CONSTRUCTION OF *cis*-FUSED HYDRINDANE SKELETON WITH A LACTONE TETHER UTILIZING INTRAMOLECULAR DIELS-ALDER REACTION

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Abstract – Synthetically important, *cis*-fused hydrindane skeleton having quaternary angular stereogenic centers was selectively furnished by intramolecular Diels-Alder reaction of ester-tethered precursor via *endo* transition state. The reaction was applicable for a construction of the steroidal BCD ring system with *cis*-hydrindane framework.

Hydrindane skeletons, a 6/5-fused bicyclic system, have been widely found in biologically active compounds, representatively such as a steroidal CD ring.¹ Many of the naturally occurring steroidal compounds have a *trans* stereochemistry on the CD ring juncture, and consequently, considerable efforts have been devoted for development of efficient construction methods of *trans*-hydrindane skeletons.² Among them, an intramolecular Diels-Alder approach has been explored for the predominant formation of the *trans*-hydrindanes (Scheme 1-a).³ In general, this approach preferentially gave the *trans*-hydrindane skeleton, and only minor cases have been reported for providing the *cis*-fused hydrindanes.⁴ On the other hand, the intermolecular Diels-Alder reaction between cyclopentenones and dienes are a promising and reliable approach for the formation of *cis*-hydrindanes due to the inherent stereospecificity of Diels-Alder reactions (Scheme 1-b).^{5,6}

Scheme 1. Reaction modes of Diels-Alder reaction

Hydrindanes having a *cis* stereochemistry have also been an important class of a substructure of bioactive natural compounds. For example, pinguisone showing antifeedant activity is a natural sesquiterpene possessing a furan-fused *cis*-hydrindane skeleton.⁷ Sarmentogenin and ouabagenin are aglycons of cardiac glycosides rhodexin A⁸ and ouabain,⁹ respectively, having unusual *cis*-fused AB and CD rings on their steroidal frameworks. Andrastins are meroterpenoids containing the *cis*-hydrindane substructure, and reported to inhibit the activity of the ras protein farnesyltransferase, thus being a promising lead compound for novel anticancer agents (Figure 1).¹⁰ All of these natural products commonly possess two quaternary carbons on the ring juncture of the *cis*-hydrindane. Therefore, use of sterically hindered tetra-substituted cyclopentenones as a dienophile is enforced in the forementioned intermolecular Diels-Alder strategy for the construction of *cis*-hydrindanes of such natural products. This means that dienes used in this strategy are often limited to sufficiently activated compounds such as Danishefsky's dienes, and this situation is really found in the past literatures.¹¹ In this paper, we describe the Diels-Alder reaction between highly electron-deficient tetra-substituted cyclopentene and unactivated dienes taking advantage of the intramolecular fashion using ester-tethered substrates of dienes and dienophiles, leading to a useful scaffold of natural compounds containing the *cis*-hydrindanes which have quaternary angular carbons.

Figure 1. Natural compounds containing the *cis*-hydrindane substructure

Methyl 2-methylcyclopenten-3-one-1-carboxylate (**2a**)¹² is considered as a highly activated dienophile for Diels-Alder reaction. However, this compound has never used as a Diels-Alder dienophile with unactivated dienes probably due to steric congestion, although several examples have been reported that similar tetra-substituted cyclopentenone derivatives are conducted to intermolecular Diels-Alder reaction with dienes activated by one or more alkoxy substituents. In regard to the cycloaddition reaction of the compound **2a**, photochemical [2+2] addition with allenes is only one example to the best of our knowledge.¹³

In fact, the Diels-Alder reaction of **2a** ($R = \text{Me}$) with the simple unactivated diene **1** did not proceed under thermal conditions in an intermolecular fashion in our hands. We then decided to try the corresponding intramolecular cycloaddition by using the ester-tethered substrate **3**,¹⁴ which was prepared from the carboxylic acid **2b** ($R = \text{H}$) and 2,4-hexadien-1-ol under dehydrative condensation conditions.

Gratifyingly, the intramolecular Diels-Alder reaction of the substrate **3** cleanly proceeded at 180 °C (sealed tube) to give the *cis*-hydrindane **4** in 91% yield. The reaction was *endo* selective (via *endo*-TS), which was confirmed by the NOE observation experiments (Scheme 2).

Scheme 2. Successful Diels-Alder reaction for *cis*-hydrindane

Encouraged by the above results, we applied this strategy for the construction of the steroidal BCD ring system with *cis*-hydrindane framework. The Diels-Alder substrate **9** was designed for this purpose, and synthesized according to Scheme 3. Commercially available cyclohexanedione **5** was converted to the *iso*-butyl enol ether **6** following the literature method,¹⁵ and the product **6** was allowed to react with *trans*-propenyl Grignard reagent followed by acidic hydrolysis to afford the dienone **7** in good yield. DIBAL reduction of **7** gave the alcohol **8**, which was subjected to esterification with carboxylic acid **2** using EDCI and DMAP to furnish the Diels-Alder substrate **9** in an efficient manner.

Scheme 3. Preparation of a precursor for steroidal BCD ring system with *cis*-hydrindane framework

With the substrate compound **9** in hand, we investigated optimal conditions for the intramolecular Diels-Alder reaction to establish the lactone-tethered tricyclic system formation (Table 1). Although the reaction did not proceed under toluene reflux condition (entry 1), the desired cycloadducts were formed in refluxing xylene in low yield (entry 2). Favorably the reaction was largely improved at 145 °C in a sealed tube to realize 73% yield, whose *endo/exo* ratio was 53/20 (entry 3). The reaction was found to be highly susceptible to the temperature, and the yield was decreased at 160 °C (entry 4) and considerable decomposition was observed in short time at 180 °C in *o*-dichlorobenzene (entry 5). The stereostructure of the product **10a** was unambiguously determined by X-ray crystallography (Figure 2) to be an *endo*-adduct, which was predominant product via the similar *endo* transition state in the case of Scheme 2.¹⁶ Thus, the best condition of the intramolecular Diels-Alder reaction of **9** was established, and efficient approach for the tetracyclic framework **10** including the *cis*-hydrindane and the ester tether was accomplished. These compounds would be versatile scaffolds for bioactive natural compounds containing the *cis*-hydrindane substructure.

Table 1. Diels-Alder Reaction for steroidal BCD ring with *cis*-hydrindane framework

entry	solvent	temp	time (h)	% yield (10a/10b)
1	toluene	reflux	14	no reaction
2	xylene	reflux	18	17 / 19
3	xylene	145 °C (sealed tube)	18	53 / 20
4	xylene	160 °C (sealed tube)	18	18 / 16
5	<i>o</i> -dichlorobenzene	180 °C (sealed tube)	1.5	complex mixture

Figure 2. ORTEP drawing of the *endo*-adduct **10a**

In this paper, we have described the efficient intramolecular Diels-Alder strategy for the *cis*-hydrindane skeleton construction, between highly congested tetra-substituted cyclopentenone and unactivated dienes using ester-tethered substrates of dienes and dienophiles. These reactions would serve for providing useful scaffolds of various compounds containing the *cis*-hydrindanes having quaternary angular carbons such as illustrated in Figure 1. Further applications of these reactions for natural product syntheses are now under investigation in our laboratory.

EXPERIMENTAL

All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial suppliers and used as received. Anhydrous solvents were prepared by distillation over CaH₂, or purchased from commercial suppliers. ¹H and ¹³C NMR spectra were measured on a JEOL ECX 400 or a Varian GEMINI 300 instrument, using CHCl₃ (7.26 ppm for ¹H) and CDCl₃ (77.0 ppm for ¹³C) as an internal reference. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. *J* values were in hertz. Mass spectra were measured on a JEOL JMS-GCmate II or a JEOL JMS-AX 505 HAD mass spectrometer, and the ionization method was electron impact (EI, 70 eV). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica Silica Gel 60N (spherical, neutral, 40-50 μm).

(2*E*,4*E*)-Hexadienyl 2-Methyl-3-oxo-cyclopent-1-ene-1-carboxylate (3). To a stirred solution of the carboxylic acid **2b** (440 mg, 3.14 mmol) in CH₂Cl₂ (15 mL) were added DMAP (192 mg, 1.57 mmol), EDCI (900 mg, 4.70 mmol), and 2,4-hexadien-1-ol (463 mg, 4.70 mmol) at room temperature. After stirred for 24 h at the same temperature, the mixture was concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 20:1) to give the ester **3** (581 mg, 84%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 6.35–6.27 (1H, m), 6.12–6.03 (1H, m), 5.84–5.63 (2H, m), 4.76 (2H, d, *J* = 6.9 Hz), 2.79–2.74 (2H, m), 2.48–2.45 (2H, m), 2.05 (3H, s), 1.77 (3H, d, *J* = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 209.3, 165.0, 154.1, 147.1, 135.4, 131.6, 130.1, 122.8, 65.5, 33.8, 26.4, 18.1, 9.9; IR (neat) 2929, 1700, 1447 cm⁻¹; MS (EI) *m/z* 220 (M⁺); HRMS (EI) calcd for C₁₃H₁₆O₃ (M⁺) 220.1100, found 220.1095.

6,6a-Dimethyl-3,3a,6,6a,8,9-hexahydro-1*H*,7*H*-indeno[3*a*,4-*c*]furan-1,7-dione (4). A stainless sealed tube including a solution of the ester **3** (25.0 mg, 0.114 mmol) and BHT (2.5 mg, 0.0114 mmol) in toluene (1.1 mL) was heated at 180 °C for 24 h. After removal of the solvent in *vacuo*, the residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 5:1) to give the lactone **4** (23.0 mg, 91%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 5.89–5.86 (1H, m), 5.77–5.74 (1H, m), 4.51–4.48 (1H, m), 4.15–4.10 (1H, m), 3.11–3.05 (1H, m), 2.39–2.31 (1H, m), 2.16–2.01 (3H, m), 1.87–1.82 (1H, m), 1.21 (3H, s), 0.99 (3H, d, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 217.0, 176.5, 136.5, 123.1, 67.6, 54.2, 52.3, 40.3, 39.9, 34.3, 23.1, 17.8, 17.1; IR (neat) 2978, 1757, 1734 cm^{-1} ; MS (EI) m/z 220 (M^+); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ (M^+) 220.1100, found 220.1092; Mp 141–143 $^\circ\text{C}$.

3-Isobutyl-6,6-dimethylcyclohex-2-en-1-one (6). To a stirred solution of 4,4-dimethylcyclohexane-1,3-dione (5.00 g, 35.6 mmol) in benzene (100 mL) were added *p*-TsOH (355 mg, 1.86 mmol) and *i*-BuOH (6.7 mL, 72.5 mmol) at room temperature. After reflux with Dean-Stark apparatus for 15 h, the reaction mixture was diluted with Et_2O and the reaction was quenched with saturated aqueous NaHCO_3 . The water phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 3:1) to give the vinylogous ester **6** (5.57 g, 80%) as a pale yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 5.23 (1H, s), 3.58 (2H, d, $J = 6.6$ Hz), 2.43 (2H, t, $J = 5.8$ Hz), 2.17–2.15 (1H, m), 1.80 (2H, t, $J = 6.3$ Hz), 1.15 (6H, s), 0.98 (6H, d, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 204.2, 175.8, 100.8, 74.4, 39.9, 34.8, 27.5, 26.0, 24.4, 18.9; IR (neat) 1655, 1611 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$ (M^+) 196.1463, found 196.1463.

(E)-4,4-Dimethyl-3-(prop-1-en-1-yl)cyclohex-2-en-1-one (7). To a stirred suspension of Mg (604 mg, 24.9 mmol) in THF (48 mL) was added *trans*-propenyl bromide (2.1 mL, 24 mmol) at room temperature and heated at reflux for 1.5 h. To a solution of the vinylogous ester **6** (201 mg, 1.02 mmol) in THF was added the above Grignard reagent (0.5 M in THF, 6.2 mL, 3.06 mmol) at 0 $^\circ\text{C}$. After stirred for 80 min at room temperature, 10% aqueous HCl was added to the mixture at 0 $^\circ\text{C}$. After stirred for 5 min at the same temperature, the water phase was extracted with Et_2O . The combined organic phases were washed with brine, dried over MgSO_4 , filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 5:1) to give the dienone **7** (112 mg, 66%) as a pale yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 6.26–6.08 (2H, m), 5.97 (1H, s), 2.43–2.38 (2H, m), 1.85–1.81 (5H, m), 1.16 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 199.4, 166.3, 132.6, 127.8, 121.5, 37.5, 34.6, 34.3, 26.8, 19.0; IR (neat) 1665 cm^{-1} ; MS (EI) m/z 164 (M^+); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{16}\text{O}$ (M^+) 164.1201, found 164.1203.

(E)-4,4-Dimethyl-3-(prop-1-en-1-yl)cyclohex-2-en-1-ol (8). To a stirred solution of the dienone **7** (51.7 mg, 0.314 mmol) in CH_2Cl_2 (2.0 mL) was added DIBAL (1.0 M in toluene, 0.9 mL, 0.9 mmol) at 0 $^\circ\text{C}$. After stirred for 15 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl at 0 $^\circ\text{C}$. The filtrate was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in *vacuo*.

The residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 2:1) to give the alcohol **8** (50.2 mg, 96%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 5.96 (1H, d, *J* = 15.3 Hz), 5.89–5.80 (1H, m), 5.65 (1H, d, *J* = 3.3 Hz), 4.18 (1H, br s), 1.92–1.84 (1H, m), 1.74 (3H, d, *J* = 6.3 Hz), 1.60–1.38 (4H, m), 1.06 (3H, s), 1.00 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 147.0, 129.4, 126.1, 123.1, 66.7, 35.6, 33.7, 29.0, 28.0, 27.8, 18.5; IR (neat) 3329 cm⁻¹; MS (EI) *m/z* 166 (M⁺); HRMS (EI) calcd for C₁₁H₁₈O (M⁺) 166.1358, found 166.1380.

(E)-4,4-Dimethyl-3-(prop-1-en-1-yl)cyclohex-2-en-1-yl-2-methyl-3-oxo-cyclopent-1-ene-1-carboxylate (9). To a solution of carboxylic acid **2b** (108 mg, 0.774 mmol) and alcohol (82.7 mg, 0.497 mmol) in CH₂Cl₂ (5.0 mL) were added EDCI (195 mg, 1.02 mmol) and HOBt·H₂O (30.4 mg, 0.249 mmol) at room temperature. After stirred for 35 min, the mixture was diluted with CH₂Cl₂ and the organic phase was washed with saturated aqueous NaHCO₃ and 10% aqueous citric acid, dried over MgSO₄, filtered, and concentrated in *vacuo*. The residue was used for the next reaction without further purification because of instability against column chromatography on silica gel.

¹H NMR (300 MHz, CDCl₃) δ 5.96 (1H, d, *J* = 16.5 Hz), 5.93–5.82 (1H, m), 5.69 (1H, d, *J* = 3.8 Hz), 5.42 (1H, q, *J* = 4.7 Hz), 2.79–2.73 (2H, m), 2.47–2.44 (2H, m), 2.03 (3H, s), 2.00–1.92 (1H, m), 1.83–1.78 (1H, m), 1.75 (3H, d, *J* = 6.1 Hz), 1.71–1.63 (1H, m), 1.58–1.46 (1H, m), 1.10 (3H, s), 1.03 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 209.7, 165.1, 154.9, 149.7, 128.8, 127.1, 117.6, 70.3, 35.1, 33.8, 33.5, 27.9, 27.3, 26.4, 25.1, 18.4, 9.9; IR (neat) 1713, 1645, 1570 cm⁻¹; MS (EI) *m/z* 288 (M⁺); HRMS (EI) calcd for C₁₈H₂₄O₃ (M⁺) 288.1726, found 288.1753.

8,8,10,10a-Tetramethyl-2,3,5a,6,7,8,10,10a-octahydro-4H-cyclopenta[7,8]naphtha-[1,8-*bc*]furan-1,4(3a1*H*)-dione (10a and 10b). A stainless sealed tube including a solution of the ester **9** (30.2 mg, 0.104 mmol) in xylene (0.9 mL) was heated at 145 °C for 18 h. After removal of the solvent in *vacuo*, the residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 4:1) to give the lactones **10a** (16.0 mg, colorless prism, 53%) and **10b** (5.9 mg, pale yellow prism, 20%).

10a: ¹H NMR (300 MHz, CDCl₃) δ 5.43 (1H, t, *J* = 2.5 Hz), 4.70–4.62 (1H, m), 3.14 (1H, d, *J* = 8.5 Hz), 2.48–2.34 (1H, m), 2.15–1.99 (1H, m), 1.96–1.88 (4H, m), 1.64–1.52 (3H, m), 1.20 (6H, s), 1.15 (3H, s), 1.01 (3H, d, *J* = 7.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 217.4, 176.6, 146.9, 128.2, 77.0, 56.4, 53.2, 43.0, 42.4, 36.4, 34.9, 33.6, 32.5, 29.5, 29.4, 26.0, 18.0, 16.5; IR (neat) 1761, 1734 cm⁻¹; MS (EI) *m/z* 288 (M⁺); HMRS (EI) calcd for C₁₈H₂₄O₃ (M⁺) 288.1726, found 288.1758; Mp 175–177 °C.

10b: ¹H NMR (300 MHz, CDCl₃) δ 5.47 (1H, t, *J* = 3.0 Hz), 4.72–4.65 (1H, m), 2.77–2.64 (2H, m), 2.49–2.27 (3H, m), 2.19–2.11 (1H, m), 2.08–2.01 (1H, m), 1.63–1.48 (2H, m), 1.35–1.29 (1H, m), 1.12 (6H, s), 1.01 (3H, s), 0.98 (3H, d, *J* = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 216.0, 178.8, 138.8, 126.3, 76.7, 53.2, 52.6, 41.6, 34.6, 34.5, 33.2, 31.4, 29.8, 28.8, 25.7, 16.6, 14.1; IR (neat) 1750 cm⁻¹; MS (EI) *m/z* 288 (M⁺); HRMS (EI) calcd for C₁₈H₂₄O₃ (M⁺) 288.1726, found 288.1699; Mp 156–158 °C.

Deposition number CCDC-1421053 for compound **10a**. Free copies of the data can be obtained via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES (AND NOTES)

1. H. Nemoto and K. Fukumoto, *Tetrahedron*, 1998, **54**, 5425.
2. Selected examples; (a) V. Jeso, C. Aquino, X. Cheng, H. Mizoguchi, M. Nakashige, and G. C. Micalizio, *J. Am. Chem. Soc.*, 2014, **136**, 8209; (b) W. H. Kim, J. H. Lee, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2009, **131**, 12576; (c) N. Kotoku, Y. Sumii, T. Hayashi, and M. Kobayashi, *Tetrahedron Lett.*, 2008, **49**, 7078; (d) C. C. Browder and F. G. West, *Synlett*, 1999, 1363; (e) M. Ihara, S. Suzuki, N. Taniguchi, K. Fukumoto, and C. Kabuto, *J. Chem. Soc., Chem. Commun.*, 1991, 1168.
3. (a) N. Azzi, E. Griffen, M. Light, and B. Linclau, *Chem. Commun.*, 2006, 4909; (b) S. A. Selkälä and A. M. Koskinen, *Eur. J. Org. Chem.*, 2005, 1620; (c) G. Zhou, Q.-Y. Hu, and E. J. Corey, *Org. Lett.*, 2003, **5**, 3979; (d) H. Urabe, K. Kusaka, D. Suzuki, and F. Sato, *Tetrahedron Lett.*, 2002, **43**, 285; (e) K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 6920; (f) K. A. Parker and T. Iqbal, *J. Org. Chem.*, 1987, **52**, 1620; (g) M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1984, **25**, 2121.
4. (a) R. Munakata, H. Katakai, T. Ueki, J. Kurosaka, K.-I. Takao, and K.-I. Tadano, *J. Am. Chem. Soc.*, 2004, **126**, 11254; (b) M. F. Hossain, R. N. Yadav, S. Mondal, A. Jana, and S. Ghosh, *Tetrahedron*, 2013, **69**, 7956; (c) D. F. Taber and Y. Song, *J. Org. Chem.*, 1996, **61**, 7508.
5. (a) K. L. Handore, B. Seetharamsingh, and D. S. Reddy, *J. Org. Chem.*, 2013, **78**, 8149; (b) M. E. Jung and D. Yoo, *Org. Lett.*, 2011, **13**, 2698; (c) W. H. Kim, J. H. Lee, B. Aussedat, and S. J. Danishefsky, *Tetrahedron*, 2010, **66**, 6391; (d) A. Chrobok, E. Gössinger, R. Kalb, E. Orglmeister, and J. Schwaiger, *Tetrahedron*, 2007, **63**, 8326; (e) F. Fringuelli, F. Pizzo, A. Taticchi, T. D. J. Halls, and E. Wenkert, *J. Org. Chem.*, 1982, **47**, 5056.
6. Recent reports on *cis*-hydrindane synthesis except using Diels-Alder reaction; (a) G. Liu, G. Mei, R. Chen, H. Yuan, Z. Yang, and C.-C. Li, *Org. Lett.*, 2014, **16**, 4380; (b) T. J. K. Findley, D. Sucunza, L. C. Miller, D. T. Davies, and D. J. Procter, *Chem. Eur. J.*, 2008, **14**, 6862.
7. (a) V. Benesova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, 1969, **34**, 1810; (b) V. Benesova, Z. Samek, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, 1969, **34**, 582.
8. H. Nawa, *Proc. Japan Acad.*, 1951, **27**, 436.
9. (a) R. Thomas, P. Gray, and J. Andrew, *Adv. Drug Res.*, 1990, **19**, 312; (b) P. S. Steyn and F. R.

Heerden, *Nat. Prod. Rep.*, 1998, 397.

10. (a) K. Shiomi, R. Uchida, J. Inokoshi, H. Tanaka, Y. Iwai, and S. Omura, *Tetrahedron Lett.*, 1996, **37**, 1265; (b) S. Omura, J. Inokoshi, R. Uchida, K. Shiomi, R. Masuma, T. Kawakubo, H. Tanaka, Y. Iwai, S. Kosemura, and S. Yamamura, *J. Antibiot.*, 1996, **49**, 414; (c) R. Uchida, K. Shiomi, J. Inokoshi, T. Sunazuka, H. Tanaka, Y. Iwai, H. Takayanagi, and S. Omura, *J. Antibiot.*, 1996, **49**, 418.
11. (a) M. E. Jung and M. Guzaev, *Org. Lett.*, 2012, **14**, 5169; (b) M. E. Jung, D. Ho, and H. V. Chu, *Org. Lett.*, 2005, **7**, 1649; (c) M. E. Jung and P. Davidov, *Angew. Chem. Int. Ed.*, 2002, **41**, 4125; (d) J. M. Eagan, M. Hori, J. Wu, K. S. Kanyiva, and S. A. Snyder, *Angew. Chem. Int. Ed.*, 2015, **54**, 7842; (e) R. Baker, D. L. Selwood, C. J. Swain, N. M. H. Webster, and J. Hirshfield, *J. Chem. Soc., Perkin Trans. 1*, 1988, 471.
12. For preparation, see Supporting Information.
13. Y. Tobe, J.-I. Sato, T. Sorori, K. Kakiuchi, and Y. Odaira, *Tetrahedron Lett.*, 1986, **27**, 2905.
14. Similar intramolecular Diels-Alder reaction of carbon-tethered substrates to form carbocyclic products have been reported, see: M. Ihara, A. Kawaguchi, H. Ueda, M. Chihiro, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1331.
15. R. P. Gandhi, B. Vig, and S. M. Mukherji, *J. Indian Chem. Soc.*, 1959, **36**, 299.
16. CCDC 1421053 includes the crystallographic data for this manuscript.