Tetrahedron Letters 51 (2010) 5525–5528

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Convenient synthesis of a marine cyclopentanoid: untenone A

Takahiro Kunitada [a], Rikiya Omatsu [a], Nobuo Tanaka [a], Nobuyuki Imai [a,†], Tsutomu Inokuchi [b], Junzo Nokami [a,*]

[a] Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, Ridai-cho, Kita-ku, Okayama 700-0005, Japan
[b] Department of Bioscience and Biotechnology, Faculty of Engineering, Okayama University, Tsushima-naka, Kita-ku, Okayama 700-8530, Japan

ARTICLE INFO

Article history:
Received 11 June 2010
Accepted 3 July 2010
Available online 18 August 2010

ABSTRACT

(±)-Untenone A, one of the marine cyclopentanoids, has been conveniently synthesized via (±)-*cis*-1-hexadecylcyclopent-2-en-1,4-diol **9** which has been produced from 1-hexadecylcyclopenta-1,3-diene **6** via photo-oxidation and the following reduction. The key step of the present synthesis is the selective alkylation of cyclopenta-1,3-diene to form **6**. Optically active (−)- and (+)-untenone A have been prepared from (−)- and (+)-**9**, respectively, after enzymatic kinetic resolution of (±)-**9**.

Biologically active natural compounds which have cyclopentane skeletons are one of the most popular and attractive synthetic targets called 'cyclopentanoids'. This is because there are many cyclopentanoids in natural products which are expected to have clinical utilities, although enough amounts of them are not supplied for investigation of their properties in detail. Therefore, many chemists have so far made their strong efforts to prepare them conveniently from cheap and easily available chemicals.[1]

In 1993, a marine natural oxylipin 'untenone A' (**1**) was isolated by Kobayashi et al.[2a] from the Okinawan marine sponge *Plakortis* sp. and its structure was determined as a cyclopentanoid having a linear *n*-hexadecyl side chain as shown in Figure 1, although the compound was optically inactive (racemic) ($[\alpha]_D^{19}$ +0.2 (*c* 2.1, $CHCl_3$))[2a] in contrast to the optically active compound prepared separately (lit.[3a] $[\alpha]_D^{27}$ −63.7 (*c* 2.63, $CHCl_3$), lit.[4e] $[\alpha]_D^{26}$ −79.7 (*c* 1.00, $CHCl_3$)). It was reported that the compound inhibited the cell proliferation of L1210 leukemia at IC_{50} 0.4 μg/mL[2b] and was considered to be a precursor in the biosynthesis of manzamenone A (**2**)[4a–c] which was reported to display inhibitory activity against protein kinase C.[4c] More recently, plakevulin A (**3**)[4d] was isolated from extracts of an Okinawan *Plakortis* sponge (SS-973), and the compound was reported to exhibit the cytotoxicity against murine leukemia L1210 and carcinoma KB cells, and also the inhibitory activity against DNA polymerases α and β.[4c,f]

The synthesis of (±)-,[4c,d,5] (−)-,[3,4e,f] and (+)-untenone A (**1**)[3b] has already been reported, in which three groups adopted the method using a nucleophilic alkyl group for introduction of the side chain into electrophilic cyclopentane rings cyclopentenones: namely, either 1-bromohexadecane (2.5 equiv) with SmI_2 (5.3 equiv) and HMPA (24.3 equiv) in THF[3b,4c] or hexadecylmagnesium bromide (3 equiv) with $CeCl_3$ in diethyl ether.[3a]

Herein, we have investigated a practical synthesis of (±)-, (−)-, and (+)-untenone A via coupling of nucleophilic cyclopentane ring (cyclopentadienyl anion) with an electrophilic side chain equivalent (1-halohexadecane) as a key step shown in a retrosynthetic process (Scheme 1).[6]

Cyclopentadienyl anion, prepared from freshly distilled cyclopenta-1,3-diene (10 mmol) with sodium hydride (10 mmol) in THF at 0 °C, was treated with *n*-$C_{16}H_{33}Br$ (**4a**, 5 mmol) in THF at −25 °C for 1 h to give an inseparable mixture of 1-hexadecylcyclopenta-1,3-diene **6** and its regioisomers 5-hexadecylcyclopenta-1,3-diene **5** and 2-hexadecylcyclopenta-1,3-diene **7** in a ratio of **5**:**6**:**7** = 5:5:1, although the use of longer reaction time and higher reaction temperature resulted in the formation of a larger amount of undesirable product **7**. The major product **5** was revealed to be selectively isomerized to **6** via 1,5-hydrogen shift by standing the reaction mixture (after workup) for 1.0–1.5 h at 25 °C, resulting in a mixture of **6** and **7** in a ratio of ca. 10:1 (**6**:**7**). Next, we investigated the effect of a leaving group of haloalkane on this coupling reaction and found that *n*-$C_{16}H_{33}I$ (**4b**) gave a better yield than **4a**. Thus, the synthesis of **6** was completed by selective alkylation and 1,5-hydrogen shift sequence by treatment of sodium cyclopentanide (40 mmol) with **4b** (20 mmol) at −40 °C for 30 min and by leaving the resulting mixture at room temperature for 1.5 h (Scheme 2).

Conversion of **6** to our key compound (±)-**9** was performed via photochemical oxidation of **6** (ca. 20 mmol; crude product obtained by the reaction shown in Scheme 2) to peroxide **8** by an irradiation of halogen lamp (150 W) under bubbling of oxygen in the presence of rose Bengal in MeOH–THF (1:1 (v/v), 200 mL) at −40 °C for 30 h and then the reduction of **8** to *cis*-1-hexadecylcyclopent- 2-ene-1,4-diol **9** by treatment with thiourea in 87% overall yield based on **4b** (Scheme 3).[7]

* Corresponding author.
E-mail address: nogami@dac.ous.ac.jp (J. Nokami).
† Present address: Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.181

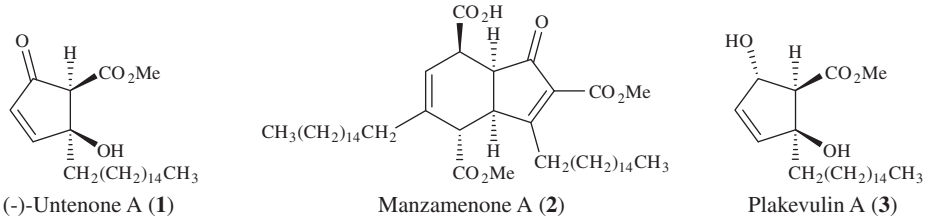
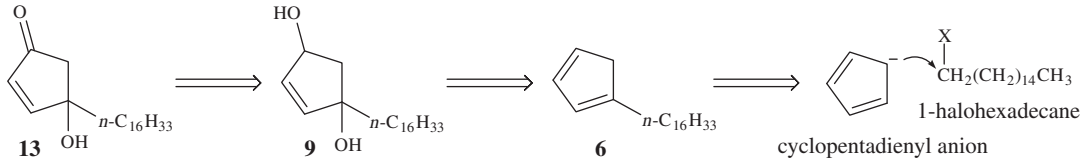
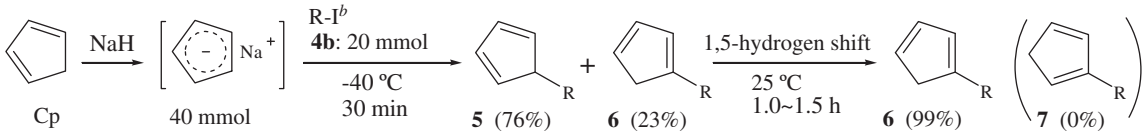


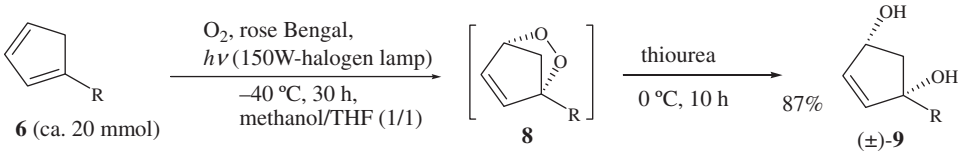
Figure 1.



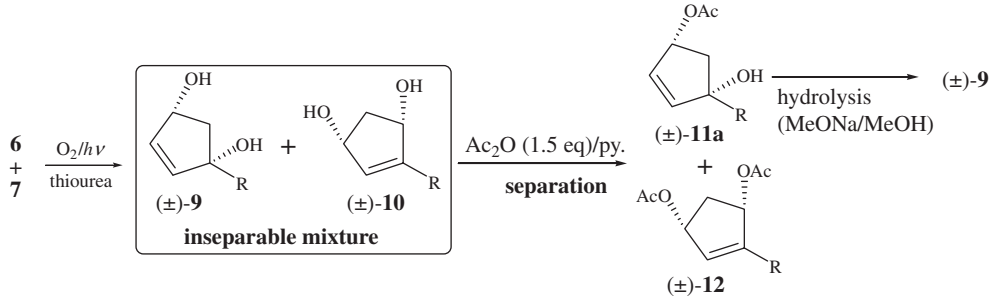
Scheme 1. Retrosynthetic study of cyclopentenone derivative **13** from cyclopentadiene.



Scheme 2. Alkylation of cyclopenta-1,3-diene (Cp) to **6**. Reagents: (a) Yields based on **4b** are shown in parentheses. (b) A THF solution of n-$C_{16}H_{33}$–I (0.5 equiv to sodium cyclopentadienide) was added dropwise.



Scheme 3. Preparation of key compound (±)-**9** form **6**. R = n-$C_{16}H_{33}$.

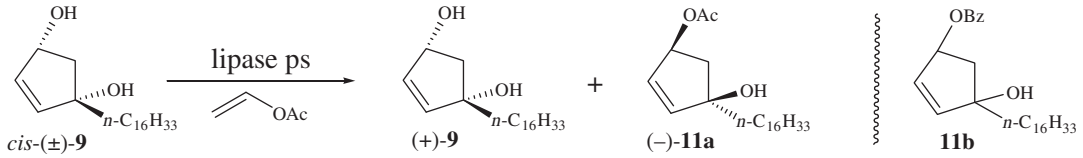


Scheme 4. Preparation of (±)-**9** from a mixture of **6** and **7**. R = n-$C_{16}H_{33}$.

On the other hand, similar treatment of a mixture of **6** and **7**, obtained by alkylation of cyclopenta-1,3-diene, gave a mixture of **9** and **10**, each of which was inseparable by column chromatography on silica gel. Therefore, pure (±)-**9** was obtained via acetylation of the mixture with acetic anhydride (1.5 equiv) in pyridine to a mixture of mono-acetate **11a** and di-acetate **12**, followed by a separation of the produced **11a** from **12** by column chromatography on silica gel, and then hydrolysis (Scheme 4).

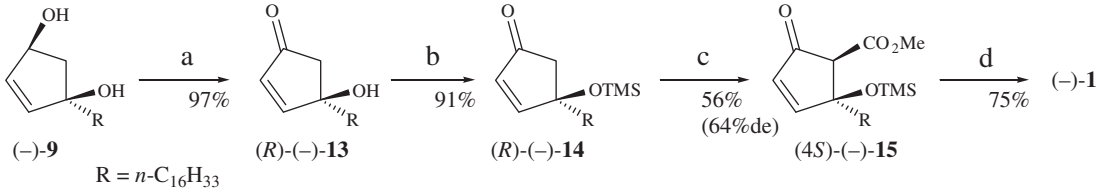
For the synthesis of optically active untenone A, we tried an enzymatic kinetic resolution[8,9] of (±)-**9** to obtain highly optically active (+)- and (−)-**9** using inexpensive and easy handling lipase. By testing the commercially available Lipase PS Amano SD and IM, we adopted Lipase PS Amano IM (immobilized on diatomaceous earth), because IM was more active than SD. That is, IM gave the same optical purity of (+)-**9** and (−)-**11a** as in the case of SD in shorter reaction time using a smaller amount of lipase (entries 2

Table 1
Enzymatic kinetic resolution of (±)-**9** for (+)-**9** and (−)-**11a**



Entry	*cis*-(±)-**9** (mmol)	Enzyme (enzyme/(±)-**9**)[a]	Solvent[b] (mL)	Temp (°C)	Time (h)	(+)-**9**		(−)-**11a**		*E*[d]
						Yield (%)	ee[c] (%)	Yield (%)	ee[c] (%)	
1	0.5	Amano SD (2)	A (6)	25	30	41	80	58	65	11
2	0.5	Amano SD (1)	A (6)	20	36	54	62	44	88	30
3	0.5	Amano IM (0.1)	A (6)	25	8	43	86	55	66	13
4	0.5	Amano IM (0.1)	A (6)	20	8	57	62	41	89	32
5	0.5	Amano IM (0.1)	A (6)	20	12	49	80	49	85	30
6	0.5	Amano IM (0.1)	A (6)	20	20	46	83	45	84	30
7	3.0	Amano IM (0.1)	A (36)	20	24	50	73	43	88	34
8[e]	1.46	Amano IM (0.1)	A (17)	20	8	86[f]	90	12		
9	0.5	Amano IM (0.1)	B (6)	20	12	54	67	46	83	22
10	0.5	Amano IM (0.1)	B (6)	20	18	46	88	53	79	24
11	0.5	Amano IM (0.1)	C (6)	20	18	53	69	46	84	24
12	0.5	Amano IM (0.1)	C (6)	20	24	44	91	55	79	27
13	3.0	Amano IM (0.1)	C (36)	20	24	42	69	57	58	8
14	3.0	Amano IM (0.1)	C (36)	20	24	34	89	66	55	7
15	0.5	Amano IM (0.1)	D (6)	20	20	35	95	63	63	15
16	0.5	Amano IM (0.1)	E (8)	20	5	44	76	53	74	15

[a] Weight ratio (w/w).
[b] (A) vinyl acetate/hexane = 1/1 (v/v), (B) vinyl acetate/hexane = 1/5 (v/v), (C) vinyl acetate/hexane = 1/11 (v/v), (D) vinyl acetate/hexane = 1/11 in the presence of Bu^{t}OMe (10 mol %), (E) Bu^{t}OMe (8 mL) with vinyl acetate (5 mmol).
[c] Determined by HPLC analysis of their benzoate **11b** (CHIRALCEL OD, 5% *i*-PrOH in hexane as eluent).[10]
[d] Enantiomeric ratio, *E* value, was used to evaluate enantioselectivity. $E = (V_A/K_A)/(V_B/K_B)$ where V_A, K_A and V_B, K_B denote maximal velocities and Michaelis constants of the fast- and slow-reacting enantiomers, respectively. The (1*R*,4*S*)-enantiomer reacted faster than the (1*S*,4*R*)-enantiomer.[11]
[e] (**+**)-**9** (73% ee; obtained in entry 7) was used.
[f] 43% yield based on (**±**)-**9**.



Scheme 5. Synthesis of (−)-untenone A ((−)-**1**). Reagents and conditions: (a) IBX (3 equiv), EtOAc, at 80 °C for 4 h; (b) TMSCl (4 equiv), imidazole (6 equiv), CH_2Cl_2, at 0 °C for 1 h; (c) LDA (2.2 equiv of *n*-BuLi and *i*-Pr_2NH), HMPA (2.2 equiv), $NCCO_2Me$ (2.4 equiv), THF, at −78 °C; then at −40 °C for 1 h; (d) concd HCl (cat.), MeOH, at rt for 30 min, and recrystallization from hexane.

and 4). To employ this kinetic resolution for a lager scale synthesis, we examined the reaction in detail in different solvent systems as shown in Table 1.

As a result, a solvent system A using a mixed solvent hexane and vinyl acetate 1:1 (v/v) was revealed to be the most effective, and we could obtain an enough amount of optically active (−)-**11a** and/or (+)-**9**, even in a larger scale reaction.

Optically active (−)- and (+)-untenone A (**1**) were prepared from (−)-**11a** (88% ee), and (+)-**9** (90% ee) obtained in entries 7 and 8 of Table 1, respectively, according to the reported method as shown in Scheme 5 (here the step of (−)-**9** to (−)-**1** is shown).[3,4c,f]

Oxidation of the alcohol (−)-**9** (88% ee, 406 mg, 1.25 mmol), derived from the hydrolysis of (−)-**11a**, with *o*-iodoxybenzoic acid (IBX) (3 equiv) in ethyl acetate at 80 °C for 4 h afforded (−)-**13** (mp 48.2–49.0 °C, $[\alpha]_D^{25}$ −39.4 (c 1.0, $CHCl_3$)) almost quantitatively. Trimethylsilylation of the alcohol (−)-**13** by an excess amount of TMSCl (4 equiv) and imidazole (6 equiv) in dry dichloromethane at 0 °C for 5 h gave (−)-**14** (mp 32.0–32.5 °C, $[\alpha]_D^{25}$ −13.2 (*c* 1.0, $CHCl_3$)) in 91% yield. According to the reported reaction conditions,[3,4c,f] methoxycarbonylation of (−)-**14** was carried out by treatment with LDA and methyl cyanocarbonate (Mander's reagent)[12] in the presence of HMPA in THF at −78 °C to give (−)-**15** in 56% yield (64% de). Desilylation of (−)-**15** by stirring with a catalytic amount of concd HCl in methanol at room temperature for 30 min afforded a diastereomeric mixture of (−)-untenone A which was recrystallized from hexane to give pure (−)-untenone A, (−)-**1** (mp 64.5–66.0 °C; $[\alpha]_D^{26}$ −73.3 (*c* 0.60, $CHCl_3$), in 75% yield (99% ee) (in 37% yield from (−)-**9**) (Scheme 3). Similarly, (+)-**9** (90% ee) was converted to (+)-untenone A (+)-**1** (99% ee) in 41% yield from (+)-**9**. Total yield of (−)- and (+)-untenone A was 16–18% (99% ee).[13]

(±)-Untenone A was prepared in 44% overall yield (based on 1-iodohexadecane) via seven steps similar to the method for the synthesis of optically active untenone A as shown in Schemes 2, 3 and 5.

References and notes

1. Previously, we have reported one of marine cyclopentanoids (+)-brefeldin A and several carbocyclic nucleosides (−)-neplanocin and (+)- and (−)-carbovirs,

in which we constructed those compounds from highly optically active cyclopentenones derived from cyclopenta-1,3-diene and nucleophilic side chain equivalents; (+)-brefeldin A: (a) Nokami, J.; Ohkura, M.; Dan-oh, Y.; Sakamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 2409; (−)-Neplanocin: (b) Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. *Synlett* **1994**, 491; (+) and (−)-carbovirs: (c) Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chem. Lett.* **1994**, 1071.

2. Discovery of *untenone A* and its bioactivities: (a) Ishibashi, M.; Takeuchi, S.; Kobayashi, J. *Tetrahedron Lett.* **1993**, *34*, 3749; (b) Kobayashi, J. *Kagaku to Seibutsu* **1993**, *31*, 659.
3. Synthesis of optically active *untenone A*: (a) Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron Lett.* **1995**, *36*, 1893; (b) Miyaoka, H.; Watanuki, T.; Saka, Y.; Yamada, Y. *Tetrahedron* **1995**, *51*, 8749. and Ref. 4e.
4. Synthesis and bioactivities of *manzamenones*: (a) Tsukamoto, S.; Takeuchi, S.; Ishibashi, M.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 5255; (b) Doncaster, J. R.; Ryan, H.; Whitehead, R. C. *Synlett* **2003**, 651; (c) Saito, F.; Takeuchi, R.; Kamino, T.; Kuramochi, K.; Sugawara, F.; Sakaguchi, K.; Kobayashi, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1975. Synthesis and bioactivities of *plakevulin A*: (d) Saito, F.; Takeuchi, R.; Kamino, T.; Kuramochi, K.; Sugawara, F.; Sakaguchi, K.; Kobayashi, S.; Tsuda, M.; Kobayashi, J. *Tetrahedron Lett.* **2004**, *45*, 8069; (e) Mizutani, H.; Watanabe, M.; Honda, T. *Synlett* **2005**, 793; (f) Kuramochi, K.; Saito, F.; Takeuchi, R.; Era, T.; Takemura, M.; Kobayashi, J.; Sakaguchi, K.; Kobayashi, S.; Sugawara, F. *Tetrahedron* **2006**, *62*, 8006.
5. Synthesis of (±)-*untenone A*: (a) Takeda, K.; Nakayama, I.; Yoshii, E. *Synlett* **1994**, 178; (b) Kuhn, C.; Skaltsounis, L.; Monneret, C.; Florent, J.-C. *Eur. J. Org. Chem.* **2003**, 2585; Synthesis of (±)-*untenone A* and (±)-*manzamenone A, C and F*: (c) Al-Busafi, S.; Whitehead, R. C. *Tetrahedron Lett.* **2000**, *41*, 3467.
6. In the synthesis of (±)-clavulone I and II, a kind of prostanoids having *Z*-oct-2-enyl side chain on cyclopentenone ring, 5-(oct-2-ynyl)cyclopenta-1,3-diene was derived by an alk-2-ynylation of a cyclopentadienyl anion with 1-iodo-2-octyne: (a) Corey, E. J.; Mehrotra, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3384; (b) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1985**, *26*, 2411; Benzyloxy- and methoxymethylation of cyclopenta-1,3-diene were also employed for a prostaglandin synthesis: (c) Corey, E. J.; Koellikerf, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, *93*, 1489. for synthesis of carbocyclic nucleosides; (d) Madhavan, G. V. B.; Martin, J. C. *J. Org. Chem.* **1986**, *51*, 1287. and for preparation of the aglycon of allosamidin; (e) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526.
7. Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876–977.
8. Enzymatic kinetic resolution of cyclopent-2-ene-*cis*-1,4-diol derivatives: (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726–4735; (b) Biadatti, T.; Esker, J. L.; Johnson, C. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2313–2320.
9. Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298.
10. Optical purity of (+)-**14** and (−)-**16a** was determined by HPLC analysis (CHIRALCEL OD, 5% *i*-PrOH in hexane as eluent) after their respective conversion to (+)-**16b** and (−)-**16b**.
11. (a) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695; (b) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294; (c) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812.
12. (a) Mander, L.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425; (b) Crabtree, S. R.; Mander, L.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 56; (c) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148.
13. HPLC analysis of untenone A was performed using CHIRALCEL OD ($5\varphi \times 250$ mm) (Daicel Chemical Co., Ltd) and hexane/2-propanol (20/1, v/v).