Tetrahedron 66 (2010) 637–640

Contents lists available at ScienceDirect

Tetrahedron

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

On the structure of penipratynolene and WA

Ya-Jun Jian, Yikang Wu *

State Key Laboratory of Bio-organic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 2 September 2009
Received in revised form 24 October 2009
Accepted 17 November 2009
Available online 7 December 2009

Keywords:
Natural products
Phenol ether
Coupling
Acetylene
Propargylic alcohol

ABSTRACT

The antipode of the structure proposed for the natural product penipratynolene in the literature was synthesized in high enantiopurity via an chiron approach and fully characterized. However, substantial differences were observed between the physical and spectroscopic data of the synthetic sample and those reported for the natural penipratynolene. Possible causes for the discrepancies are proposed on the basis of acquisition and comparison of additional data. The present work also provides the only piece of synthetic evidence for an antifungal natural product WA, the corresponding acid of the antipode of natural penipratynolene.

1. Introduction

Penipratynolene (**1**, Fig. 1) was isolated from *Penicillium bilaiae* Chalabuda by Kimura and co-workers.[1] The structure of **1** was established on the basis of its spectroscopic data, with the absolute configuration determined by the method of Mosher.[1] Compound **1** has been shown to possess nematicidal activity. Up to now, no synthetic records can be found in the literature.

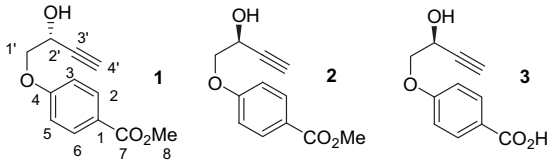
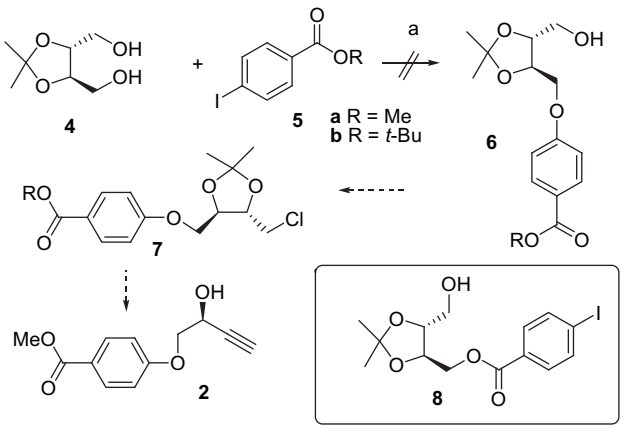


Figure 1. The structures of the proposed structure for penipratynolene (**1**), its antipode (**2**), and WA (**3**).

As an extension of another projects currently undergoing in our labs, we synthesized the antipode of **1** (i.e., **2**) to confirm the structure proposed for the natural product. Initially, such an endeavor was expected to be straightforward and uneventful because of the simplicity of the structure. However, the outcome turned out to be more complicated than we had expected. Not only the identity of the title itself, but also that of the corresponding carboxylic acid appears to need re-examination as detailed below.

2. Results and discussions

Our initial route to **2** is outlined in Scheme 1. We expected that after Cu(I)-mediated Ullmann coupling of the known[2] diol **4** with methyl *p*-iodobenzoate **5a**, the resulting alcohol **6a** would be readily converted into the target structure **2** via the corresponding chloride **7**. Unfortunately, such attempts led to no **6** but only the unexpected ester **8** in 50% yield under the well-established and broadly employed $Me_2NCH_2CO_2H\cdot HCl/Cs_2CO_3/DMF$[3] conditions. Use of *tert*-butyl *p*-iodobenzoate (**5b**) in place of **5a** did not result in any improvement. Again, ester **8** was obtained (18%), along with unreacted starting materials.



Scheme 1. (a) $Me_2NCH_2CO_2H\cdot HCl/CuI/Cs_2CO_3/DMF/100^{\circ}C/18$ h.

* Corresponding author. Fax: +86 21 64166128.
E-mail address: yikangwu@mail.sioc.ac.cn (Y. Wu).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.073

Then, we tried the $Me_4Phen/CuI/Cs_2CO_3$/toluene[4a–b] conditions on **5a**. Again, no desired **6a** but **8** (31%) was formed. However, application of the same set of conditions on **5b** gave the corresponding coupling product **6b** in 26% yield (along with 8% of **8**, entry 1, Table 1). Encouraged by the above result, we next tried to improve the yield of **6b** by varying the reactions conditions.

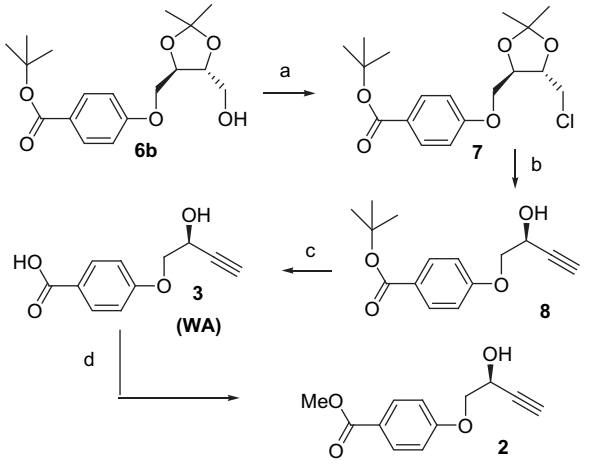
Table 1
Results of coupling between **4** and **5b**[a]

Entry	**4** (equiv)[b]	Conditions	Yield of **6b** and **8**
1	1.0	Cs_2CO_3 (1.0 equiv)/80 °C/30 h	26% (**6b**), 8% (**8**)
2	2.0	Cs_2CO_3 (1.2 equiv)/110 °C/41 h	21% (**6b**), 3% (**8**)
3	3.0	Cs_2CO_3 (2.0 equiv)/110 °C/24 h	41% (**6b**), 8% (**8**)
4	3.0	Cs_2CO_3 (2.0 equiv)/110 °C/18 h	61% (**6b**), 11% (**8**)

[a] All runs were performed in toluene under argon in the presence of CuI (5 mol% with respect to **5a**) and Me_4Phen (10 mol% with respect to **5a**) with the concentration of **5a** being 2.0 M.
[b] Molar equivalents with respect to **5a**.

Increase the molar ratio of the diol **4** in the reaction appeared to be a straightforward choice. However, application of more forcing conditions (entry 2) at the same time did not seem to yield any improvements. Further increase of the amount of added **4** and Cs_2CO_3 but shortening the reaction time raised the yield of **6b** to 41% (entry 3), suggesting that too long reaction time might cause hydrolysis of the products. Indeed, when shortening the reaction time to 18 h, the desired **6b** could be isolated in 61% yield (entry 4).

With **6b** in hand, we proceeded along the route shown in Scheme 2. The terminal hydroxyl group was converted into a chloride using NCS/Ph_3P.[4c] The resulting **7** was treated[5] with LDA to afford the propargyl alcohol **8**, which was of 99% ee as determined by chiral HPLC. The *tert*-butyl ester was then hydrolyzed with F_3CCO_2H in CH_2Cl_2 before further elaboration into the corresponding methyl ester **2** by reaction[4d] with CH_2N_2.



Scheme 2. (a) Ph_3P/NCS/rt/12 h, 91%. (b) LDA/THF/−78 °C/2 h, then −40 °C/1 h, 82%. (c) F_3CCO_2H/CH_2Cl_2/rt/2 h, 100%. (d) CH_2N_2, 92%.

The ^1H NMR data (Table 2) of **2** (the antipode of **1**) are consistent with those reported[1] for the natural penipratynolene (**1**). However, subsequent acquired ^{13}C NMR, also in CD_3COCD_3 as reported in the literature,[1] showed irrefutable differences from that in the literature (Table 3). Because ^{13}C NMR is usually more sensitive to structural changes than ^1H NMR, these discrepancies seemingly suggested natural penipratynolene might have a structure different from **1**.

Table 3
Comparison of ^{13}C NMR of **1**and **2**

1 (67.5 MHz, CD_3COCD_3)	**2** (75 MHz, CD_3COCD_3)	**2** (75 MHz, $CDCl_3$)
51.9 (q, C-8)	51.9	51.9
61.1(d, C-2′)	61.0	61.1
71.4 (t, C-1′)	72.6	71.3
74.6 (d, C-4′)	74.6	74.6
80.8 (s, C-3′)	83.3	80.8
114.3 (d, C-3 and C-5)	115.1	114.2
123.5 (s, C-1)	123.6	123.3
131.7 (d, C-2 and C-6)	132.1	131.6
161.9 (s, C-4)	163.2	161.8
166.7 (s, C-7)	166.7	166.7

We noticed that Kimura did not mention why their NMR spectra were recorded in CD_3COCD_3 rather than the more commonly employed $CDCl_3$. To exclude any possibility of typographic errors in their paper, we also recorded ^1H and ^{13}C NMR of **2** in $CDCl_3$ for comparison.

As shown in Table 2, the ^1H NMR of **2** in $CDCl_3$ is apparently different from that of Kimura's, confirming that their ^1H NMR was indeed acquired in CD_3COCD_3. However, the ^{13}C NMR of **2** taken in $CDCl_3$ turned out to be essentially identical to that of **1** in CD_3COCD_3 (Table 3). As the two sets of data agree so well with each other, it seems highly likely that Kimura's ^{13}C NMR was actually recorded in $CDCl_3$ but somehow by mistake CD_3COCD_3 was reported in the paper. Consequently, the structure originally assigned to natural penipratynolene seemingly remained to stand.

Then, disproving information turned up: The melting point of **2** was determined to be 113–115 °C (white powder, re-crystallized from benzene), while that for natural penipratynolene **1** is 246–248 °C (white needles, re-crystallized from benzene). The optical rotation ($[\alpha]_D^{26}$ +3.88 (*c* 0.2, EtOH)) for **2** is also incompatible with that[1] for **1** ($[\alpha]_D^{20}$ −11.2 (*c* 0.2, EtOH)). As **2** is supposed to be the antipode of **1**, a value around +11 would be expected.

Unable to explain these discrepancies, we looked into the literature for relevant information. Then, we found that in 1989 Arai[6] and co-workers already reported isolation of the same compound (**1**, without any trivial name) from *Penicillium fructigenum* Takeuchi, though no information about how the absolute configuration was determined was provided. Their ^1H and ^{13}C NMR (both recorded in $CDCl_3$) and mp data were fully consistent with ours. The specific rotation ($[\alpha]_D$ −12.3 (*c* 0.1, $CHCl_3$)) was also compatible with that of this work ($[\alpha]_D$ +12.46 (*c* 0.1, $CHCl_3$)) and rather close to Kimura's (recorded in EtOH!).

In efforts to reconcile those incompatible data, we looked into the literature again and found that the acid **3** in fact is also a natural

Table 2
Comparison of ^1H NMR of natural penipratynolene **1** (Ref. 1) and its synthetic antipode **2** (this work)

1 (270 MHz, CD_3COCD_3)	**2** (300 MHz, CD_3COCD_3)	**2** (300 MHz, $CDCl_3$)
2.97 (d, *J*=1.5 Hz, 1H, H-4′)	2.97 (d, *J*=2.4 Hz, 1H)	2.73 (d, *J*=4.7 Hz, 1H)
3.84 (s, 3H, H-8)	3.84 (s, 3H)	3.89 (s, 3H)
4.19 (dd, *J*=3.5, 6.7 Hz, 2H, H-1′)	4.20 (dd, *J*=4.8, 10.2 Hz, 1H) 4.15 (dd, *J*=3.4, 9.8 Hz, 1H)	4.24–4.08 (m, 2H)
4.74 (ddd, *J*=1.5, 3.5, 6.7 Hz, 1H, H-2′)	4.79–4.70 (m, 1H)	4.84–4.75 (m, 1H)
4.89 (br s, 1H, H-2′ OH)	4.96 (br d, *J*=6.0 Hz, 1H)	2.55 (br s, 1H, OH)
7.07 (d, *J*=8.8 Hz, 2H, H-3 and H-5)	7.06 (d, *J*=9.0 Hz, 2H)	6.95 (d, *J*=8.2 Hz, 2H)
7.96 (d, *J*=8.8 Hz, 2H, H-2 and H-6)	7.96 (d, *J*=8.0 Hz, 2H)	8.00 (d, *J*=8.2 Hz, 2H)

product, which was first isolated in 1998 by Yang[7] et al. (without given any specific rotation data) and later by Gloer[8] et al. from another source with full characterization. It was therefore hoped that a full agreement of all data could be found between the synthetic and the natural **3**, if discrepancy between **1** and **2** could not be solved (Table 4).

Table 4
Comparison[a] of ^{13}C NMR of synthetic and natural **3**[7,8]

Yang's (100 MHz, CD_3COCD_3)	Gloer's (75 MHz, $CDCl_3$)	This work (75 MHz, CD_3COCD_3)
167.3	167.3 (C-7)	167.5
163.4	163.5 (C-4)	163.3
132.5	132.6 (2C, C-2/C-6)	132.5
124.1	124.1 (C-1)	123.9
115.3	115.3 (2C, C-3/C-5)	115.2
83.5	83.5 (C-3′)	83.4
74.7	74.8 (C-4′)	74.8
72.8	72.8 (C-1′)	72.7
61.3	61.3 (C-2′)	61.2

[a] For comparison, the same numbering system for **1** is adopted here.

Yang's ^1H and ^{13}C NMR (both acquired in CD_3COCD_3) as well as mp (126–128 °C) were consistent with ours (128–129 °C; cf. also Gloer's 126–127 °C). However, as they did not measure the optical rotation, complete data comparison hence could be made only with Gloer's.

According to Gloer[8] both their ^1H and ^{13}C NMR were recorded in $CDCl_3$. However, in our hands the acid **3** turned out to be insoluble in $CDCl_3$ (or $CHCl_3$). It was therefore impossible for us to collect similar data in $CDCl_3$. Nevertheless, as the ^{13}C NMR data of **3** and the natural WA of Yang,[7] both acquired in CD_3COCD_3, are fully consistent with those of Gloer's,[8] it appears that the actual NMR solvent in Gloer's experiment was also CD_3COCD_3. Comparison of the three sets of ^1H NMR data (Table 5) lends strong support for this deduction.

Table 5
Comparison[a] of ^1H NMR of synthetic and natural **3**[7,8]

Yang's (400 MHz, CD_3COCD_3)	Gloer's (300 MHz, $CDCl_3$)	This work (300 MHz, CD_3COCD_3)
8.00 (dd, *J*=8.8, 4.8 Hz, 2H, H-2 and H-6)	7.99 (distorted d, *J*=7.5 Hz, 2H, H-2 and H-6)	8.00 (d, *J*=8.4 Hz, 2H)
7.07 (dd, J=8.8, 4.8 Hz, 2H, H-3 and H-5)	7.06 (distorted d, *J*=7.5 Hz, 2H, H-3 and H-5)	7.06 (d, *J*=8.5 Hz, 2H)
4.92 (br s, 1H, OH)		4.97 (br s, OH, 1H)
4.75 (m, 1H, H-2′)	4.74 (ddd, *J*=6.7, 4.7, 2.2 Hz, 1H, H-2′)	4.75 (m, 1H)
4.19 (m, 2H, H-1′)	4.20 (dd, *J*=9.7, 4.7 Hz, 1H, H-1′)	4.21 (dd, *J*=4.4, 9.6 Hz, 1H)
	4.16 (dd, *J*=9.7, 6.7 Hz, 1H, H-1′)	4.15 (dd, *J*=5.8, 9.9 Hz, 1H)
2.98 (d, *J*=2.2 Hz, 1H, H-4′)	2.96 (d, *J*=2.2 Hz, 1H, H-4′)	2.98 (d, *J*=1.4 Hz, 1H)

[a] For comparison, the same numbering system for **1** is adopted here.

The seemingly excellent match of the data between the synthetic and the natural **3** was then challenged by a large difference in specific rotation: the former is $[\alpha]_D^{27}$ +10.85 (*c* 0.40, MeOH) while the latter is $[\alpha]_D^{24}$ +80 (*c* 0.40, MeOH). In the beginning we thought a wrong solvent might be mentioned here. As $CHCl_3$, the most common one for measuring optical rotation, is not applicable here (because **3** is insoluble in it), acetone seemed to be the most likely one they used. Unfortunately, the specific rotation in acetone turned out to be even smaller ($[\alpha]_D^{27}$ +7.45 (*c* 0.40, acetone)). As we do not have the access to the natural **1** and **3**, it appears that a complete solution to the puzzling structural problem of these compounds embedded in the literature data in several papers published over some 10 years can be eventually found only in the future.

3. Conclusions

In efforts to confirm the structures of the corresponding natural products proposed in the literature, compounds **2** and **3** were synthesized for the first time via an unambiguous route in very high enantiopurity. The melting point, optical rotation, and ^1H as well as ^{13}C NMR data for these two compounds were thus acquired with high reliability to clear up the hidden confusions created by the contradicting data encapsulated in earlier documents. Careful comparison of the physical and spectroscopic data of the synthetic samples with the corresponding natural ones reported in the literature revealed that some of the previous investigators highly likely misreported the solvents employed for recording the NMR and specific rotation. While the NMR data for synthetic **2** and **3** are in excellent consistence with those reported for the natural ones, unignorable discrepancies are found in melting points and specific rotations: The mp and [α] for **1**[1] (of (*R*) configuration) are 246–248 °C and −11.2 (*c* 0.2, EtOH), respectively, while the corresponding values for the synthetic **2** (of (*S*) configuration) are 113–115 °C[9] and +3.88 (*c* 0.2, EtOH) (but +12.46 (*c* 0.1, $CHCl_3$)), respectively. A minor difference also exists in the UV spectrum: the spectrum of **1** contains an extra shoulder at 271 nm compared with that of **2**, which suggests presence of an additional UV absorption species in the natural **1**. Similarly, the large value of specific rotation for natural **3** ($[\alpha]_D^{24}$ +80 (*c* 0.40, MeOH)[8]) is apparently unreasonable judging from the value measured on pure synthetic one ($[\alpha]_D^{28}$ +10.85 (*c* 0.40, MeOH) or $[\alpha]_D^{27}$ +7.45 (*c* 0.42, acetone)).[10]

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR. EIMS and EI-HRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESI-MS and ESI-HRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. The melting point was uncorrected. Dry THF was distilled from Na/Ph_2CO under N_2. Dry CH_2Cl_2 was distilled over CaH_2 and kept over 4 Å molecular sieves. All other solvents and reagents were commercially available and used as received without any further purification.

4.2. Coupling of diol 4 with iodide 5b leading to 6b

A mixture of **4** (162 mg, 1.00 mmol), **5b** (90 mg, 0.29 mmol), CuI (3 mg, 0.015 mmol), Me_4Phen (7 mg, 0.03 mmol), and Cs_2CO_3 (198 mg, 0.67 mmol) in toluene (0.5 mL) under argon was vigorously stirred in an oil bath (100 °C) for 18 h. After being cooled to ambient temperature, the mixture was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (3:1 PE/EtOAc) on silica gel gave **6b** as a colorless oil (60 mg, 0.18 mmol, 61%): $[\alpha]_D^{27}$ +10.49 (*c* 0.84, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.95

(d, J=8.8 Hz, 2H), 6.93 (d, J=8.9 Hz, 2H), 4.32 (dt, J=7.6, 4.9 Hz, 1H), 4.22 (dd, J=5.0, 9.9 Hz, 1H), 4.17–4.09 (m, 2H), 3.93 (dd, J=3.9, 12.2 Hz, 1H), 3.77 (dd, J=4.2, 11.9 Hz, 1H), 2.16 (br s, 1H, OH), 1.60 (s, 9H), 1.49 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 161.7, 131.4, 125.0, 113.9, 109.9, 80.7, 78.9, 75.2, 68.3, 62.1, 28.2, 27.1, 26.9; FTIR (film) 3491, 2983, 2934, 1708, 1606, 1510, 1369, 1295, 1252, 1161, 849, 772 cm^{-1}. ESI-MS m/z 361.1 ([M+Na]$^+$); ESI-HRMS calcd for $C_{18}H_{26}O_6Na$ ([M+Na]$^+$) 361.16216, found 361.16220.

4.3. Conversion of alcohol 6b into chloride 7

NCS (51 mg, 0.38 mmol) and PPh_3 (100 mg, 0.38 mmol) were added in turn to a solution of alcohol **6b** (85 mg, 0.25 mmol) in dry CH_2Cl_2 (1.5 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature overnight before being diluted with EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (15:1 PE/EtOAc) gave the chloride **7** as a colorless oil (81 mg, 0.23 mmol, 91%): $[\alpha]_D^{28}$ +11.11 (c 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J=9.3 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H), 4.34–4.17 (m, 4H), 3.75 (dd, J=4.7, 11.7 Hz, 1H), 3.70 (dd, J=5.4, 11.5 Hz, 1H), 1.58 (s, 9H), 1.48 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 161.7, 131.4, 125.2, 113.9, 110.6, 80.6, 77.8, 77.5, 68.5, 44.3, 29.7, 28.2, 27.1; FTIR (film) 2982, 2932, 1709, 1606, 1510, 1369, 1294, 1251, 1161, 1115, 849, 771 cm^{-1}. ESI-MS m/z 379.1 ([M+Na]$^+$); ESI-HRMS calcd for $C_{18}H_{25}ClO_5Na$ ([M+Na]$^+$) 379.12827, found 379.12718.

4.4. Conversion of chloride 7 into alkyne 8

A solution of chloride **7** (266 mg, 0.75 mmol) in THF (2 mL) was added to a solution of LDA (freshly prepared from i-Pr_2NH (0.73 mL, 5.2 mmol) and n-BuLi (2.5 M, 2 mL, 5.0 mmol)) in THF (5 mL) stirred at −78 °C under argon. Stirring was then continued at the same temperature for 2 h and −40 °C for 1 h. Aq satd NH_4Cl was added, followed by EtOAc. The phases were separated. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (5:1 PE/EtOAc) gave alkyne **8** as a colorless oil (177 mg, 0.68 mmol, 82%): $[\alpha]_D^{26}$ +12.12 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J=8.7 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 4.79 (br s, 1H), 4.19 (dd, J=3.9, 9.9 Hz, 1H), 4.13 (dd, J=3.0, 9.9 Hz, 1H), 2.79 (d, J=3.8 Hz, 1H, OH), 2.55 (d, J=1.8 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 161.4, 131.4, 125.2, 114.0, 80.8, 80.7, 74.5, 71.3, 61.1, 28.2; FTIR (film) 3440, 3295, 2977, 2933, 2119, 1705, 1606, 1582, 1510, 1369, 1297, 1255, 1161, 849, 772 cm^{-1}. ESI-MS m/z 285.1 ([M+Na]$^+$); ESI-HRMS calcd for $C_{15}H_{18}O_4Na$ ([M+Na]$^+$) 285.10973, found 285.10994.

4.5. Conversion of 8 into 3

A solution of CF_3CO_2H (0.48 mL, 6.4 mmol) and **8** (14 mg, 0.064 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature for 2 h. The solvent was removed on a rotary evaporator. The residue was diluted with toluene and evaporated again (repeating three times). The remainder was then chromatographed on silica gel (15:1 CH_2Cl_2/MeOH) to afford acid **3** as a white solid (13 mg, 0.063 mmol, 100%): mp 128–129 °C (lit.[7] 126–128 °C; lit.[8] 126–127 °C), $[\alpha]_D^{28}$ +10.85 (c 0.40, MeOH), $[\alpha]_D^{27}$ +7.45 (c 0.42, acetone) (lit.[8] $[\alpha]_D^{24}$ +80 (c 0.40, MeOH)). EIMS m/z (%) 206 (M$^+$, 38), 191 (14), 151 (45), 138 (34), 133 (23), 121 (100), 105 (19), 65 (53); EI-HRMS calcd for $C_{11}H_{10}O_4$ (M$^+$) 206.0579, found 206.0576.

4.6. Conversion of 3 into 2

A solution of acid **3** (66 mg, 0.32 mmol) in Et_2O (2 mL) was treated with an excess of CH_2N_2 (ethereal solution, freshly prepared from aq KOH and N-nitroso-N-methyl-urea in Et_2O) at 0 °C. When TLC showed completion of the reaction (ca. 10 min), the solvent was evaporated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 n-hexane/EtOAc) to give methyl ester **2** as a white solid (65 mg, 0.29 mmol, 91% yield): mp 113–115 °C (lit.[1] mp 246–248 °C for **1**) (lit.[6] mp 111–112 °C for **1**), UV λ_{max} (MeOH) 254 nm (without any shoulder at 271 nm) (lit.[1] UV λ_{max} (MeOH) 254, 271 (sh) nm for **1**). $[\alpha]_D^{26}$ +3.88 (c 0.2, EtOH) (lit.[1] $[\alpha]_D^{26}$ −11.2 (c 0.2, EtOH) for **1**); $[\alpha]_D$+ 12.46 (c 0.1, $CHCl_3$) (lit.[6] $[\alpha]_D$+ 12.3 (c 0.1, $CHCl_3$)). The ee value was determined to be 99.1% by HPLC on a CHFT-IRALPAK IC column (0.46 cm×25 cm) eluting with 80:20 n-hexane/i-PrOH at a flow rate of 0.7 mL/min with the UV detector set to 214 nm (t_R=14.68 and 16.09 min for the major and minor isomers, respectively). FTIR (KBr) 3458, 3234, 2948, 2927, 2849, 2118, 1693, 1607, 1510, 1437, 1323, 1291, 1259, 1170, 1038, 850, 773 cm^{-1}. EIMS m/z (%) 220 (M$^+$) (29), 165 (41), 135 (43), 121 (87), 43 (100); EI-HRMS calcd for $C_{12}H_{12}O_4$ (M$^+$) 220.0736, found 220.0737.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20025207, 20272071, 20372075, 20321202, 20672129, 20621062, 20772143), and the Chinese Academy of Sciences ('Knowledge Innovation' project, KGCX2-SW-209, KJCX2.YW.H08).

References and notes

1. Nakahara, S.; Kusano, M.; Fujioka, S.; Shimada, A.; Kimura, Y. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 257–259.
2. Hungerbuehler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687–702.
3. Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243–246 and references cited therein.
4. (a) Wolter, M.; Nordmann, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976; (b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286; (c) Chun, J.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 348–354; (d) Arndt, F. *Org. Synth.* **1935**, *5*, 3–5.
5. (a) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett.* **1988**, *29*, 2737–2740; (b) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046.
6. Arai, K.; Kimura, K.; Mushiroda, T.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2937–2939.
7. Yang, J.; Qi, X.-L.; Li, W.; Shao, G.; Yao, X.-S.; Kitanaka, S. *Chin. Chem. Lett.* **1998**, *9*, 539–540.
8. Oh, H.; Swenson, D. C.; Gloer, J. B.; Shearer, C. A. *J. Nat. Prod.* **2003**, *66*, 73–79.
9. Note that the melting point for natural **1** isolated by Arai (Ref. 6) is 111–112 °C, rather close to ours (113–115 °C).
10. Note that as the ee value for synthetic **2** (and consequently **3**) is already as high as 99.1%, the [α] for **3** in any case does not seem likely to be as large as +80.