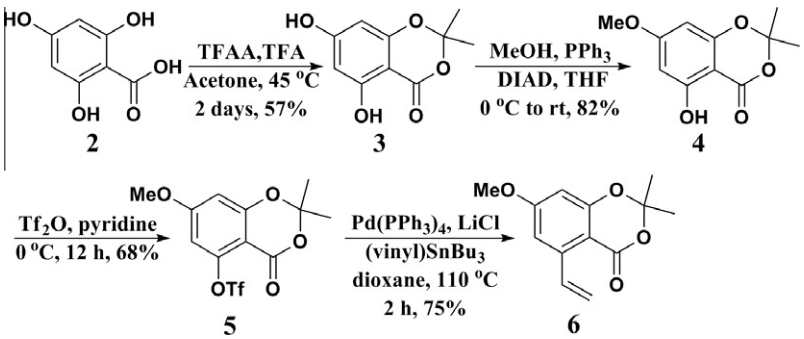
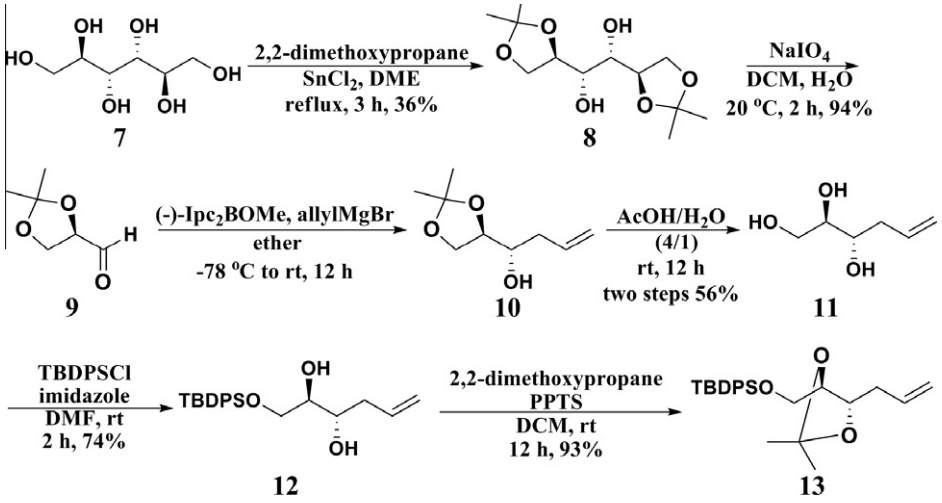


Figure 2. Retrosynthetic analysis of L-783277.



Scheme 1. Synthesis of fragment I.

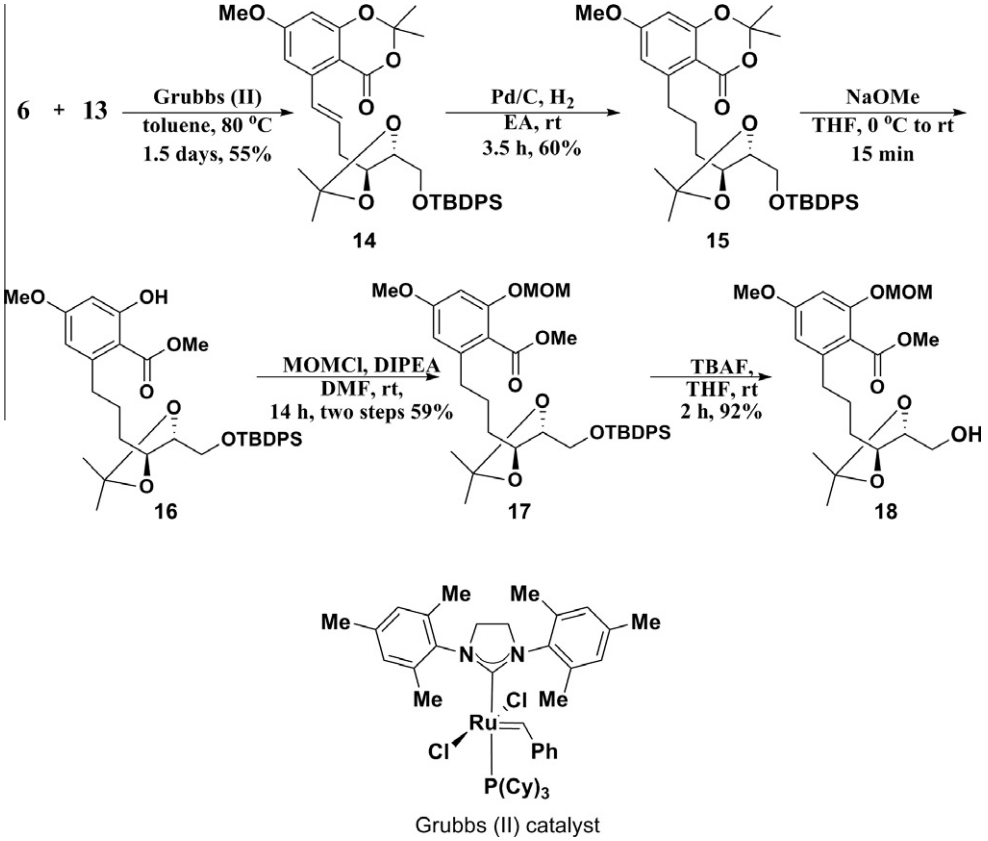


Scheme 2. Synthesis of fragment II.

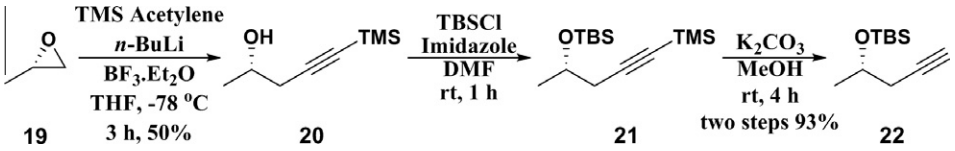
C6′–C7′ bond followed by Yamaguchi macrolactonization could furnish the framework of L-783277.

The fragment I (**6**) was prepared according to known synthetic route[15] as described in Scheme 1. This synthesis commenced with commercially available 2,4,6-trihydroxybenzoic acid **2** (50 g), which was treated with TFA and TFAA in acetone to afford 35 g (57% yield) of the corresponding acetonide **3** on the basis of modified Danishefsky's method.[16] The crude acetonide **3** was purified through recrystallization (24 g of crystalline **3**) with EtOH (crude 1 g/2 mL) and the resulting mother liquor was subjected to SiO_2 flash column chromatography purification. Regioselective methylation on the 4-hydroxy group of compound **3** was accomplished by Mitsunobu reaction[17] in 82% yield. The phenol **4** was readily converted into the corresponding triflate **5**. This triflate was subjected to Stille coupling reaction[18] to furnish styrene **6** in a yield of 75%.

Enantiomerically pure D-(*R*)-glyceraldehyde acetonide **9** was prepared from D-mannitol in two steps according to the literature method.[19] The asymmetric Brown allylation[20] of aldehyde **9** using (−)-Ipc_2BOMe yielded the desired allylic alcohol **10** in high diastereoselectivity (92:8 determined with ^1H NMR). The deprotection of acetonide group on compound **10** was carried out with AcOH to afford the triol **11**. The primary alcohol group of triol **11** was



Scheme 3. Assembly of fragments I and II.

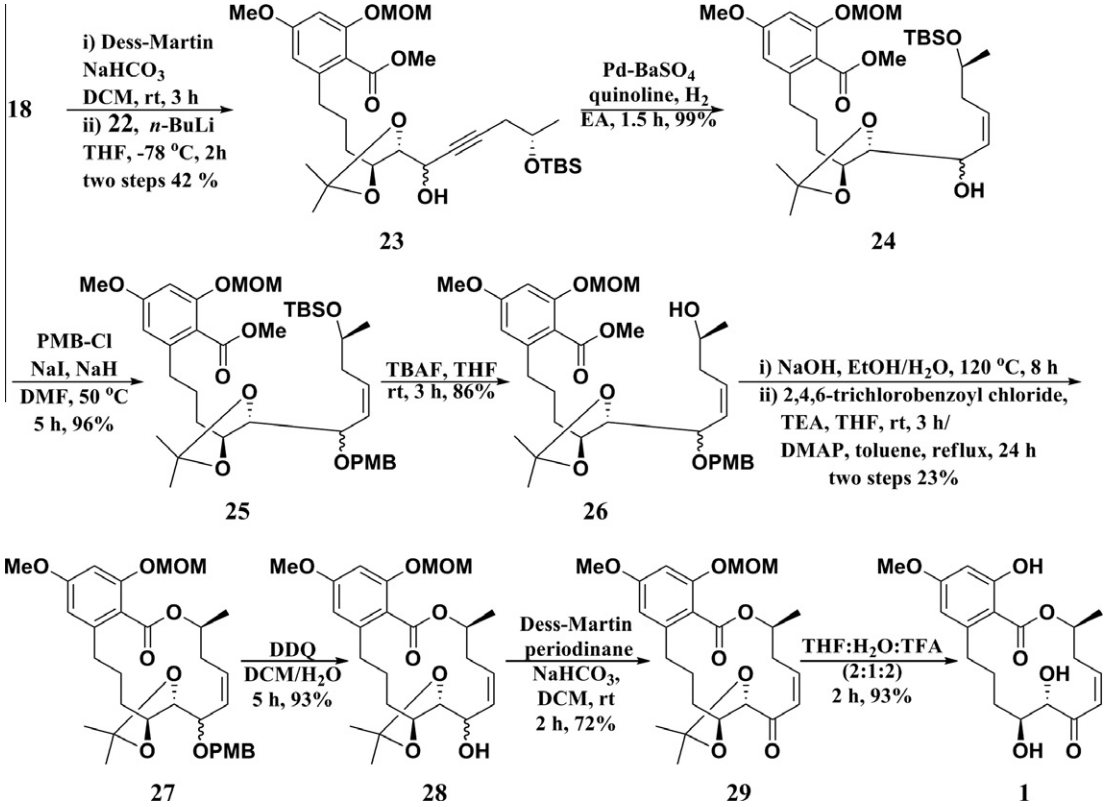


Scheme 4. Synthesis of fragment III.

selectively protected with TBDPSCl to provide diol **12** which was then elaborated into acetonide **13**, C2′–C6′fragment II (Scheme 2). With fragments I and II in hand, we were in a position to address their assembly and adopted olefin cross metathesis strategy using Grubbs 2nd generation catalyst to furnish the styrene **14** (cis: trans = 3:7 determined with ^{1}H NMR) as described in Scheme 3. This ruthenium carbene-based olefin metathesis reaction was effected in 55% yield. The transesterification of compound was conducted with NaOMe to provide methyl ester **16**. Almost quantitative (96%) protection of phenol group in **16** with MOM group, followed by TBAF-mediated desilylation of compound **17**, furnished compound **18**. It is instructive to recognize that the protection of phenol group in compound **16** is necessary to avoid a side reaction called decarboxylation during the course of saponification of methyl ester which is a critical step for macrolactonization as illustrated in Scheme 5.[21]

The preparation of the fragment III, alkyne **22**, commenced with commercially available (*S*)-(−)-propylene oxide **19**, which underwent ready conversion into secondary alcohol **20** upon treatment with lithium trimethylsilylacetylene at −78 °C in the presence of $BF_3{\cdot}Et_2O$ (Scheme 4).[22] TBS-protection of the alcohol **20** followed by TMS-deprotection of silyl ether **21** using K_2CO_3 provided the desired fragment III in 93% yield over two steps.

The primary alcohol **18** was smoothly oxidized to the corresponding aldehyde with Dess–Martin periodinane. This aldehyde was attacked by lithium acetylide derivative **22** to afford a 1:2 ratio of allylic alcohol diastereomers **23** in 42% yield. The resulting C6′ secondary alcohol in compound **23**, which causes a diastereomeric mixture, should be oxidized to the corresponding ketone and it was not necessary to separate these diastereomers. This acetylene addition reaction satisfied the completion of the entire carbon framework construction of L-783277. In exploring most suitable base for this acetylene addition reaction, the use of EtMgBr instead of *n*-BuLi required higher reaction temperature (50 °C) and led to cleavage of MOM protecting group on C2 oxygen. The acetylene **23** was submitted to partial hydrogenation reaction using Lindlar catalyst to give the corresponding cis-olefin **24** in a yield of 99%. PMB group which is an orthogonal protecting group to TBS was installed on allylic alcohol in compound **24** using NaH in the presence of NaI in a yield exceeding 95%. TBS group in **25** was then selectively deprotected with TBAF. Saponification of the methyl ester of compound **26** proceeded with sodium hydroxide in ethanol at 120 °C for 8 h to give a pivotal intermediate which constitutes the retron for the lactonization. The stage was set for the crucial macrolatonization event which was accomplished using modified Evans version[23] of Yamaguchi's method.[24] It is noteworthy that Hofmann and Altmann performed this macrolactonization under Mitsunobu conditions[12] in over 59% yields and Mukaiyama conditions[25] were also adopted by Tatsuta et al. for this macrolactonization in the course of LL-Z1640-2 synthesis. The selective deprotection of PMB group in **27** was readily carried out with DDQ to yield allylic alcohol **28**, which was then oxidized to cis-enone compound **29** with Dess–Martin periodinane. Finally,



Scheme 5. Total synthesis of L-783277.

simultaneous cleavage of acetonide and MOM protecting groups in compound **29** using TFA furnished L-783277 in 93% yield. This synthetic L-783277 proved to be identical with the naturally occurring L-783277, as judged by NMR[26] and high-resolution mass spectral data (calcd $[M+Na]^+ = 387.1420$, found $[M+Na]^+ = 387.1416$). To the best of our knowledge, we report here for the first time the optical rotation value of L-783277, $[\alpha]_D^{24.5} + 8.8$ (c 0.5, $CHCl_3$).

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MODHRD, KRF-2007-355-C00027).

References and notes

1. Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, *1*, 22–36.
2. Delmotte, P.; Delmotte-Plaque, J. *Nature* **1953**, *171*, 344.
3. Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318.
4. Ellestad, G. A.; Lovell, F. M.; Perkinson, N. A.; Hargreaves, R. T.; McGahren, W. J. *J. Org. Chem.* **1978**, *43*, 2339–2343.
5. Nair, M. S. R.; Carey, S. T. *Tetrahedron Lett.* **1980**, *21*, 2011–2012.
6. Zhao, A.; Lee, S. H.; Mojena, M.; Jenkins, R. G.; Patrick, D. R.; Huber, H. E.; Goetz, M. A.; Hensens, O. D.; Zink, D. L.; Vilella, D.; Dombrowski, A. W.; Lingham, R. B.; Huang, L. *J. Antibiot.* **1999**, *52*, 1086–1094.
7. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561–1566.
8. Zhang, J.; Yang, P. L.; Gray, N. S. *Nat. Rev. Cancer* **2009**, *9*, 28–39.
9. (a) Cohen, M. S.; Zhang, C.; Shokat, K. M.; Taunton, J. *Science* **2005**, *308*, 1318–1321; (b) Kwak, E. L.; Sordella, R.; Bell, D. W.; Godin-Heymann, N.; Okimoto, R. A.; Brannigan, B. W.; Harris, P. L.; Driscoll, D. R.; Fidias, P.; Lynch, T. J.; Rabindran, S. K.; McGinnis, J. P.; Wissner, A.; Sharma, S. V.; Isselbacher, K. J.; Settleman, J.; Haber, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 7665–7670.
10. Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, D. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4234–4239.
11. (a) Jogireddy, R.; Dakas, P.-Y.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem. Eur. J.* **2009**, *15*, 11498–11506; (b) Dakas, P.-Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6899–6902.
12. Hofmann, T.; Altmann, K.-H. *Synlett* **2008**, 1500–1504.
13. Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem. Eur. J.* **2009**, *15*, 11490–11497.
14. Jogireddy, R.; Barluenga, S.; Winssinger, N. *ChemMedChem* **2010**, *5*, 670–673.
15. Tranchimand, S.; Tron, T.; Gaudin, C.; Iacazio, G. *Synth. Commun.* **2006**, *36*, 587–597.
16. Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *114*, 655–659.
17. (a) Kamisuki, S.; Takahashi, S.; Mizushina, Y.; Hanashima, S.; Kuramochi, K.; Kobayashi, S.; Sakaguchi, K.; Nakata, T.; Sugawara, F. *Tetrahedron* **2004**, *60*, 5695–5700; (b) Mitsunobu, O. *Synthesis* **1981**, 1–28.
18. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
19. Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6–13.
20. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404.
21. (a) Pettigrew, J. D.; Wilson, P. D. *J. Org. Chem.* **2006**, *71*, 1620–1625; (b) Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271–2277.
22. (a) Sellès, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4621–4625; (b) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *25*, 391–394.
23. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.
24. (a) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9; (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
25. Tatsuta, K.; Takano, S.; Sato, T.; Nakano, S. *Chem. Lett.* **2001**, *30*, 172–173.
26. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 6.50 (d, J = 11.8 Hz, 1H), 6.30 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H), 6.26–6.19 (m, 1H), 5.32–5.26 (m, 1H), 4.88 (d, J = 4.9 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.31–4.29 (m, 1H), 3.74 (m, 1H), 3.73 (s, 3H), 3.09–3.00 (m, 1H), 2.67–2.61 (m, 2H), 2.44–2.36 (m, 1H), 1.63–1.53 (m, 1H), 1.40–1.35 (m, 2H), 1.32 (d, J = 6.2 Hz, 3H); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 12.12 (s, 1H), 6.36 (dd, J = 3.5 Hz, J = 11.9 Hz, 1H), 6.29 (d, J = 2.6 Hz, 1H), 6.26 (d, J = 2.6 Hz, 1H), 6.21 (dd, J = 2.4 Hz, J = 11.2 Hz, 1H), 5.39–5.36 (m, 3H), 4.48–4.47 (m, 1H), 3.80–3.77 (m, 1H), 3.67 (s, 3H), 3.57 (d, J = 5.2 Hz, 1H), 3.35–3.22 (m, 2H), 2.96–2.88 (m, 1H), 2.54–2.42 (m, 2H), 2.11 (d, J = 10.4 Hz, 1H), 1.39 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, 200.07, 171.91, 166.63, 164.48, 147.66, 146.42, 126.32, 109.36, 104.59, 99.05, 81.22, 73.10, 73.25, 55.58, 37.24, 36.67, 33.12, 29.05, 20.85.