Tetrahedron Letters 49 (2008) 4279–4281

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of diversifolide and structure revision

Kazumasa Matsuo [a], Hiromasa Yokoe [b], Kozo Shishido [b,*], Mitsuru Shindo [c,*]

[a] Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, 6-1, Kasugako-en, Kasuga 816-8580, Japan
[b] Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan
[c] Institute for Materials Chemistry and Engineering, Kyushu University, 6-1, Kasugako-en, Kasuga 816-8580, Japan

ARTICLE INFO

Article history:
Received 7 April 2008
Revised 23 April 2008
Accepted 25 April 2008
Available online 29 April 2008

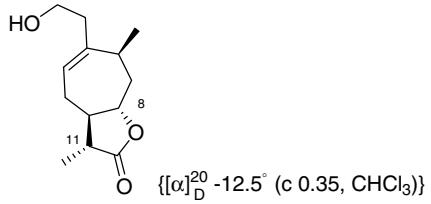
Keywords:
Natural product
Structure revision
Sesquiterpene lactone
Stereoselective synthesis

ABSTRACT

The synthesis of diversifolide and its structural revision are reported. We synthesized the assigned structure of diversifolide via two methods, but the NMR spectra of the synthetic material did not match those of the natural material. Through careful investigation, we found that the spectra were identical with those of 11-*epi*-sundiversifolide.

Diversifolide is a novel dinorxanthane sesquiterpene lactone that was isolated from *Tithonia T. diversifolia* (Hernsl.) A. Gray (Compositae) by Kuo in 1999.[1] Although its absolute configuration was not defined in this Letter, the structure was assigned as shown in Figure 1, using spectroscopic analyses including ^{1}H and ^{13}C NMR, IR and HRMS.[2] Sundiversifolide,[3] its stereoisomer, is a potent allelochemical, and related xanthanolides recently have been found to exhibit intriguing biological profiles such as antimalarial[4] and antitumor activity,[5] inhibition of farnesylation of the human lamin-B[6] as well as allelopathic activity.[3] Consequently, diversifolide would also be expected to show some biological activity, even allelopathy, although to date no bioassay of diversifolide has been reported. Herein, we describe the revision of the structure of diversifolide by total synthesis and the determination of its absolute configuration.

Recently, we have reported the total synthesis of sundiversifolide,[7] which is a diastereomer of diversifolide at the C-8 and C-11 positions. We therefore commenced the synthesis from **3** isolated as an isomeric side product in the hydrogenation of the butenolide **2**.[7b] The key conversion of **3** to 'diversifolide' is thus the stereochemical inversion at C-8. Dehydration of **3**, followed by the regioselective reduction of the epoxide afforded 11-*epi*-sundiversifolide (**4**).[7a] After protection of the alcohol as a TBDPS ether, the lactone moiety was opened by diethylamine with aluminum trichloride to give the hydroxy amide **5**. Next, the alcohol at C-8 was oxidized by TPAP, and the resulting ketone **6** was reduced by SmI_2 to afford



1

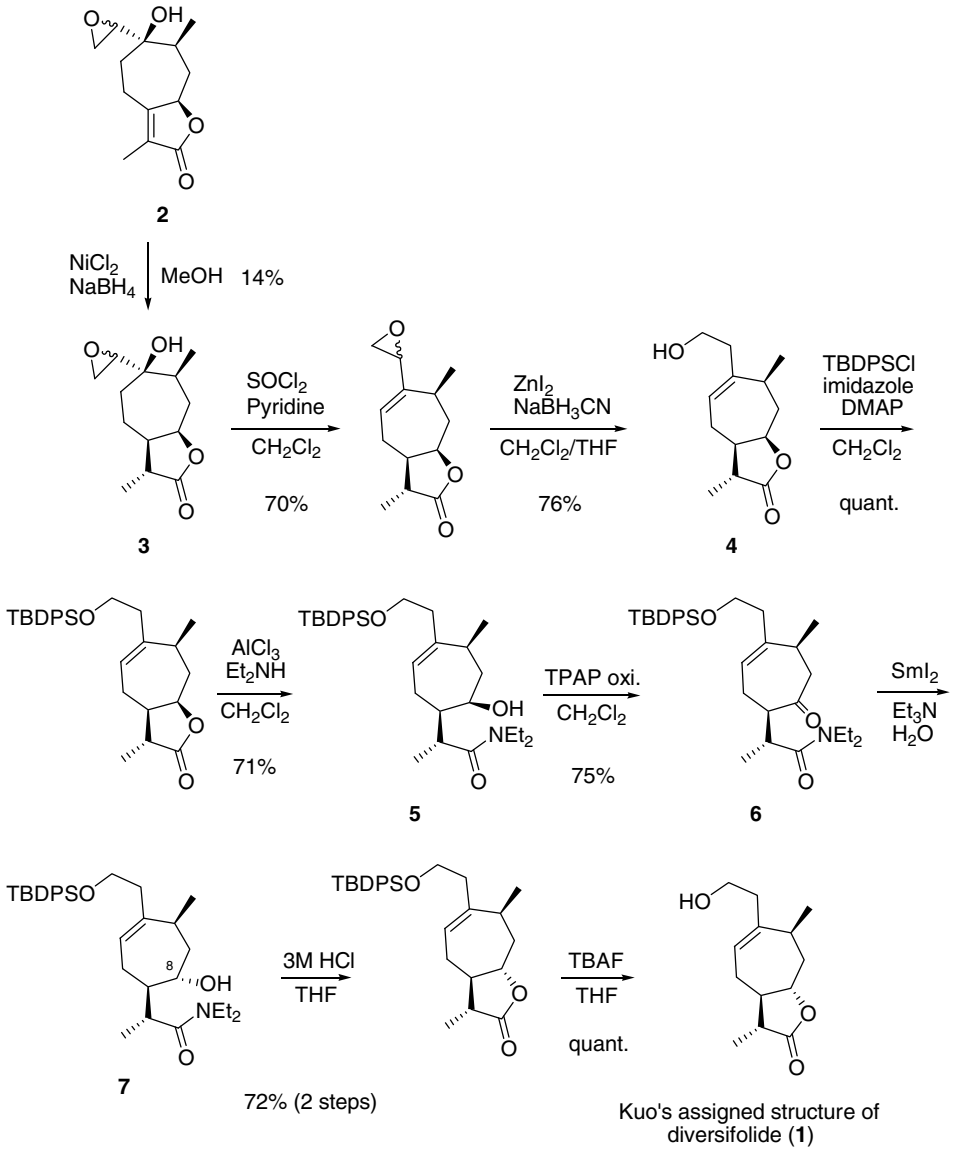
Figure 1. Kuo's assigned structure of diversifolide (**1**).

the alcohol **7** with the desired configuration at C-8.[8] After lactonization by acid, followed by deprotection, the synthetic **1** was obtained (Scheme 1). Alternatively, **1** was also prepared from the bicyclic lactone **8**, which has been utilized for the synthesis of (−)-xanthatin.[9] Thus, the lactone **8** was treated with LDA and MeI to give the undesired isomer **9** as a single product, the structure of which was determined by NOE. Attempted inversion at C-11 using kinetic protonation conditions produced a chromatographically separable 1:1 mixture of diastereoisomers, the desired isomer of which was desilylated to give **1** (Scheme 2). However, the ^{1}H and ^{13}C NMR spectra of **1** did not match those for the natural material reported by Kuo.[1] Since the stereochemistry was confirmed by the NOE spectra as shown in Figure 2, Kuo's proposed stereochemistry is incorrect.

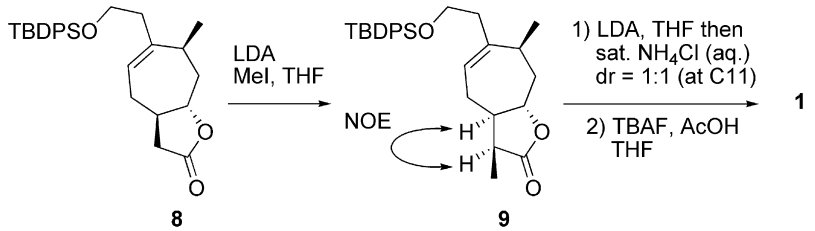
We speculated that since their spectra indicated the same carbon framework, the correct structure should be the diastereomer of **1**. After careful examination of the NMR spectra of the synthetic intermediates, we noticed that all the spectral data of the synthetic intermediate **4**, 11-*epi*-sundiversifolide (the C8-epimer of Kuo's

* Corresponding authors.
E-mail addresses: shishido@ph.tokushima-u.ac.jp (K. Shishido), shindo@cm.kyushu-u.ac.jp (M. Shindo).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.141



Scheme 1. Synthesis of diversifolide (**1**) with Kuo's assigned structure.



Scheme 2. Alternative synthesis of **1**.

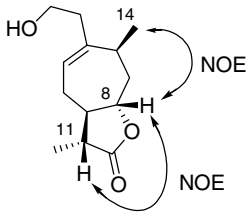
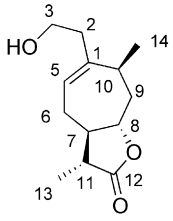


Figure 2. NOE experiments of synthetic diversifolide (**1**).

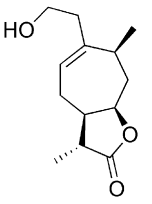
assigned structure), were identical with the reported values except for the chemical shift of the proton at C-8, which was 4.50 ppm; Kuo reported it to be 4.65 ppm (Table 1).[10] Despite this slight disparity, we conclude that the natural diversifolide is most likely the compound represented by **4**. The optical rotation allowed us to determine the absolute configuration of the diversifolide as shown in **4**.

In summary, we have determined the revised structure **4** for diversifolide by comparison of the spectra of the synthetic

Table 1
Comparison of spectra of **1**, **4**, and that reported for the natural product



synthetic diversifolide (**1**)



11-*epi*-sundiversifolide (**4**)

No.	Synthetic diversifolide (**1**)[b]		11-*epi*-Sundiversifolide (**4**)[b]		Reported structure[a]	
	δ_C	δ_H[d]	δ_C	δ_H[c]	δ_C	δ_H
1	144.1		142.4		142.3	
2	43.9	2.28–2.35 m	39.6	2.17–2.48 m	39.2	2.15–2.46 m
3	60.7	3.65–3.73 m	61.1	3.64–3.71 m	61.1	3.63 t
4						
5	124.8	5.60 dd	121.7	5.49 dd	121.6	5.45 br dd
6	27.3	2.28–2.35 m 2.01 m	26.4	2.17–2.48 m	26.3	2.15–2.46 m
7	51.8	1.59–1.64 m	45.0	2.17–2.48 m	45.0	2.15–2.46m
8	81.9	4.28 ddd	79.1	4.50 ddd	79.1	4.65 ddd
9	36.6	1.66 ddd 2.25 ddd	35.17	1.90 ddd 1.98 ddd	35.1	1.86 ddd 1.97 ddd
10	33.8	2.54 ddq	35.24	2.17–2.48 m	35.2	2.15–2.46 m
11	41.9	2.28–2.35 m	39.3	2.17–2.48 m	39.5	2.15–2.46 m
12	178.6		179.4		179.4	
13	12.5	1.22 d	13.9	1.23 d	13.9	1.19 d
14	18.2	1.16 d	20.6	1.16 d	20.5	1.12 d

[a] ^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz.
[b] ^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz.
[c] Coupling constants: $J_{5-6\alpha}$ = 5.8, $J_{5-6\beta}$ = 8.6, J_{7-8} = 8.6, $J_{8-9\alpha}$ = 2.4, $J_{8-9\beta}$ = 11.3, $J_{9\alpha-9\beta}$ = 13.4, $J_{9\alpha-10}$ = 6.9, $J_{9\beta-10}$ = 13.4, J_{10-14} = 6.9, J_{11-13} = 7.2.
[d] Coupling constants: $J_{5-6\alpha}$ = 3.1, $J_{5-6\beta}$ = 9.3, J_{7-8} = 10.3, $J_{8-9\alpha}$ = 2.7, $J_{8-9\beta}$ = 12.4, $J_{9\alpha-9\beta}$ = 12.7, $J_{9\alpha-10}$ = 3.7, $J_{9\beta-10}$ = 3.7, J_{10-14} = 7.6, J_{11-13} = 6.9.

compound **1**, of that reported for the natural product, and of that of the synthetic intermediate **4**. Since sundiversifolide has fascinating allelopathic activity, it can be reasonably assumed that diversifolide should also show promising bioactivity. The allelopathic assay of this compound is now in progress.

Acknowledgement

We thank Professor Takenori Kusumi, The University of Tokushima, for his advice on the structure revision of diversifolide.

References and notes

1. Kuo, Y.-H.; Lin, B.-Y. *Chem. Pharm. Bull.* **1999**, *47*, 428.
2. Stereochemical information, such as NOE experiments, has not been reported.
3. Ohno, S.; Tomita-Yokotani, K.; Kosemura, S.; Node, M.; Suzuki, T.; Amano, M.; Yasui, K.; Goto, T.; Yamamura, S.; Hasegawa, K. *Phytochemistry* **2001**, *56*, 577.
4. Joshi, S. P.; Rojatkar, S. R.; Nagasampagi, B. A. *J. Med. Aromat. Plant Sci.* **1997**, *19*, 366.
5. (a) Ahn, J.-W.; No, Z.; Ryu, S.-Y.; Zee, O.-P.; Kim, S.-K. *Nat. Prod. Sci.* **1995**, *1*, 1; (b) Roussakis, C.; Chinou, I.; Vayas, C.; Harvala, C.; Verbist, J. F. *Planta Med.* **1994**, *60*, 473.
6. Kim, Y. S.; Kim, J. S.; Park, S.-H.; Choi, S.-U.; Lee, C. O.; Kim, S.-K.; Kim, Y.-K.; Kim, S. H.; Ryu, S. Y. *Planta Med.* **2003**, *69*, 375.
7. (a) Yokoe, H.; Sasaki, H.; Yoshimura, T.; Shindo, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2007**, *9*, 969; (b) Ohtsuki, K.; Matsuo, K.; Yoshikawa, T.; Moriya, C.; Tomita-Yokotani, K.; Shishido, K.; Shindo, M. *Org. Lett.* **2008**, *10*, 1247.
8. Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123.
9. Yokoe, H.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 3504.
10. *Spectra of the synthetic* **1**: IR: ($CHCl_3$) cm^{-1}: 3020, 2935, 1768; MS: (EI) *m*/*z* 224 (M^+); HRMS (EI) *m*/*z* calcd for $C_{13}H_{20}O_3$ (M^+): 224.1412, found 224.1409; $[\alpha]_D^{20}$ −29.7 (*c* 0.37, $CHCl_3$); spectra of the synthetic **4**: IR ($CHCl_3$) cm^{-1}: 2958, 1764; MS (EI) *m*/*z* 224 (M^+), 194 (base peak); HRMS (EI) *m*/*z* calcd for $C_{13}H_{21}O_3$ (M^+): 224.1412, found 224.1412; $[\alpha]_D^{20}$ −32.4 (*c* 0.37, $CHCl_3$).