Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6527–6530

An olefin disconnection strategy for the practical synthesis of (+)-brefeldin A: olefin cross metathesis and intramolecular Horner–Wadsworth–Emmons olefination☆

Seung-Yong Seo,[a] Jae-Kyung Jung,[b] Seung-Mann Paek,[a] Yong-Sil Lee,[a] Seok-Ho Kim[a] and Young-Ger Suh[a,*]

[a]*College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea*
[b]*College of Pharmacy, Chungbuk National University, Cheongju 361-763, Republic of Korea*

Received 17 March 2006; revised 3 July 2006; accepted 10 July 2006
Available online 1 August 2006

Abstract—The practical and convergent total synthesis of (+)-brefeldin A has been achieved by an olefin disconnection strategy. Key features of the total synthesis include the efficient formation of C2 and C10 olefins, employing an olefin cross metathesis (CM) reaction and an intramolecular HWE olefination, respectively.

We recently reported the total synthesis of (+)-brefeldin A, employing the stereoselective Pd(0)-catalyzed cyclization and *trans*-vinylogous ester anion strategy.[1] As a part of our ongoing studies directed toward the synthesis of the diversified brefeldin A analogs, we have been interested in more practical and versatile synthetic strategy, which enables us to establish the structure-activity relationship of this medicinally important macrolactone.[2] Herein, we report the olefin-disconnection strategy for the synthesis of (+)-brefeldin A, which exploits olefin cross metathesis (CM)[3] and intramolecular Horner–Wadsworth–Emmons (HWE) olefination[4] for the efficient elaboration of two internal *trans*-olefins as well as the 13-membered lactone skeleton of the target molecule.

As indicated by the retrosynthetic plan in Figure 1, our synthetic approach developed for the practical and convergent synthesis of brefeldin A was guided by two olefins disconnection strategy. At the starting point of our present synthesis, one example of intramolecular HWE olefination in the synthesis of brefeldin A was reported.[5a] However, for our synthesis, we decided to

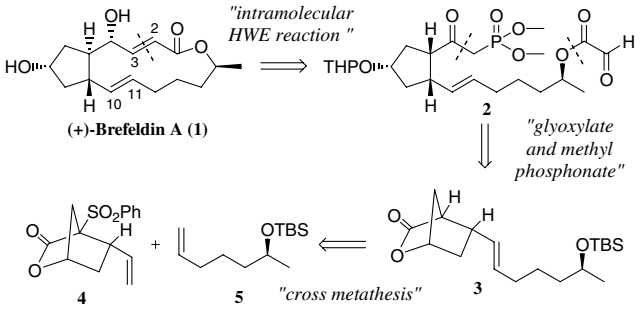


Figure 1. Retrosynthetic analysis.

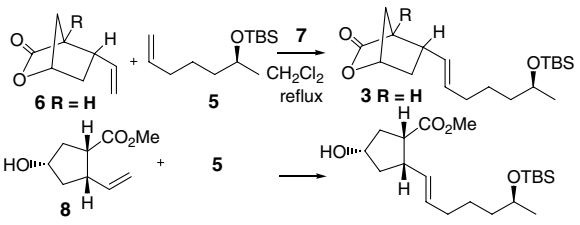
pursue the reversed HWE strategy, because our unique reversed strategy envisages synthetic versatility as well as some crucial advantages in terms of stereoselectivity, yield and synthetic efficiency in combination of the requisite building blocks. Thus, the initial disconnection of the C2–C3 (refer to the numbering system of brefeldin series) olefin in upper side chain would lead to the key precursor **2** for an intramolecular HWE olefination. The fully functionalized glyoxylate-phosphonate **2** could be effectively obtained from our unique bicyclic lactone **3** by employing the direct phosphonate addition to the lactone moiety followed by the introduction of glyoxylate ester. For the second disconnection of C10–C11 olefin, we explored a tactic adopting the olefin cross metathesis reaction of the bicyclic lactone **4** and **5**.[5b,6]

☆This work is taken in part from the PhD thesis of S.-Y. Seo, Seoul National University, 2004.

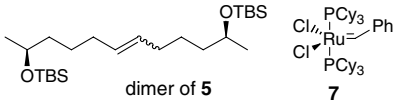
* Corresponding author. Tel.: +82 2 880 7875; fax: +82 2 888 0649; e-mail: ygsuh@snu.ac.kr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.038

Table 1. Cross metathesis of bicyclic lactones



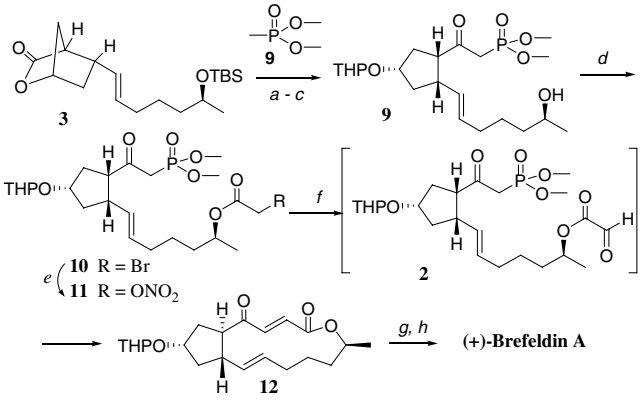
Entry	Compounds	Time (h)	Yields (%)[a]	*E*:*Z*[b]
1	**4**	48	15 (91)[c]	4–5:1
2	**6**	24	79 (88)[c]	7:1
3	**8**	24	32 (90)[c]	4:1
4	**6**+**5** dimer	12	88	7:1



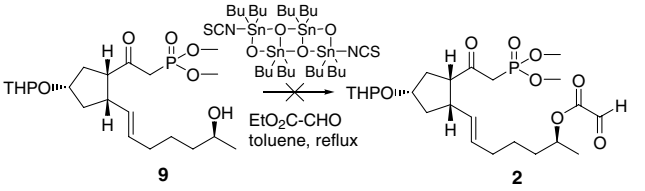
[a] Isolated yields after column chromatography.
[b] Determined by the ^{1}H NMR spectra of the product mixture.

We commenced our synthesis by preparation of the requisite bicyclic lactone **3** as shown in Table 1. The known bicyclic lactone **4**[7] was initially desulfonylated to the corresponding lactone **6** (6% Na/Hg, $B(OH)_3$, MeOH) with the highly strained bicyclic lactone moiety intact.[1,8] With both substrates **5**[9] and **6** in hand, the projected CM reaction was attempted (entry 2). To our delight, the CM of **5** and **6**, in the presence of 1st-generation Grubbs' catalyst **7**, in refluxing CH_2Cl_2 proceeded smoothly to give the desired intermediate **3** possessing (*E*)-olefin in an excellent yield, along with a small amount of the (*Z*)-isomer (*E*:*Z* = 7:1). When 3 equiv of **5** was subjected to the cross metathesis conditions, the homodimer of **5** was readily recovered. Interestingly, the homodimer proved to be as reactive as monomer **5** in terms of yield and reaction time[10] (entry 4). On the other hand, the CM reaction of the more sterically hindered substrate **4** or ring-opened hydroxycyclopentane intermediate **8** resulted in incomplete conversion (entries 1 and 3). It should be noted that lactone **6** as an optimum substrate for CM reaction provides a considerably improved *E*/*Z* selectivity compared to that of the previous report,[5b] combined with the excellent chemical yield and an economical benefit using 1st-generation Grubbs catalyst.

The side chain tethered lactone **3** was converted to the phosphonate **9**, as shown in Scheme 1, through a three-step sequence (lactone opening with phosphonate anion, THP protection, and TBS deprotection), for the intramolecular HWE reaction. To this end, it was necessary to introduce the glyoxylate ester moiety (e.g., **9** → **2**) to the secondary alcohol of **9**. We initially attempted direct coupling of **9** with ethyl glyoxylate in the presence of Otera's catalyst[11] (Eq. 1). However, this ester exchange failed to provide the desired intermediate **2**. It was found that the preparation and isolation of the glyoxylate ester **2** is quite difficult due to facile elimination of the glyoxylate and polymerization.



Scheme 1. Reagents and conditions: (a) *n*-BuLi, **9**, THF, −78 °C, 85%; (b) DHP, PPTS, CH_2Cl_2; (c) TBAF, THF, 91% for two steps; (d) bromoacetyl bromide, Et_3N, DMAP, CH_2Cl_2, 0 °C; (e) $AgNO_3$, CH_3CN, 90% for two steps; (f) NaOAc, DMSO, then, *i*Pr_2NEt, LiCl, CH_3CN, 59%; (g) PPTS, MeOH; (h) $NaBH_4$, MeOH, −78 °C, 71% for two steps.

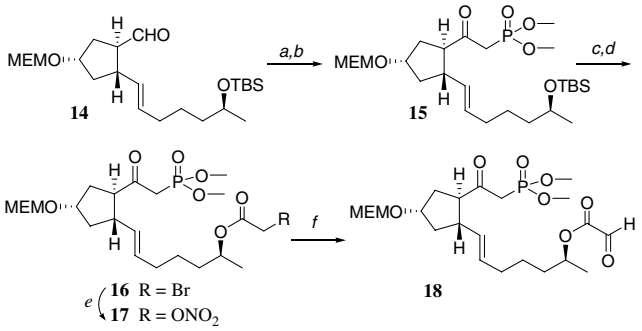


(1)

After numerous attempts,[12] the Kornblums oxidation[13] emerged as the most attractive approach, which involves the transformation of α-bromo ester to the corresponding glyoxylate ester via a nitrate ester. Thus, alcohol **10** was acylated to bromoacetate **11**, which in turn was treated with $AgNO_3$ in acetonitrile to afford nitrate ester **12** in 90% overall yield. Considering the high electrophilicity of glyoxylate, the intramolecular HWE reaction was directly executed after oxidation of nitrate ester **12** (NaOAc, DMSO). Upon treatment of crude **2** with LiCl and *i*Pr_2NEt, the cyclization by the stereoselective HWE olefination proceeded smoothly to afford macrolactone **12**[14] with a spontaneous isomerization at the ring junction. To the best of our knowledge, this is the first successful synthetic application of the glyoxylate-bearing phosphonate as a substrate for the intramolecular HWE reaction.

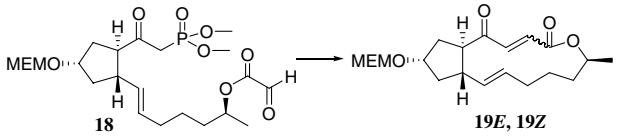
Finally, THP deprotection of **12** with PPTS in MeOH and stereoselective reduction of C4 carbonyl afforded (+)-brefeldin A (**1**), which was identical in all aspects with the natural product.

We have also investigated the cyclization of the *trans*-disubstituted precursor **18**, derived from the known *trans*-aldehyde **14**[1a] as shown in Scheme 2. The addition of phosphonate **9** anion to aldehyde **14**, followed by the TPAP, oxidation, afforded β-keto phosphonate **15**. After silyl deprotection of **15**, the resulting alcohol was converted to cyclization precursor **18** in a similar manner to that applied for **2**. Interestingly, the HWE olefination of trans-substituted precursor **18** provided the moderate selectivity for the new olefin geometry as shown in Table 2 (entries 1 and 2).



Scheme 2. Reagents and conditions: (a) *n*-BuLi, **9**, THF, −78 °C; (b) TPAP, NMO, 4A MS, CH_2Cl_2; (c) TBAF, THF, 80% for three steps; (d) bromoacetyl bromide, Et_3N, DMAP, CH_2Cl_2, 0 °C; (e) $AgNO_3$, CH_3CN, 90% for two steps; (f) NaOAc, DMSO.

Table 2. Cyclization of the *trans*-isomer (**18**) of **2**



Entry	Reaction condition	Yields (%)[a]	*E*:*Z*[b]
1	LiCl, *i*Pr$_2$NEt, CH_3CN, 0 °C	45	1.5:1
2	LiCl, *i*Pr$_2$NEt, CH_3CN, rt	74	1.4:1
3	K_2CO_3, 18-crown-6, toluene, 70 °C	70	1:20

[a] Isolated yields after column chromatography.
[b] Determined by the ^{1}H NMR spectra of the mixture.

The difference in the stereoselectivities of cis-precursor **2** and trans-isomer **13** implies that the complete epimerization of the cyclization product would proceed under basic conditions after an initial cyclization of **2** to the cis-isomer of **13**. Furthermore, these results proved the importance of the initial stereochemistry at the cyclopentane ring junction for the stereoselective macrocyclization.[15] It is noteworthy that treatment of **18** with K_2CO_3 in the presence of 18-crown-6 provided the exclusive formation of stereoisomer **19** (entry 3), which may also be useful for securing a variety of (+)-brefeldin A analogs.

In summary, we have developed a practical and versatile total synthesis of (+)-brefeldin A. The salient features of this convergent synthetic route include the efficient olefin cross metathesis of bicyclic lactone **6** and the intramolecular HWE olefination of unprecedented precursor **12**. Moreover, the dictation effect of the C5 stereochemistry on the C2 olefin geometry in HWE cyclization was uncovered. These synthetic studies seem to provide a timely contribution to the development of a variety of (+)-brefeldin A analogs. Preparation of (+)-brefeldin A library as an extended application of our synthetic route is in progress and the results will be forthcoming.

Acknowledgements

This work was supported by grant from the Center for Bioactive Molecular Hybrids, Yonsei University, and in part by the Research Institute of Pharmaceutical Science, Seoul National University.

References and notes

1. (a) Suh, Y.-G.; Jung, J.-K.; Suh, B.-C.; Lee, Y.-C.; Kim, S.-A. *Tetrahedron Lett.* **1998**, *39*, 5377; (b) Suh, Y.-G.; Seo, S.-Y.; Jung, J.-K.; Park, O.-H.; Jeon, R.-O. *Tetrahedron Lett.* **2001**, *42*, 1691; (c) 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.
2. For examples of (+)-brefeldin A derivatives, see: (a) Zhu, J.-W.; Nagasawa, H.; Nagura, F.; Mohamad, S. B.; Uto, Y.; Ohkura, K.; Hori, H. *Bioorg. Med. Chem.* **2000**, *8*, 455; (b) Fox, B. M.; Vroman, J. A.; Fanwick, P. E.; Cushman, M. *J. Med. Chem.* **2001**, *44*, 3915.
3. For recent reviews concerning CM reactions, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900, and references cited therein.
4. (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
5. (a) Raddatz, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 286; (b) Wang, Y.; Romo, D. *Org. Lett.* **2002**, *4*, 3231.
6. During our synthesis of (+)-brefeldin A, Romo group reported a synthesis of (+)-brefeldin A employing cross metathesis.
7. Suh, Y.-G.; Jung, J.-K.; Kim, S.-A.; Shin, D.-Y.; Min, K.-H. *Tetrahedron Lett.* **1997**, *38*, 3911.
8. (a) Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Lee, K.-O.; Suh, Y.-G. *Org. Lett.* **2004**, *6*, 429; (b) Compound **6**: $[\alpha]_D^{20}$ −104.1 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63 (ddd, H, $J = 17.0$, 10.3, 7.9 Hz), 5.10 (d, 2H, $J = 18.1$ Hz), 5.03 (s, 1H), 4.81 (s, 1H), 2.91 (m, 1H), 2.80 (m, 1H), 2.20–2.26 (m, 2H), 1.71–1.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8, 137.4, 116.5, 80.4, 47.8, 40.5, 40.0, 34.2; LRMS (EI) *m*/*z* 138 (M^+).
9. The intermediate **5** was prepared from (*R*)-(−)-epichlorohydrin by the following sequence: (a) CuBr, THF, −10 °C, 90%; (b) LAH, Et_2O, rt; (c) TBSCl, imidazole, DMF, 85% for two steps. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.75 (ddt, 1H, $J = 16.8$, 10.0, 6.6 Hz), 4.98–4.87 (m, 2H), 3.76–3.70 (m, 1H), 2.02–1.96 (m, 2H), 1.47–1.27 (m, 4H), 1.07 (d, 3H, $J = 6.0$ Hz), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 114.3, 68.4, 39.1, 33.7, 25.9, 25.0, 23.8, 18.1, −4.4, −4.7; IR (KBr) 2932, 2858, 1640, 1253, 835, 774 cm^{-1}; LRMS (EI) *m*/*z* 171 ($M-C_4H_9^+$); HRMS (EI) calcd for $C_9H_{19}O_1Si_1$ ($M-C_4H_9^+$) 171.1205. Found 171.1203.
10. For a related report, see: Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71.
11. Otera, J.; Dan-Ho, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
12. Other attempts, such as deprotection of dimethoxyacetate or bis(methylthio)acetate as well as glycolate oxidations, gave the starting material back or caused decomposition of the substrate.
13. (a) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865; For recent applications, see: (b) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113; (c) Snider, B. B.; Liu, T. *J. Org. Chem.* **1999**, *64*, 1088; (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1990**, *55*, 1901; (e) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850.
14. Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 and 7.72 (two ds, 1H, $J = 15.9$ Hz), 6.40 and 6.39 (two ds, 1H,

$J = 15.9$ Hz), 5.83–5.72 (m, 1H), 5.50–5.42 (m, 1H), 4.65–4.52 (m, 2H), 4.13 (m, 1H), 3.79 (m, 1H), 3.44 (m, 1H), 2.71–2.92 (m, 1H), 2.60–2.40 (m, 1H), 2.25–1.23 (m, 16H), 1.26 (d, 3H, $J = 6.0$ Hz); LRMS (FAB) m/z 279 ($M-C_5H_7O^+$); HRMS (FAB) calcd for $C_{16}H_{23}O_4$ ($M-C_5H_7O^+$) 279.1596. Found 279.1598.

15. For the related report with regard to C15 stereochemistry of brefeldin A, see Ref. 5a.