BCSJ

Formation of Isomerized *E*,*Z*-Configured 1,3-Dienes in Construction of Macrocyclic Trienes by Diene-Ene RCM

Ryukichi Takagi,* Kenji Tanaka, Koumei Yamamoto, Yoshikazu Hiraga, Satoshi Kojima, and Manabu Abe

Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima, Hiroshima 739-8526

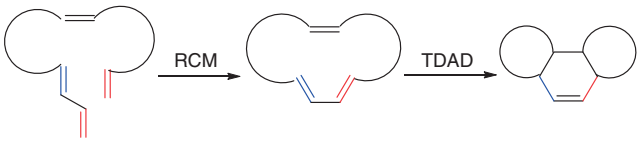
E-mail: rtakagi@hiroshima-u.ac.jp

Received: August 25, 2014; Accepted: September 11, 2014; Web Released: September 19, 2014

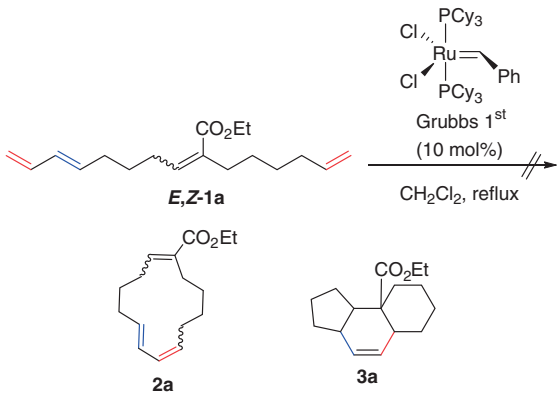
Construction of macrocyclic trienes by diene-ene RCM of tetraenes was examined. In the reactions, macrocyclic trienes were obtained as a mixture of two isomers with *E*,*Z*-configured 1,3-diene moiety. The formation of two isomers can be understandable by the *E*–*Z* isomerization of the initially generated ruthenium–alkenyl carbene intermediate.

Naturally occurring macrocyclic compounds exhibit a wide range of biological activities and are attractive molecules as synthetic targets.[1] Various types of reactions, such as macrolactonization, Horner–Wadsworth–Emmons reaction, alkylation of β-ketoesters, Stille coupling, ring-closing metathesis (RCM), and amidation, have been used to construct the macrocyclic ring. Among them, RCM is a most attractive strategy due to the accessibility to the RCM-precursor and the tolerance to various functional groups.[2] However, the geometry of the double bond formed by RCM is difficult to control.[3] Moreover, in the case of diene-ene RCM, the formation of ring contracted macrocyclic compounds via ethanolysis of the diene moiety may also interfuse.[3a]

Grubbs ruthenium–carbene complexes have both powerful metathetic ability and versatile nonmetathetic applications.[4,5] On the basis of their properties, several tandem processes involving the ruthenium-catalyzed olefin metathesis reaction were developed over the past decade.[6] In the course of our studies on development of a novel tandem reaction involving RCM,[7] we designed a combination of macrocyclization by diene-ene RCM and transannular Diels–Alder reaction (TADA) for constructing tricyclic frameworks (Scheme 1). However, satisfactory results for the tandem RCM/TADA protocol were not obtained. On behalf of the tandem RCM/TADA product, the RCM products, i.e. macrocyclic trienes, were obtained as an unpredicted mixture of two isomers with *E*,*Z*-configured 1,3-diene moiety. In this paper, the details of the macrocyclization by diene-ene RCM of teraenes are reported.



Scheme 1. Hypothesized tandem RCM/TADA protocol.



Scheme 2. Reaction of tetraenes *E*- or *Z*-**1a** with Grubbs 1st catalyst.

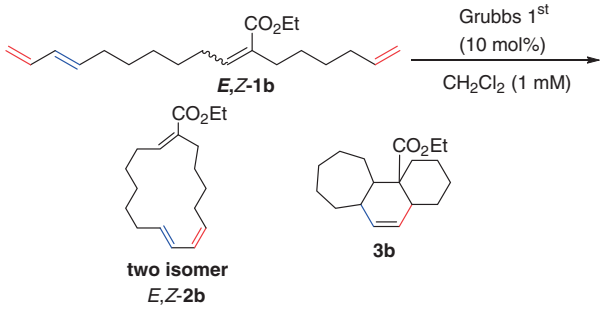
First, we examined the reaction of tetraenes *E*- and *Z*-**1a** with Grubbs 1st catalyst to construct a 5-6-6 ring system via the tandem RCM/TADA protocol (Scheme 2). Although several reaction conditions were attempted, the formation of the complex mixture by self cross-metathesis and/or the recover of tetraenes *E*- or *Z*-**1a** with low isolated yield was observed.

Next, the reaction of tetraenes *E*- and *Z*-**1b**, which was expected to construct a 7-6-6 ring system via the tandem RCM/TADA protocol, was examined (Table 1). In these reactions, the first step of the tandem protocol, RCM of tetraenes *E*- and *Z*-**1b**, proceeded to afford macrocyclic trienes *E*- and *Z*-**2b**, respectively, although the TADA product, 7-6-6 ring system **3b**, was not obtained. Interestingly, macrocyclic trienes *E*- and *Z*-**2b** were observed by ^{1}H NMR as a mixture of two isomers. According to the coupling constants of the two isomers in ^{1}H NMR measurement, the newly formed 1,3-diene moieties by diene-ene RCM were assigned as a *E*,*Z*-configuration, respectively (Figure 1).[8] However, the two-dimensional structure of the two isomers was not clearly determined due to the overlap of the methylene-proton signals in ^{1}H NMR. At this moment, the possibility of regio-isomerization via [1,5]-sigmatropic migration of hydrogen cannot be dismissed.[9]

The effects of additives (*p*-benzoquinone[10] and Ti(O*i*-Pr)$_4$[11]) on the reaction of tetraenes *E*- or *Z*-**1b** with Grubbs 1st catalyst were also examined (Table 1, Entries 2, 3, 5, and 6). The reaction was accelerated by the addition of Ti(O*i*-Pr)$_4$ and proceeded at room temperature. However, the additives affected neither the ratio of the two isomers nor the reaction yield.

With macrocyclic trienes *E*- and *Z*-**2b** in hand, the construction of a 7-6-6 ring system by TADA was also attempted under various conditions. However, tricyclic product **3b** was not obtained. Therefore, tetraene *E*-**1c**, which was expected to afford an electronically more reactive macrocyclic triene toward TADA reaction, was used for the reaction with Grubbs 1st catalyst (Scheme 3). The treatment of tetraene *E*-**1c** with

Table 1. Reaction of Tetraenes *E*- or *Z*-**1b** with Grubbs 1st Catalyst



Entry	Tetraene	Conditions	Product[a),b)]
1	*E*-**1b**	reflux, 18 h	*E*-**2b**:48% (1.4:1)
2		*p*-benzoquinone (20 mol %), reflux, 1.5 h	*E*-**2b**:36% (1.7:1)
3		Ti(O*i*-Pr)$_4$ (1.0 equiv), rt, 19 h	*E*-**2b**:43% (1.8:1)
4	*Z*-**1b**	reflux, 17 h	*Z*-**2b**:57% (10:1)
5		*p*-benzoquinine (20 mol %), reflux, 1.5 h	*Z*-**2b**:65% (7:1)
6		Ti(O*i*-Pr)$_4$ (1.0 equiv), rt, 19 h	*Z*-**2b**:51% (10:1)

a) Isolated yield. b) The ratio of two isomers are in parentheses. The ratio was determined by ^{1}H NMR analysis of the crude product.

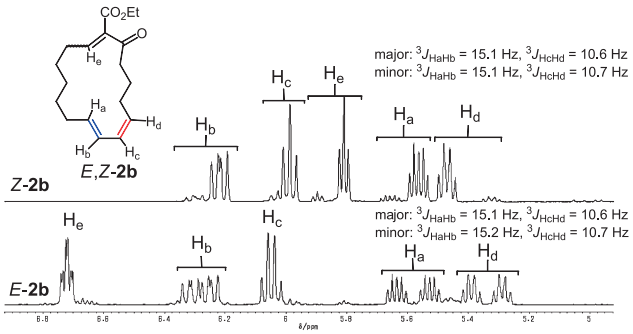
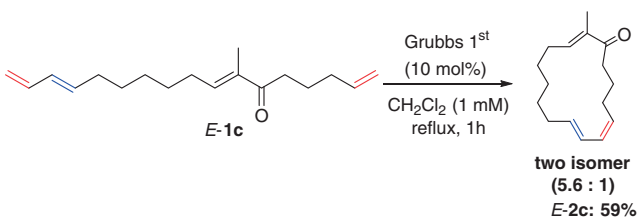


Figure 1. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of *E*- and *Z*-**2b**.



Scheme 3. Reaction of tetraene *E*-**1c** with Grubbs 1st catalyst.

Grubbs 1st catalyst afforded macrocyclic triene *E*-**2c** as a mixture of two isomers with similar selectivity to the reaction of tetraene *Z*-**1b** (Figure 2).[8] In the ^{1}H NMR spectra of macrocyclic triene *E*-**2c**, the methylene-proton signals were

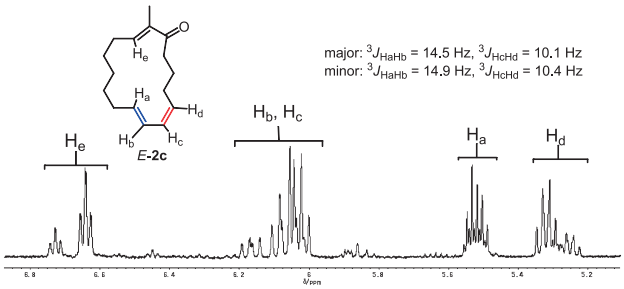


Figure 2. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of *E*-**2c**.

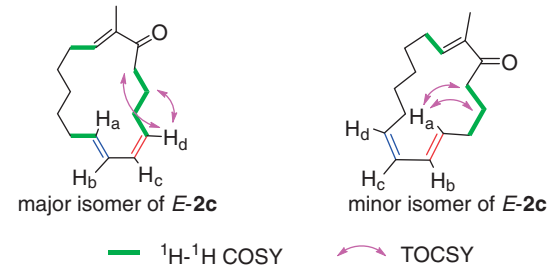
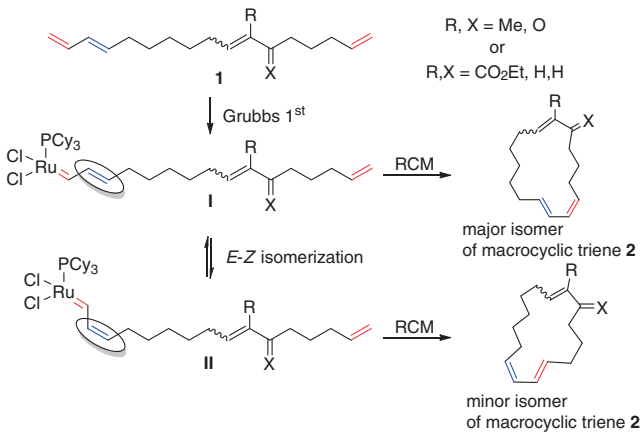


Figure 3. Two isomers of *E*-**2c** based on the key ^{1}H–^{1}H COSY and TOCSY correlations.



Scheme 4. Proposed mechanism for the reaction of tetraene **1** with Grubbs 1st catalyst.

moderately separated. On the basis of the key ^{1}H–^{1}H COSY and TOCSY correlations, the two isomers of macrocyclic triene *E*-**2c** were assigned to the predicted *E*,*Z*-configured 1,3-diene as a major isomer and the isomer of *E*,*Z*-1,3-diene moiety (Figure 3). The formation of the isomerized *E*,*Z*-configured 1,3-diene can be understood by considering the *E*–*Z* isomerization from ruthenium–alkenyl carbene complex **I** to **II** (Scheme 4).[12] At the end, heating triene *E*-**2c** at 250 °C gave the 7-6-6 ring system as a single isomer, although the reaction yield (18%) was low.

In conclusion, the diene-ene RCM of tetraenes **1** with Grubbs 1st catalyst was examined and macrocyclic trienes **2** were obtained as a mixture of two isomers with *E*,*Z*-configured 1,3-diene moiety. The formation of two isomers can be understandable by the *E*–*Z* isomerization of the initially generated ruthenium–alkenyl carbene intermediate **I**. The results may be in accordance with the formation of three isomers in the RCM-macrocyclization of trienes, which was briefly reported

by Fürstner et al.[3a] To the best of our knowledge, this paper is a first distinct report of the *E*–*Z* isomerization of the ruthenium–alkenyl carbene intermediate in diene RCM. The *E*–*Z* isomerization should be also considered in the design of diene RCM.

Experimental

General Procedure for the Reaction of Tetraene 1 with Grubbs 1st Catalyst. To a solution of tetraene **1** in CH_2Cl_2 (1.0 or 10 mM) was added Grubbs 1st catalyst (10 mol %). The reaction mixture was refluxed. After the reaction was complete, the reaction mixture was cooled to room temperature and treated with DMSO (50 equiv relative to Grubbs 1st catalyst).[13] After 3 h, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

***E*-2b**: pale yellow oil; IR (thin film): 3016, 2978, 2927, 2858, 1709, 1643, 1457, 1365 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.72 (t, $J = 8.3$ Hz, 1H, H_e), 6.31 (dd, $J = 10.5$, 5.1 Hz, minor-H_b), 6.25 (dd, $J = 15.2$, 10.5 Hz, major-H_b), 6.06 (t, $J = 10.5$ Hz, major-H_c), 6.04 (t, $J = 10.5$ Hz, minor-H_c), 5.64 (dt, $J = 15.2$, 7.5 Hz, major-H_a), 5.53 (dt, $J = 15.1$, 7.5 Hz, minor-H_a), 5.39 (dt, $J = 10.5$, 8.7 Hz, minor-H_d), 5.29 (dt, $J = 10.5$, 8.5 Hz, major-H_d), 4.18 (q, $J = 7.1$ Hz, 2H), 2.27–2.22 (m, 2H), 2.20–2.05 (m, 6H), 1.49–1.35 (m, 10H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 168.3, 142.6, 142.4, 132.9 (×3), 132.5, 129.7 (×2), 129.3, 128.0, 127.8, 60.3, 31.1, 30.8, 29.8, 29.5, 29.3, 29.1, 28.3 (×2), 28.0, 27.8, 27.7 (×2), 26.9, 26.8, 26.7, 26.2, 26.1, 26.0, 14.3; HR-EIMS m/z [M^+] calcd for $C_{18}H_{28}O_2$ 276.2089, found: 276.2100.

***Z*-2b**: pale yellow oil; IR (thin film): 3016, 2978, 2927, 2858, 1712, 1639, 1446, 1377 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 6.30 (dd, $J = 15.1$, 10.7 Hz, minor-H_b), 6.22 (dd, $J = 15.1$, 10.6 Hz, major-H_b), 6.03 (t, $J = 10.7$ Hz, minor-H_c), 5.99 (t, $J = 10.6$ Hz, major-H_c), 5.90 (t, $J = 6.6$ Hz, minor-H_e), 5.81 (t, $J = 6.7$ Hz, major-H_e), 5.66 (dt, $J = 15.1$, 7.4 Hz, minor-H_a), 5.56 (dt, $J = 15.1$, 7.4 Hz, major-H_a), 5.47 (dt, $J = 10.6$, 8.4 Hz, major-H_d), 5.32 (dt, $J = 10.7$, 8.5 Hz, minor-H_d), 4.20 (q, $J = 7.1$ Hz, 2H), 2.46 (q, $J = 6.7$ Hz, 2H), 2.28 (t, $J = 6.4$ Hz, 2H), 2.23 (t, $J = 6.7$ Hz, 2H), 2.14–2.06 (m, 4H), 1.49–1.44 (m, 4H), 1.42–1.33 (m, 4H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 142.5, 133.1, 132.3, 129.5, 129.3, 127.4, 60.0, 33.3, 30.4, 29.0, 28.4 (×2), 27.6, 27.4, 27.2, 25.5, 14.3; HR-EIMS m/z [M^+] calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2095.

***E*-2c**: pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ 6.72 (tq, $J = 7.6$, 1.3 Hz, minor-H_e), 6.64 (tq, $J = 7.5$, 1.3 Hz, major-H_e), 6.16 (dd, $J = 14.9$, 11.0 Hz, minor-H_b), 6.11–6.00 (m, major-H_b, H_c), 5.53 (dt, $J = 14.9$, 7.4 Hz, minor-H_a), 5.52 (dt, $J = 14.5$. 7.2 Hz, major-H_a), 5.32 (dt, $J = 10.1$, 8.5 Hz, major-H_d), 5.25 (dt, $J = 10.4$, 8.3 Hz, minor-H_d), 2.62 (t, $J = 6.6$ Hz, major-2H), 2.57 (t, $J = 6.1$ Hz, minor-2H), 2.29–2.22 (m, 2H), 2.14–2.06 (m, 2H, major-2H), 2.06–2.03 (m, minor-2H), 1.91–1.84 (m, minor-2H), 1.82–1.72 (m, major-2H), 1.78 (d, $J = 1.3$ Hz, 3H), 1.54–1.45 (m, 2H), 1.44–1.39 (m, 2H), 1.34–1.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 143.4, 137.5, 134.1, 130.1, 129.0, 126.9, 35.8, 30.6, 28.1, 27.4, 26.9, 26.6, 25.3, 24.7, 11.5; HR-EIMS m/z [M^+] calcd for $C_{16}H_{24}O$ 232.1827; found 232.1829.

NMR and MS measurements were made using JEOL JMN-LA500 and JEOL SX-102A instruments, respectively, at the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University. We appreciate the reviewers of the manuscript for valuable comments.

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge on J-STAGE.

References

1 For some recent reviews: a) H. Hussain, I. R. Green, K. Krohn, I. Ahmed, *Nat. Prod. Rep.* **2013**, *30*, 640. b) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, *Chem. Rev.* **2013**, *113*, 4567. c) B. Chatterjee, S. Bera, D. Mondal, *Tetrahedron: Asymmetry* **2014**, *25*, 1.

2 For some recent reports: a) J. Xie, Y. Ma, D. A. Horne, *Tetrahedron* **2011**, *67*, 7485. b) M. S. Kwon, S. H. Sim, Y. K. Chung, E. Lee, *Tetrahedron* **2011**, *67*, 10179. c) A. D. Wadsworth, D. P. Furkert, J. Sperry, M. A. Brimble, *Org. Lett.* **2012**, *14*, 5374. d) L. N. Aldrich, C. B. Berry, B. S. Bates, L. C. Konkol, M. So, C. W. Lindsley, *Eur. J. Org. Chem.* **2013**, 4215.

3 a) D. Gallenkamp, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 9232. b) Y. Wang, M. Jimenez, A. S. Hansen, E.-A. Raiber, S. L. Schreiber, D. W. Young, *J. Am. Chem. Soc.* **2011**, *133*, 9196. c) C. Wang, F. Haeffner, R. R. Schrock, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2013**, *52*, 1939. d) V. M. Marx, M. B. Herbert, B. K. Keitz, R. H. Grubbs, *J. Am. Chem. Soc.* **2013**, *135*, 94. e) L. E. Rosebrugh, M. B. Herbert, V. M. Marx, B. K. Keitz, R. H. Grubbs, *J. Am. Chem. Soc.* **2013**, *135*, 1276. f) C. Wang, M. Yu, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Chem.—Eur. J.* **2013**, *19*, 2726.

4 For a recent review on Grubbs ruthenium–carbene complexes: G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746.

5 For some recent reviews of nonmetathetic reactions catalyzed by Grubbs ruthenium–carbene complexes: a) V. Dragutan, I. Dragutan, *J. Organomet. Chem.* **2006**, *691*, 5129. b) B. Schmidt, *Pure Appl. Chem.* **2006**, *78*, 469. c) V. Dragutan, I. Dragutan, L. Delaude, A. Demonceau, *Coord. Chem. Rev.* **2007**, *251*, 765. d) B. Alcaide, P. Almendros, A. Luna, *Chem. Rev.* **2009**, *109*, 3817.

6 For some recent representative reports: a) H. Fuwa, T. Noguchi, K. Noto, M. Sasaki, *Org. Biomol. Chem.* **2012**, *10*, 8108. b) S. Fustero, P. Bello, J. Miró, A. Simón, C. del Pozo, *Chem.—Eur. J.* **2012**, *18*, 10991. c) M. Arisawa, Y. Fujii, H. Kato, H. Fukuda, T. Matsumoto, M. Ito, H. Abe, Y. Ito, S. Shuto, *Angew. Chem., Int. Ed.* **2013**, *52*, 1003.

7 a) K. Tanabe, A. Fujie, N. Ohmori, Y. Hiraga, S. Kojima, K. Ohkata, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1597. b) R. Takagi, K. Yamamoto, Y. Hiraga, S. Kojima, M. Abe, *J. Organomet. Chem.* **2013**, *723*, 171.

8 a) The isomer ratios of *E*-, *Z*-**2b** and *E*-**2c** were not changed by heating in the attempt of TADA to construct a tricyclic ring system. Moreover, The coalescence between the two isomers in the VT-^1H NMR measurement (r.t. to 100 °C) of *E*-**2c** was not observed. b) The key ^1H NMR data of triene **2** for the determination of the relative setereochemistry is summarized in Supporting Information.

9 a) A. Ndibwami, S. Lamothe, P. Soucy, S. Goldstein, P. Deslongchamps, *Can. J. Chem.* **1993**, *71*, 714. b) Y.-C. Xu, A. L. Roughton, R. Plante, S. Goldstein, P. Deslongchamps, *Can. J. Chem.* **1993**, *71*, 1152. c) Y.-C. Xu, A. L. Roughton, P. Soucy, S. Goldstein, P. Deslongchamps, *Can. J. Chem.* **1993**, *71*, 1169.

10 S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160.

11 a) Q. Yang, W.-J. Xiao, Z. Yu, *Org. Lett.* **2005**, *7*, 871. b) E. B. Pentzer, T. Gadzikwa, S. T. Nguyen, *Org. Lett.* **2008**, *10*, 5613.

12 S. T. Diver, *Coord. Chem. Rev.* **2007**, *251*, 671.

13 Y. M. Ahn, K. Yang, G. I. George, *Org. Lett.* **2001**, *3*, 1411.