Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 62 (2006) 10859–10864
Tetrahedron

Remarkable synthesis and structure of allene type zerumbone

Takashi Kitayama,[a,*] Tomomi Masuda,[a] Kumi Sakai,[a] Chika Imada,[a] Yuji Yonekura[a] and Yasushi Kawai[b]

[a]*Department of Advanced Bioscience, Graduate School of Advanced Bioscience, Kinki University, Nara 631-8505, Japan*
[b]*Nagahama Institute of Bio-Science and Technology, Nagahama, Shiga 526-0829, Japan*

Received 7 August 2006; revised 30 August 2006; accepted 31 August 2006
Available online 22 September 2006

Abstract—The ring expansion of zerumbone to a 12-membered ring was studied via a ring opening system or a ring closure system of zerumbone. We succeeded in the synthesis of a zerumbone derivative with 12-membered ring, an allene type zerumbone. For the first time, a Doering–LaFlamme allene synthesis method was adopted and the structure was confirmed by monocrystal X-ray diffraction. It was obtained in total 27.7% yield from zerumbone. We believe that this compound is not only an important building block in synthesizing the BC ring of paclitaxel, but also plays an important role in a novel structure formation and a reactive discovery.

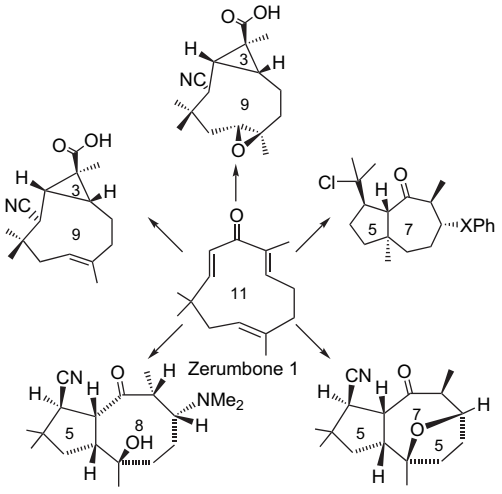
1. Introduction

Zerumbone **1**[1] having potent ability in natural materials-related diversity-oriented synthesis '*NMRDOS*'. The representative concept of diversity-oriented synthesis was established by Schreiber in 2000.[2] However, the choice of substrate is important and moreover, if the substrate is a natural material, much chemical development may be needed. Zerumbone **1**, having powerful latent reactivity and containing three double bonds, two conjugated and one isolated, and a double conjugated carbonyl group in an 11-membered ring structure, is a monocyclic sesquiterpene found as the major component of the essential oil of wild ginger, *Zingiber zerumbet* Smith. It is anticipated to be a powerful tool in the implementation of green chemistry with respect to the provision of materials followed on from the cultivation of ginger.

Also, zerumbone as a natural resource showed attractive reactivity and could be converted into various structures (e.g., transannular and ring contracting skeletons).[3–7] Crystallized zerumbone is obtained quite simply by direct steam distillation from the rhizome of *Z. zerumbet* Smith in more than 3% yield per dry rhizome.[8] In addition, the growth of the plant is very fast. From the viewpoint of purification and reactivity, zerumbone is a powerful resource that exceeds the camphor obtained from camphor trees and menthol obtained from peppermint trees. These have been chemically applied in the chemical industry as typical natural products.

We built the foundation for the industrial use of zerumbone by establishing novel methods such as asymmetric induction, ring scission, and transannular reactions. Since many quite useful polycyclic compounds exist in nature, the development of the transannular reaction and the construction of various transannular products are very important in organic and material chemistry.

As shown in Scheme 1, we examined the transannular reaction of zerumbone in detail and succeeded in the development of many useful transannular products. Thus, since it leads to synthetically difficult products using reactive diversity from the 11-membered structure of zerumbone and the range of the application such as synthesizing the various analogues is very wide, it will be necessary to continue further development of zerumbone chemistry in the future.

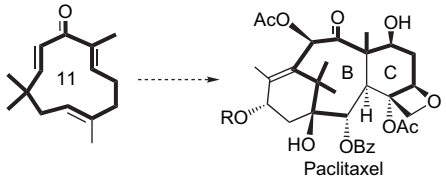


Scheme 1.

* Corresponding author. Tel.: +81 742 43 7415; fax: +81 742 43 8976; e-mail: kitayama@nara.kindai.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.08.102

With respect to an opposite aspect, however, it is analogized that the skeleton formation of non-natural system is very difficult since in the structure of the zerumbone derivatives formed using the character and the skeleton of zerumbone as a natural resource, it is very difficult to get rid of the category of the structure that exists naturally and to form a novel skeleton. If the ring structure can be increased and decreased maintaining the double conjugated system of zerumbone, various wide-ranging transannular compounds can be constructed. It is also expected to have great industrial development, and moreover, the versatile compound that is normally quite difficult to obtain might be synthesized easily from the zerumbone structure. We have insisted and imagined zerumbone as a starting material of the paclitaxel formation. If ring expansion of the 12-membered system is established maintaining double conjugate system, then the synthesis of paclitaxel approaches reality as shown in Scheme 2, namely, the BC ring of paclitaxel is corresponding to the outer carbon numbers of zerumbone with the 12-membered ring. Moreover, each position such as the carbonyl carbon, the adjacent methyl group, and *gem*-methyl group against paclitaxel and zerumbone analogue with 12-membered ring is also corresponded mutually.



Scheme 2.

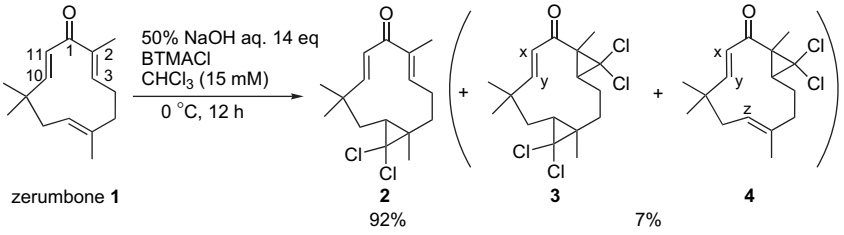
In our current research, however, we comprehended that the conservation of the double conjugated system was extremely difficult since the reactivity of double conjugated system of zerumbone was quite high. We report here that in an attempt with many reaction conditions, finally, the effective synthesis of the allene-zerumbone was accomplished. This beautiful and attractive 12-membered cyclic structure, retaining the double conjugated system, which is a non-natural system, was accomplished when Doering–LaFlamme synthesis[9] was applied.

2. Results and discussion

Sodium hydroxide (50% aq) was added to zerumbone and benzyltrimethylammonium chloride (BTMACl) as a phase transfer catalyst in chloroform at −1 to 0 °C near the coagulation temperature of the solvent. The mixture was then reacted for 12 h to afford 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-one **2** in 92% yield with the regioselectivity as shown in Scheme 3.

The synthetic development of **2** was very important in that it is possible to produce novel derivatives while maintaining the double conjugated system of zerumbone. Dichloro carbene, produced by chloroform, reacted with the isolated olefin regioselectively since there is a stable SOMO energy on the isolated olefin though stable LUMO energy contributed to the double conjugated system of zerumbone. Thus, orbital energy calculations will show important information in the forecast of the reactivity of zerumbone. Orbital energy of zerumbone was calculated in detail, and it will be reported in the near future. Controlling the reaction temperature and the concentration of the solution were the major factors in preparing **2** as shown in Table 1.

Compound **2** was obtained in 92% yield when the reaction temperature was precisely controlled at −1 to 0 °C and the concentration of zerumbone was 15 mM (run 6). However, 5,5,13,13-tetrachloro-1,6,10,10-tetramethyltricyclo[10.1.0.0^{4,6}]tridec-8-en-7-one **3** and 12,12-dichloro-1,5,5,8-tetramethylbicyclo[9.1.0]dodeca-3,7-dien-2-one **4** as by-products, whose ratio was approximately 1:1 analyzed



Scheme 3.

Table 1. Preparation of **2**

Run	Solvent	Concn (mM)	Base	Equiv	Temp (°C)	Time (h)	Yield (%), **2**	Yield (%), **3**+**4**
1	$CHCl_3$	150	NaOH (solid)	3.3	rt	12	Trace	
2	$CHCl_3$	150	50% NaOH aq	14	rt	12	66	
3	$CHCl_3$	15	50% NaOH aq	14	4	12	82	
4	$CHCl_3$	150	50% NaOH aq	14	0	12	67	
5	$CHCl_3$	40	50% NaOH aq	14	0	12	73	
6	$CHCl_3$	15	50% NaOH aq	14	0	12	92	7
7	$CHCl_3$	15	50% NaOH aq	17	0	2	86	13
8	THF	150	50% NaOH aq	3.3	rt	12	Trace	
9	$CHBr_3$	150	50% NaOH aq	14	rt	12	6[a]	

[a] Dibromo substitution.

Table 2. ^{1}H NMR spectrum of olefinic parts of **3** and **4**

Position	3		4	
	ppm	Coupling constant	ppm	Coupling constant
x	5.82	17.3 (doublet)	6.10	16.2 (doublet)
y	6.55	17.3 (doublet)	6.45	16.2 (doublet)
z	—	—	5.83–5.84	Broad

by ^{1}H NMR, were obtained if the reaction conditions were not followed precisely. They were isolated using silica gel chromatography or re-crystallization as mixtures and mainly confirmed by GC–MS (column: DB-1: 30 m, carrier gas: He, injection, and detector: 200 °C, column: 180 °C, t_R **3**: 58.6 min, **4**: 17.1 min). Moreover, ^{1}H NMR spectrum of each olefinic part (positions x, y, and z) in the mixture of **3** and **4** appeared very clear as shown in Table 2. With increasing amount of the NaOH concentration, reaction time has been greatly improved but the amount of by-products increased (run 7). It is necessary to do a complete reactive control, since it is very difficult to separate these compounds with chromatography in case of large-scale system. One explanation might be that since the differentiation of activated energy between **2** and by-products **3** or **4** is very small, it is very easy to spoil the regioselectivity even if the reaction temperature and the concentration of **1** are raised only slightly.

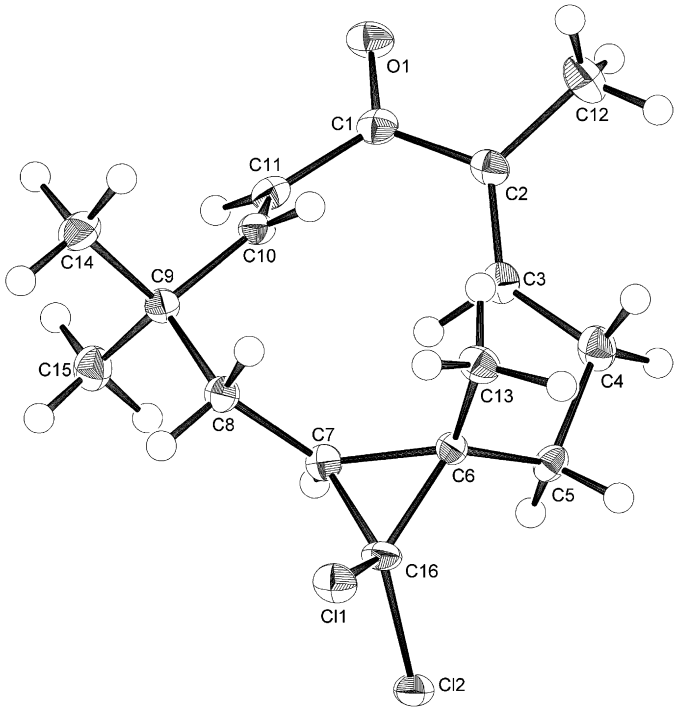
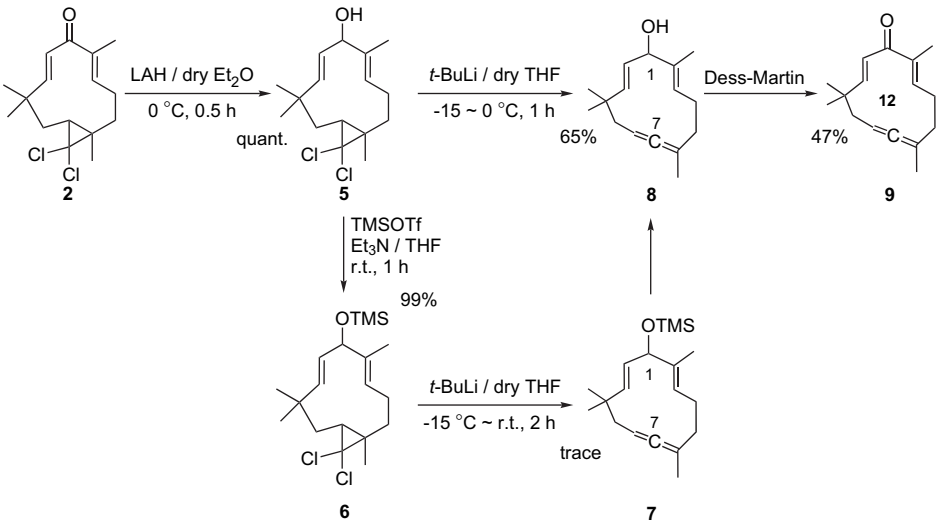


Figure 1. ORTEP drawing of the crystal structure of **2**.

Monoclinic white crystalline **2** could be prepared in a mixture of ethyl acetate and hexane to get ORTEP figure from single crystal X-ray diffraction as shown in Figure 1.

The torsion angle of olefins with double conjugated system of **2** was smaller than that of zerumbone and the structural distortion was dissolved a little since the center of gravity of the ring balance of **2** moved near 6,7-position. Concretely, though the torsion angles between C10–C11 and C1–O1 were 43.2° and 43.5°, respectively, the angles between C2–C3 and C1–O1 were 34.9° and 28.8°, respectively. When the torsion angle shows small value, structural distortion is small.

As shown in Scheme 4, **2** was reacted with $LiAlH_4$ (LAH) in anhydrous ether at 0 °C for 0.5 h to afford 6,7-dichlorocyclopropylzerumbol **5** quantitatively as a diastereomeric mixture. Compound **5** was protected by TMSOTf using Et_3N as a catalyst in THF at room temperature for 1 h to afford **6** quantitatively. Treatment of **6** with *t*-BuLi in THF at −15 °C to room temperature for 2 h gave allene type zerumbol **7** with the 12-membered system in low yield with one carbon enhancement over zerumbone. Deprotection of **7** with TsOH might give allene type zerumbol **8** quantitatively. The development of this formation is the first successful experiment, however, the yield was not high, so direct ring expansion of **5** was examined without protection. Under the same condition as the above-mentioned, **8** was obtained directly from **5** in 65% yield.



Scheme 4.

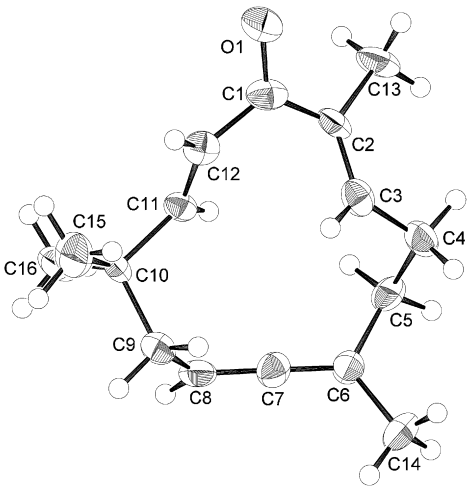
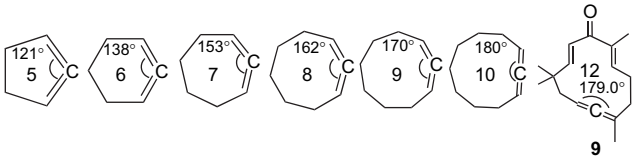


Figure 2. ORTEP drawing of the crystal structure of **9**.

Finally, Dess–Martin oxidation of **8** gave **9** with 12-membered allene system in 47% yield. Since all of the compounds **5**–**8** were diastereomers, separation and purification was quite difficult. Therefore, complete structural data were not obtained except for high-resolution mass spectroscopy. Racemic compound **9** was used to determine the structure, and spectroscopic results could be obtained completely. Moreover, monoclinic crystals of **9** could be prepared from a mixture of diethyl ether and dichloromethane to analyze the single crystal X-ray diffraction and get the preliminary structure as shown in Figure 2. This result will rapidly deepen the role of zerumbone showing potent ability in NMRDOS, and become a trigger to lead to a novel creation. It is expected that examining the reactivity of **9** might give attractive results synthetically.

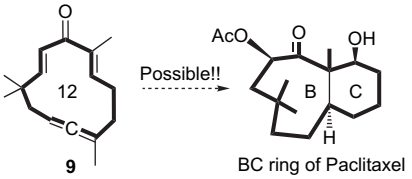
When **1** was compared to the X-ray of the structure of **9**, an interesting result was obtained. The angle of the allene part tends to be smaller than 180° when the number of the ring system is smaller than the 10-membered cyclic system as shown in Scheme 5.[10] It has been found that in spite of the structural distortion of **9** due to the double conjugated system, the angle of C6–C7–C8 in **9** was 179° and there is hardly any distortion of the allene part. This result proved that **9** was the reasonable structure to be produced easily. This might be a reason why **9** shows the beautiful structure without distortion on the allene site.



Scheme 5.

3. Conclusion

We believe that the development of the allene type zerumbone can be contributed to a novel skeleton formation. Especially the transannular reaction of **9** gives quite a different type of novel cyclic structure, e.g., paclitaxel, compared with the reaction from zerumbone **1** as shown in Scheme 6.



Scheme 6.

4. Experimental

4.1. General methods

NMR spectra were obtained at 270 MHz for protons, and 68 MHz for ^{13}C in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard unless otherwise noted. Chemical shifts δ were reported in parts per million from TMS. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were almost obtained by direct injection. The X-ray diffraction and CCDC numbers appear in Section 4.1.2. Chemicals were commercially available, were of reagent grade, and used without further purification.

4.1.1. 12,12-Dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]-dodeca-4,7-dien-6-one 2. BTMACl (10 mg) and 50% NaOH aq (2.5 mL) were added into a solution of zerumbone (1.0 g, 4.6 mmol) and chloroform (300 mL) and stirred vigorously at 0 °C for 12 h. The progress of the reaction was monitored by TLC. The mixture was washed with H_2O (3×300 mL) and brine (3×100 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (15/1) as an eluent to afford 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-one **2** as a colorless solid in 92% yield and the mixture of **3** and **4** in 7% yield. Monoclinic colorless crystalline **2** was prepared in the mixture of ethyl acetate and hexane to analyze the single crystal X-ray diffraction. Mp: 112.0–113.0 °C; IR (KBr): 2957, 1651 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (s, 3H, CH_3 at C9), 1.12 (s, 3H, CH_3 at C9), 1.24 (m, 5H, CH_3 at C1, CH at C11, and CH at C10), 1.59 (m, 1H, CH_2 at C2), 1.85 (m, 4H, CH_3 at C5 and CH at C10), 2.26–2.32 (m, 1H, CH at C2), 2.43–2.47 (m, 2H, CH_2 at C3), 6.09 (s, 2H, CH at C8 and C7), 6.15–6.20 (m, 1H, CH at C4); ^{13}C NMR: δ 11.9 (CH_3 at C5), 13.3 (CH_3 at C9), 23.7 (CH_3 at C1), 25.1 (CH_2 at C10), 29.1 (CH_3 at C9), 30.8 (C9), 35.9 (C1), 36.3 (CH at C11), 37.1 (CH_2 at C2), 41.1 (CH_2 at C10), 71.3 (Cl2), 127.7 (CH at C4), 139.3 (C at C5), 147.9 (CH at C8), 160.4 (CH at C7), 202.6 (C═O); HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{22}Cl_2O$: 300.1048, found: 300.1048.

4.1.2. Crystallographic study of 2. A colorless prism crystal, crystal size 0.20×0.30×0.02 mm^3, monoclinic, space group $P2_1/a$ (no. 14), a=8.889(9), b=18.15(2), c=9.772(10) Å, β=101.929(12)°, V=1542.5(27) $Å^3$, Z=4, D_{calcd}=1.297 g/cm^3, μ(Mo Kα)=4.11 cm^{-1}, was used for data collection. The intensity data were measured on a

Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180±1 °C. The structure was solved by direct methods (SIR97)[11] and expanded using Fourier techniques (DIRDIF99).[12] All calculations were performed using the crystal structure crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 3533 reflections (all data) and 261 variable parameters and gave $R1=0.063$ ($I>2.0\ \sigma\ (I)$) and $wR2=0.192$ (all data). The value of the goodness of fit indicator was 1.08 (Summary of Data CCDC 608648).

4.1.3. 5,5,13,13-Tetrachloro-1,6,10,10-tetramethyltricyclo[10.1.0.0^{4,6}]tridec-8-en-7-one 3. HRMS (EI–GC): *m/z* calcd mass for $C_{16}H_{22}Cl_4O$: 382.0425, found: 382.0417.

4.1.4. 12,12-Dichloro-1,5,5,8-tetramethylbicyclo[9.1.0]-dodeca-3,7-dien-2-one 4. HRMS (EI–GC): *m/z* calcd mass for $C_{16}H_{22}Cl_2O$: 300.1048, found: 300.1046.

4.1.5. 12,12-Dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]-dodeca-4,7-dien-6-ol 5. Under N_2 atmosphere, a solution of **2** (500 mg, 1.66 mmol) in dry Et_2O (5 mL) was added into a suspension of LAH (70 mg, 1.83 mmol) in dry Et_2O (10 mL) at 0 °C and stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). H_2O (50 mL) was added to the mixture carefully at 0 °C and the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (15/1) as an eluent to afford diastereomeric mixture of 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-ol **5** as a white solid quantitatively. Mp: 95.5–96.5 °C; IR (KBr): 3320, 2962 cm^{-1}; HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{24}Cl_2O$: 302.1204, found: 302.1142.

4.1.6. 2,6,10,10-Tetramethylcyclododeca-2,6,7,11-tetraen-1-ol 8. Under N_2 atmosphere, *t*-BuLi (23 mL, 26.8 mmol, 1.48 M in pentane) was dropped into a solution of **5** (810 mg, 2.68 mmol) in dry THF (48 mL) at −15 °C and then the temperature was raised to 0 °C gradually. The mixture was stirred at 0 °C for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). H_2O (50 mL) was added to the mixture carefully at 0 °C and the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to aluminum column chromatography using hexane and AcOEt (15/1) as an eluent to afford diastereomeric mixture of 2,6,10,10-tetramethylcyclododeca-2,6,7,11-tetraen-1-ol **8** as a colorless oil in 65% yield. IR (NaCl): 3329, 2957, 1956 cm^{-1}; HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{24}O$: 232.1827, found: 232.1830.

4.1.7. 2,6,10,10-Tetramethylcyclododeca-2,6,7,11-tetraen-1-one 9. Under N_2 atmosphere, Dess–Martin periodinane (460.8 mg, 1.09 mmol) was added into CH_2Cl_2 (6 mL) at room temperature and stirred until the mixture dissolved completely. Compound **8** (202 mg, 0.87 mmol) in CH_2Cl_2 (6 mL) was dropped into the Dess–Martin solution and then stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). Et_2O (30 mL) and 1 M NaOH aq (30 mL) were added into the solution and then the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (30/1) as an eluent to afford 2,6,10,10-tetramethylcyclododeca-2,6,7,11-tetraen-1-one **9** as a colorless solid in 47% yield. Monoclinic single crystal of **9** was prepared from the mixture of diethyl ether and dichloromethane to analyze the single crystal X-ray diffraction. Mp: 46.0–47.0 °C; IR (KBr): 2961, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H, CH_3 at C10), 1.07 (s, 3H, CH_3 at C10), 1.66 (s, 3H, CH_3 at C6), 1.78 (s, 3H, CH_3 at C2), 1.96 (m, 2H, CH_2 at C9), 2.08–2.26 (m, 2H, CH_2 at C5 and CH at C4), 2.28–2.52 (m, 1H, CH_2 at C4), 4.90–5.07 (br, 1H, CH at C8), 5.87 (d, 1H, J=16.33 Hz, CH at C12), 6.50 (br, 1H, CH at C3), 6.65 (d, 1H, J=16.33 Hz, CH at C11); ^{13}C NMR: δ 12.2 (CH_3 at C2), 18.3 (CH_3 at C6), 24.4 (CH_3 at C10), 26.1 (CH_2 at C4), 27.1 (CH_3 at C10), 36.1 (CH_2 at C5), 37.7 (C at C10), 45.0 (CH_2 at C9), 84.3 (CH at C8), 95.5 (C at C6), 124.6 (CH at C12), 134.8 (C at C2), 145.7 (CH at C3), 159.9 (CH at C11), 201.3 (C=O at C1), 204.5 (=C= at C7); HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{22}O$: 230.1671, found: 230.1682.

Acknowledgements

We wish to express our sincerest gratitude to Professors Seiji Sawada and Tadashi Okamoto for their valuable suggestion and discussions. We thank Dr. J. Cappiello for advice and helpful discussions. We are also grateful to Dr. Masanori Morita for the measurement of HRMS. Rhizomes of *Zingiber zerumbet* Smith and zerumbone were supplied by Taiyo Corporation. This work is supported by the Program for Promoting the Advancement of Academic Research at Private Universities and by a grant from Taiyo Corporation. This research was partially supported by the Ministry of Education, Science, Sports, and Culture, Grant-in-Aid for Scientific Research (B), 17406003, 2005.

References and notes

1. Dev, S. *Tetrahedron* **1960**, *8*, 171–180.
2. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
3. Kitayama, T.; Masuda, T.; Kawai, Y.; Hill, R. K.; Takatani, M.; Sawada, S.; Okamoto, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2805–2810.
4. Kitayama, T.; Nagao, R.; Masuda, T.; Hill, R. K.; Morita, M.; Takatani, M.; Sawada, S.; Okamoto, T. *J. Mol. Catal. B: Enzym.* **2002**, *17*, 75–79.
5. Kitayama, T.; Yokoi, T.; Kawai, Y.; Hill, R. K.; Morita, M.; Okamoto, T.; Yamamoto, Y.; Fokin, V. V.; Sharpless, K. B.; Sawada, S. *Tetrahedron* **2003**, *59*, 4857–4866.
6. Kitayama, T.; Okamoto, T.; Hill, R. K.; Kawai, Y.; Takahashi, S.; Yonemori, S.; Yamamoto, Y.; Ohe, K.; Uemura, S.; Sawada, S. *J. Org. Chem.* **1999**, *64*, 2667–2672.
7. Ohe, K.; Miki, K.; Yanagi, S.; Tanaka, T.; Sawada, S.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3627–3634.
8. Kitayama, T.; Komori, T.; Nakayama, T. The yield is unpublished data, which will be reported elsewhere in the near future.
9. Doering, W.; LaFlamme, P. M. *Tetrahedron* **1958**, *2*, 75–79.

10. Metin, B.; Yavuz, T. *Advances in Strained and Interesting Organic Molecules*; Jai: New York, NY, 2000; Vol. 8, pp 43–81.
11. Altomare, A.; Burla, M.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
12. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *The DIRDIF-99 Program System, Technical Report of the Crystallography Laboratory*; University of Nijmegen: The Netherlands, 1999.