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Intramolecular Diels–Alder reaction leading to tricyclic derivatives as intermediates of natural products synthesis

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Abstract—Tricyclic compounds **4a** and **4b** possessing a bicyclo[4.3.0] moiety, were successfully synthesized by using the intramolecular Diels–Alder reaction. The siloxy- rather than acyloxy-substituents increased the ratio of the *endo*-cylcoadducts **10** and **12**. The oxygen substitution of **9** influenced conformation of the transition state, which was stereochemically restricted by the butenolide moiety. In addition, **9b** carrying a hydroxyl group also produced **10b** in a similar ratio to **9a**. Compound **11** was the only *exo*-adduct produced in all of the entries.

1. Introduction

Among powerful tools in organic synthesis towards bioactive natural products, the intramolecular Diels–Alder reactions have promised effective access to a variety of complicated carbon-frameworks.[1] An advantage of the reaction is the simultaneous assembly of the carbon framework, coupled with stereogenic centers. An example of appropriate target molecules by the Diels–Alder reaction might be a family of such terpenoids as punctatin A **1**,[2] fukinolide **2**,[3] and chiloscyphone **3**,[4] sharing the bicyclo[4.3.0] ring system, as well as the typical *cis*-fused substitutions (Fig. 1).

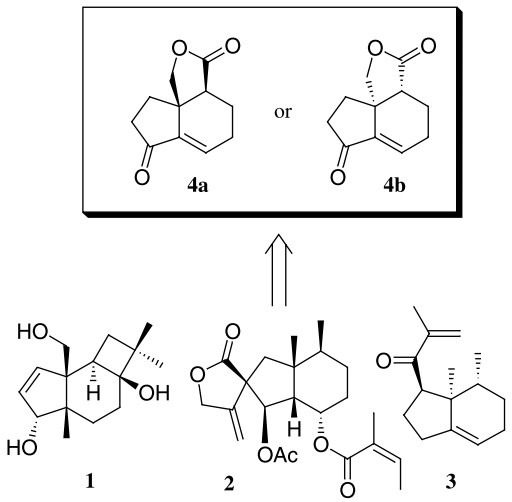

Figure 1. The natural product possessed bicyclo[4.3.0] ring system.

Synthetic access to these terpenoids has been known:[5] one method is introduction of substitutions into cyclized derivatives produced in advance. Another way is cyclization of acyclic precursors with appropriate substitutions. In this context, we investigated construction of the common structure of the above-mentioned terpenoids with the *cis*-oriented continuous substitutions by the intramolecular Diels–Alder reaction. We describe herein progress of the intramolecular Diels–Alder reaction, along with a stereochemical assessment.

2. Results and discussion

2.1. Synthesis of triene 9a–9e

The Diels–Alder substrates **9a**–**9e**, were synthesized from diacetonide **5**, readily available from D-mannitol (Scheme 1).[6] Selective removal of an acetonide of **5** using *p*-TsOH gave the corresponding diol in 74% yield, which was reacted with *n*-Bu_2SnO, followed by oxidation to give ketone **6** in 96% yield in two steps.[7] Exposure of **6** to $Ph_3PC{=}C{=}O$,[8] and removal of an acetonide gave **7**, after protection with a TIPS group. Selective acid hydrolysis gave the corresponding primary alcohol, which was oxidized by Swern oxidation, and the resulting aldehyde was submitted to the Wittig reaction with $Ph_3PCHCHO$ to yield unsaturated aldehyde **8**. Reaction of **8** with $TMSCH_2MgCl$, followed by desilylation furnished triene **9a**. After removal of the TIPS group of **9a**, the resultant **9b** could be utilized for synthesis of **9c**–**9e** by appropriate silylation and acylation (Scheme 2).

Keywords: intramolecular Diels–Alder reaction; 1,3-allylic strain; bicyclo[4.3.0] ring derivatives; terpenoid.
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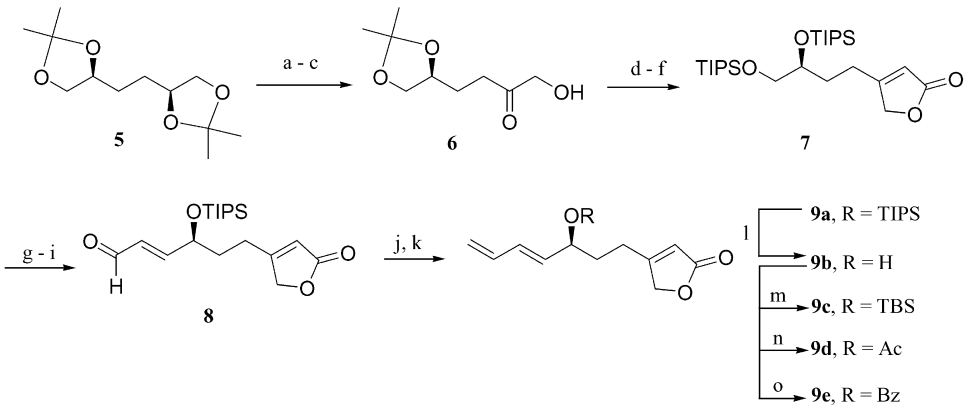
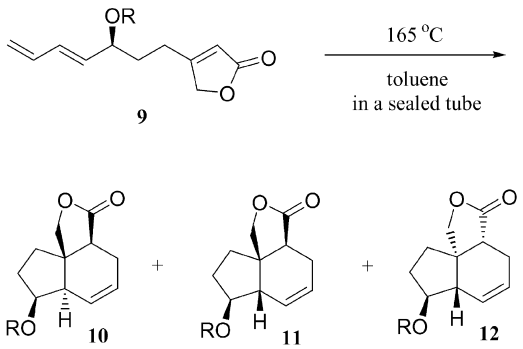


Scheme 1. *Reagents and conditions*: (a) *p*-TsOH, $CHCl_3$, MeOH, room temperature, 74%; (b) $n Bu_2SnO$, toluene, reflux; (c) NBS, $CHCl_3$, room temperature, 96% in two steps; (d) $Ph_3PC{=}C{=}O$, THF, reflux; (e) AcOH, H_2O, THF, room temperature; (f) TIPSOTf, 2,6-lutidine, $ClCH_2CH_2Cl$, 0°C, 50% in three steps; (g) HCl, EtOH, room temperature, 88%; (h) $(COCl)_2$, DMSO, Et_3N, $CHCl_3$, −60°C; (i) $Ph_3PCHCHO$, THF, reflux, 72% in two steps; (j) $TMSCH_2MgCl$, Et_2O, 0°C; (k) 1 M HCl, THF, 0°C, 53% in two steps; (l) 3 M HCl, THF, room temperature, 100%; (m) TBSCl, imidazole, DMF, room temperature, 52%; (n) Ac_2O, pyridine, room temperature, 94%; (o) BzCl, pyridine, room temperature, 56%.



Scheme 2.

2.2. Intramolecular Diels–Alder reaction

The triene **9a** in hand was submitted to the Diels–Alder reaction (0.15 M concentration at 165°C in a sealed tube).[9] As can be seen in Table 1, cyclization of **9a** afforded a 55:19:26 mixture of the adducts **10a**, **11a**, and **12a**, and their stereochemistry was determined by the NOESY correlation (Fig. 2).[10] Roush has reported a similar intramolecular Diels–Alder reaction of the triene derivatives: the main product **II**, was obtained in the *endo* manner as in the case of **12a**, bearing no 1,3-allylic strain between the substituent at C-6 and a proton at C-8 in the reaction conformation (Fig. 3).[11]

Table 1. The intramolecular Diels–Alder reaction of the butenolide derivatives **9**

Entry	Substrate	R	Yield (%)[a]	Product ratio **10**:**11**:**12**[b]
1	**9a**	TIPS	90	55:19:26
2	**9b**	H	72	56:16:28
3	**9c**	TBS	73	60:16:24
4	**9d**	Ac	90	43:21:36
5	**9e**	Bz	73	49:23:28

[a] Isolated yields.
[b] Determined by ^1H NMR analysis. Compounds **10** and **11** would be converted into the same **4a**, while **12** provided **4b**.

Furthermore, the circumstance of an OH group at C-6 would control product distribution: upon employing bulky silyl groups, **I** was obtained, while an acyl group provided **II**. Based on such observation, **9b**–**9e** were submitted to the same reaction conditions, as in the case of **9a**, to confirm the reaction outcome by altering the function at the C-3 position. Contrary to expectation, the major product was type-**10** in all of the entries. There was no obvious influence of the protective group at C-3. The reason might be that the butenolide moiety in **9** decreased the flexibility of the transition state. The transition state adopts conformations to get rid of the stereochemical influence of a substituent at C-3 (Fig. 4). Accordingly, **10a** via the transition state carrying less 1,3-diaxial strain (**pre10a**), was preferentially produced to avoid the strain, which is observed in **pre12a** (entry 1). Cyclization of **9c** provided **10c** as a major product similar to the case of **9a** (entry 3). In addition, even **9b** carrying a small volume of a hydroxyl group provided a comparable result (entry 2) to the siloxy case.[12] In the case of the acylated derivatives (**9d** and **9e**), the *endo*-adducts **10d** and **10e** decreased (entries 4 and 5), while **12d** and **12e** were produced in a similar ratio. Elucidation of these results might show that the relatively compact acyl group of **12** is more favorable than a bulky siloxy group in the sterically hindered transition state. In addition, only the type-**11** products among possible *exo*-adducts, were

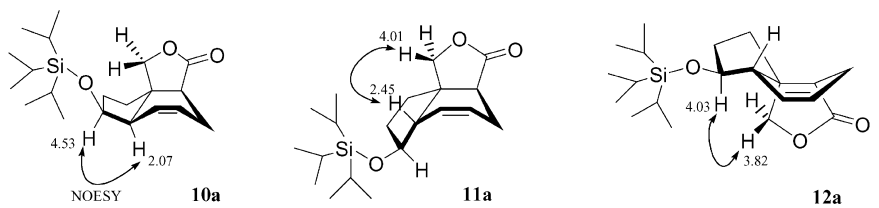


Figure 2. The NOESY correlation of the cycloadducts **10a**, **11a**, and **12a**.

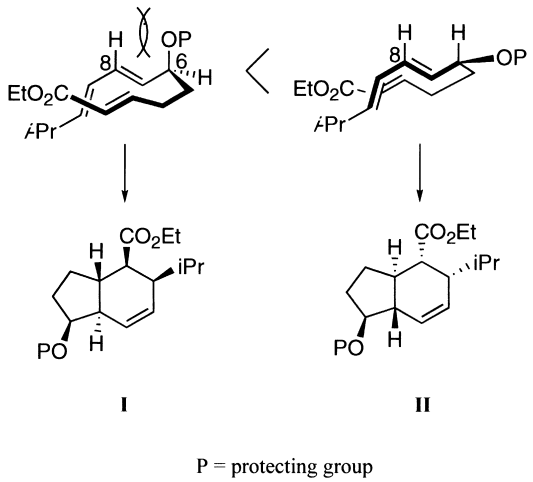


Figure 3. Transition state of Roush's cycloaddition.

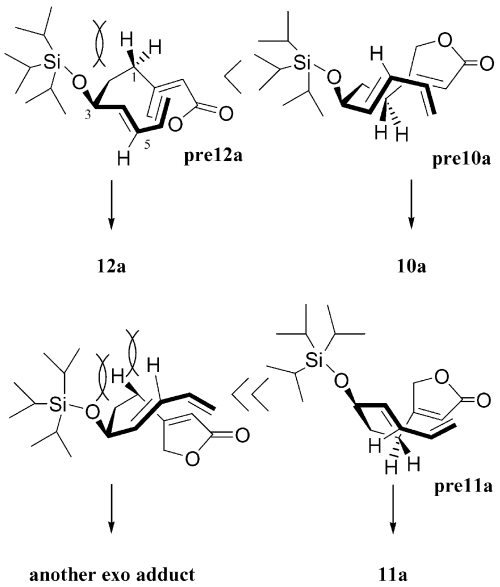
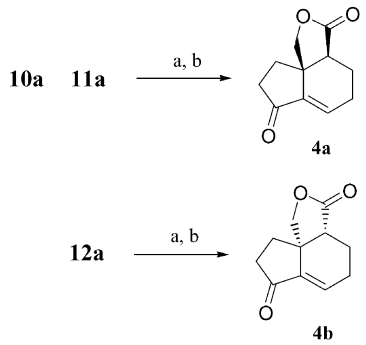


Figure 4. Transition state of cycloadducts.

produced, owing to lack of the two kinds of strains above-mentioned.

Compound **4a** and **4b** were obtained from the Diels–Alder cycloadducts **10a**, **11a**, and **12a**. Thus, removal of the TIPS group of **10a**, **11a** using 6 M HCl gave the corresponding secondary alcohol in 95% yield. The resultant alcohol was oxidized and isomerized under the SO_3·py in DMSO to give **4a** in 95% yield. Cycloadduct **12a** was converted into enantiomeric **4b** by essentially the same procedure as **4a** (Scheme 3).

In conclusion, we have synthesized **4a** and **4b** using the intramolecular Diels–Alder reaction, and demonstrated the selectivity of cycloadducts **10**–**12**. The product distribution of the cycloadducts was controlled by their transition state: the main product **10** was obtained in all of the entries, upon carrying a more bulky silyl protecting group rather than the acyl substrate. Further investigation of this synthetic approach to natural products is in progress.



Scheme 3. *Reagents and conditions*: (a) 6 M HCl, THF, room temperature, 95%; (b) SO_3·py, DMSO, Et_3N, room temperature, 95%.

3. Experimental

3.1. General

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL JNM GX-400 spectrometers in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a Hitachi M-80 B GC-MS spectrometer operating at the ionization energy of 70 eV. Optical rotations were recorded at the sodium D line and ambient temperatures with a JASCO DIP-360. Melting points were measured on a Yanaco MP-S3 and uncorrected. Silica gel-column chromatography was carried out using Katayama K.K. Silica (60–200 mesh). Thin-layer chromatography (TLC) was carried out on 0.25 mm precoated silica gel plates of Silica Gel 60 F254 (E. Merck, Darmstadt). Reaction progress was monitored by either UV (254 nm) or stained with 5% phosphomolybdic acid in ethanol as developing agent, followed in the latter case by heating on an electric plate.

3.1.1. (5*S*)-1,5,6-Trihydroxy-5,6-*O*-isopropylidene-hexan-2-one (6). To a solution of **5** (18.06 g, 78.4 mmol) in $CHCl_3$ (600 mL) and MeOH (60 mL) was added *p*-TsOH (0.75 g, 3.9 mmol): the solution was stirred at room temperature for 15 h. After addition of $NaHCO_3$ (5 g), the solvent was removed in vacuo. Purification of the crude product by column chromatography on silica-gel ($CHCl_3$–MeOH, 20:1→5:1) to give diol (4.20 g, 74% conversion yield) as a colorless oil and unreacted **5** (11.23 g): $[\alpha]_D^{20}=-11.2$ (*c* 1.00, MeOH); IR (film) 3357, 2935 cm^{-1}; δ_H 4.13 (1H, m), 4.06 (1H, dd, *J*=5.9, 8.1 Hz), 3.73 (1H, m), 3.63 (1H, dd, *J*=3.4, 11.2 Hz), 3.53 (1H, t, *J*=7.3 Hz), 3.45 (1H, dd, *J*=7.3, 11.2 Hz), 1.72–1.67 (2H, complex), 1.59–1.52 (2H, complex), 1.41 (3H, s), 1.35 (3H, s); δ_C 109.1, 76.1, 72.0, 69.4, 66.8, 30.1, 29.9, 26.9, 25.7. HRMS calcd for $C_8H_{15}O_4$ ($[M-CH_3]^+$) *m*/*z* 175.0970, found 175.0987.

To a solution of the diol (8.23 g, 43.3 mmol) in toluene (300 mL) was added dibutyltin oxide (11.30 g, 45.4 mmol): the mixture was stirred at 110°C for 21 h in an apparatus equipped with a Dean–Stark trap. The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (200 mL). To this mixture was added NBS (8.18 g, 45.4 mmol). The mixture was stirred at room temperature for 30 min, concentrated in

vacuo, and a slurry was filtered through Celite pad. The filtrate was concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 1:1) to give **6** (7.84 g, 96% from diol) as a colorless oil: $[\alpha]_D^{20}=-8.0$ (*c* 1.00, $CHCl_3$); IR (film) 3408, 2935, 1709 cm^{-1}; δ_H 4.27 (2H, s), 4.11 (1H, m), 4.04 (1H, dd, *J*=6.0, 7.8 Hz), 3.54 (1H, dd, *J*=6.6, 7.8 Hz), 2.75–2.48 (2H, complex), 1.95 (1H, m), 1.82 (1H, m), 1.38 (3H, s), 1.32 (3H, s); δ_C 208.9, 109.1, 74.7, 69.0, 68.1, 34.4, 27.4, 26.9, 25.5. HRMS calcd for $C_8H_{13}O_4$ ($[M-CH_3]^+$) *m/z* 173.0814, found 173.0785.

3.1.2. 3-[(3*S*)-Butanyl-3,4-bis(triisopropylsilyloxy)]-2-buten-4-olide (7). To a solution of **6** (11.54 g, 61.3 mmol) in THF (200 mL) was added Bestman's Ylide (20.51 g, 67.8 mmol). The mixture was stirred at 65°C for 9 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude oil was used directly for the next reaction without further purification.

To a mixture of the above product in water (30 mL) and THF (30 mL) was added AcOH (90 mL). The mixture was stirred at room temperature for 36 h. The mixture was concentrated to a half volume, and passed through on silica-gel ($CHCl_3$–MeOH, 5:1), and the eluent was concentrated in vacuo. The crude oil was used directly for the next reaction without further purification.

To a solution of the above product in 1,2-dichloroethane (100 mL) were added 2,6-lutidine (17.9 mL, 154 mmol) and TIPSOTf (20.6 mL, 77 mmol) at 0°C; the resulting mixture was stirred at the same temperature for 1.5 h. The mixture was quenched by the addition of 1 M HCl at 0°C, and then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 10:1) to give **7** (14.87 g, 50% from **6**) as a colorless oil: $[\alpha]_D^{21}=-15.5$ (*c* 1.00, $CHCl_3$); IR (film) 2943, 2866, 1782, 1751 cm^{-1}; δ_H 5.84 (1H, t, *J*=1.4 Hz), 4.74 (2H, d, *J*=1.4 Hz), 3.95 (1H, m), 3.77 (1H, dd, *J*=4.8, 9.0 Hz), 3.47 (1H, dd, *J*=9.0 Hz), 2.57–2.52 (2H, complex), 1.99–1.83 (2H, complex), 1.05 (42H, bs); δ_C 170.9, 115.1, 73.1, 71.5, 66.0, 31.7, 23.1, 18.2, 18.1, 18.0, 17.8, 12.6, 12.4, 11.9. HRMS calcd for $C_{23}H_{45}O_4Si_2$ ($[M-C_3H_7]^+$) *m/z* 441.2856, found 441.2842.

3.1.3. 3-[(3*S*,4*E*)-4-(6-Oxohexenyl)-3-triisopropylsilyloxy]-2-buten-4-olide (8). To a solution of **7** (6.76 g, 13.9 mmol) in EtOH (50 mL) was added conc. HCl (1 mL). The resulting solution was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo, purification by column chromatography on silica-gel (hexane–EtOAc, 1:1) to give alcohol (1.01 g, 88% conversion yield) as a colorless oil and unreacted **7** (5.08 g): $[\alpha]_D^{21}=+7.6$ (*c* 1.00, $CHCl_3$); IR (film) 3454, 2943, 2866, 1780, 1747 cm^{-1}; δ_H 5.85 (1H, t, *J*=1.6 Hz), 4.75 (2H, d, *J*=1.6 Hz), 3.98 (1H, m), 3.68–3.55 (2H, complex), 2.50 (2H, t, *J*=8.1 Hz), 2.02–1.78 (2H, complex), 1.08 (21H, bs); δ_C 169.9, 115.3, 73.0, 71.5, 65.4, 31.6, 24.1, 18.1, 12.6. HRMS calcd for $C_{14}H_{25}O_4Si$ ($[M-C_3H_7]^+$) *m/z* 285.1522, found 285.1559.

To a solution of oxalyl chloride (0.41 mL, 4.7 mmol) in $CHCl_3$ (10 mL) was added a solution of DMSO (0.67 mL, 9.5 mmol) in $CHCl_3$ (2 mL) dropwise at −60°C; the resulting solution was stirred at the same temperature for 15 min. To this solution was added a solution of the above alcohol (778 mg, 2.4 mmol) in $CHCl_3$ (5 mL) dropwise at the same temperature. The mixture was stirred at the same temperature for 1 h. To this reaction mixture was added Et_3N (2.6 mL, 19 mmol) and stirred at 0°C for 15 min. The mixture was quenched by the addition of saturated aqueous NH_4Cl at 0°C, and then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude oil was used directly for the next reaction without further purification.

To a solution of the above product in THF (20 mL) was $Ph_3PCHCHO$ (1.45 g, 4.8 mmol). The mixture was stirred at refluxing temperature for 12 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and filtered. The filtrate was concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 3:1→1:1) to afford **8** (605 mg, 72% in two steps) as a colorless oil: $[\alpha]_D^{21}=+22.8$ (*c* 1.00, $CHCl_3$); IR (film) 2943, 2866, 1780, 1749, 1691 cm^{-1}; δ_H (C_6D_6) 9.46 (1H, d, *J*=7.8 Hz), 6.27 (1H, ddd, *J*=1.2, 7.8, 15.6 Hz), 6.06 (1H, dd, *J*=4.8, 15.6 Hz), 5.47 (1H, t, *J*=1.4 Hz), 4.17 (1H, m), 3.87 (2H, d, *J*=1.4 Hz), 1.81 (1H, m), 1.53 (1H, m), 1.38 (1H, m), 1.20 (1H, m), 1.02–0.96 (21H, bs); δ_C (C_6D_6) 191.7, 168.4, 156.5, 132.0, 115.6, 72.2, 70.7, 34.0, 22.3, 18.2, 12.6. HRMS calcd for $C_{16}H_{25}O_4Si$ ($[M-C_3H_7]^+$) *m/z* 309.1522, found 309.1472.

3.1.4. 3-[(3*S*,4*E*,6*E*)]-4,6-Heptadienyl-3-triisopropylsilyloxy]-2-buten-4-olide (9a). To a solution of **8** (219 mg, 0.62 mmol) in Et_2O (2 mL) was added $TMSCH_2MgCl$ 1.0 M solution in Et_2O (1.2 mL, 1.2 mmol) dropwise at 0°C. The mixture was stirred at the same temperature for 20 min. The mixture was quenched by the addition of saturated aqueous NH_4Cl at 0°C, and then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude oil was used directly for the next reaction without further purification.

To a solution of the above product in THF (3 mL) was added 1 M HCl (1.5 mL) at 0°C. The mixture was stirred at the same temperature for 3.5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ at 0°C, and then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 4:1) to give **9a** (116 mg, 53% from **8**) as a colorless oil: $[\alpha]_D^{22}=+3.4$ (*c* 1.00, $CHCl_3$); IR (film) 2943, 2866, 1782, 1751, 1637 cm^{-1}; δ_H 6.33 (1H, m), 6.18 (1H, dd, *J*=10.7, 15.2 Hz), 5.83 (1H, t, *J*=1.5 Hz), 5.65 (1H, dd, *J*=6.8, 15.2 Hz), 5.20 (1H, d, *J*=16.6 Hz), 5.11 (1H, d, *J*=10.3 Hz), 4.73 (2H, d, *J*=1.5 Hz), 4.41 (1H, m), 2.53–2.38 (2H, complex), 1.89–1.84 (2H, complex), 1.05 (21H, bs); δ_C 170.4, 136.0, 135.7, 131.1, 117.5, 115.2, 73.1, 71.9, 35.6, 23.5, 18.1, 12.4. HRMS calcd for $C_{20}H_{34}O_3Si$ ($[M]^+$) *m/z* 350.2277, found 350.2254.

3.1.5. 3-[(3*S*,4*E*,6*E*)-4,6-Heptadienyl-3-hydroxy]-2-buten-4-olide (9b). To a solution of **9a** (68.3 mg, 0.20 mmol) in THF (1 mL) was added 3 M HCl (1 mL); the mixture was stirred at room temperature for 8 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ at 0°C, and then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 1:1) to give **9b** (19.3 mg, 100% conversion yield) as a colorless oil and unreacted **9a** (34.1 mg): $[\alpha]_D^{22}=-1.7$ (*c* 1.00, $CHCl_3$); IR (film) 3419, 2927, 1780, 1745, 1635 cm^{-1}; δ_H 6.37–6.21 (2H, complex), 5.84 (1H, t, *J*=1.6 Hz), 5.70 (1H, dd, *J*=7.0, 15.2 Hz), 5.24 (1H, d, *J*=15.2 Hz), 5.14 (1H, d, *J*=8.8 Hz), 4.75 (2H, d, *J*=1.6 Hz), 4.22 (1H, m), 2.55–2.48 (2H, complex), 1.86–1.80 (2H, complex); δ_C 170.0, 135.7, 135.0, 131.8, 118.4, 115.4, 73.1, 71.3, 34.2, 24.5. HRMS calcd for $C_{11}H_{14}O_3$ ($[M]^+$) *m*/*z* 194.0943, found 194.0906.

3.1.6. 3-[(3*S*,4*E*,6*E*)-3-*tert*-Butyldimethylsilyloxy-4,6-heptadienyl]-2-buten-4-olide (9c). To a solution of **9b** (16.2 mg, 0.083 mmol) in DMF (0.8 mL) was added imidazole (35.0 mg, 0.51 mmol) and TBSCl (35.0 mg, 0.23 mmol). The resulting solution was stirred at room temperature for 6 h. The reaction mixture was purified by column chromatography on silica-gel (hexane–EtOAc, 10:1) to give **9c** (13.3 mg, 52%) as a colorless oil: $[\alpha]_D^{22}=+1.0$ (*c* 1.00, $CHCl_3$); IR (film) 2929, 2856, 1780, 1751, 1637 cm^{-1}; δ_H 6.32 (1H, m), 6.16 (1H, m), 5.82 (1H, t, *J*=1.6 Hz), 5.62 (1H, dd, *J*=6.4, 15.2 Hz), 5.20 (1H, d, *J*=17.2 Hz), 5.10 (1H, d, *J*=9.6 Hz), 4.73 (2H, d, *J*=1.6 Hz), 4.25 (1H, m), 2.46–2.42 (2H, complex), 1.81–1.76 (2H, complex), 0.89 (9H, s), 0.04 (3H, s), 0.03 (3H, s); δ_C 170.3, 136.0, 135.7, 130.9, 117.5, 115.2, 73.1, 71.8, 35.3, 25.9, 24.1, 18.2, −4.2, −4.8. HRMS calcd for $C_{17}H_{28}O_3Si$ ($[M]^+$) *m*/*z* 308.1808, found 308.1785.

3.1.7. 3-[(3*S*,4*E*,6*E*)-3-Acetoxy-4,6-heptadienyl]-2-buten-4-olide (9d). To a solution of **9b** (19.3 mg, 0.099 mmol) in pyridine (1 mL) was added Ac_2O (1 mL) at 0°C. The resulting solution was stirred at room temperature for 16 h. This reaction mixture was concentrated in vacuo, purification by column chromatography on silica-gel (hexane–EtOAc, 2:1) to give **9d** (22.0 mg, 94%) as a colorless oil: $[\alpha]_D^{22}=-6.3$ (*c* 1.00, $CHCl_3$); IR (film) 2931, 1780, 1747, 1637, 1238 cm^{-1}; δ_H 6.35–6.20 (2H, complex), 5.86 (1H, t, *J*=1.8 Hz), 5.60 (1H, dd, *J*=7.2, 14.4 Hz), 5.34–5.25 (2H, complex), 5.17 (1H, m), 4.74 (2H, d, *J*=1.8 Hz), 2.46–2.42 (2H, complex), 2.06 (3H, s), 2.03–1.87 (2H, complex); δ_C 170.0, 168.9, 135.4, 134.0, 129.9, 119.4, 115.6, 73.1, 72.9, 31.7, 24.5, 21.2. HRMS calcd for $C_{13}H_{16}O_4$ ($[M]^+$) *m*/*z* 236.1049, found 236.1031.

3.1.8. 3-[(3*S*,4*E*,6*E*)-3-Benzoyloxy-4,6-heptadienyl]-2-buten-4-olide (9e). To a solution of **9b** (10.3 mg, 0.053 mmol) in pyridine (1 mL) was added BzCl (0.2 mL, 1.7 mmol). The resulting solution was stirred at room temperature for 12 h. To this reaction mixture was added MeOH (0.1 mL) at room temperature, and then stirred at the same temperature for 30 min. The mixture was quenched by the addition of 1 M HCl at 0°C, then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 3:1) to give **9e** (8.8 mg, 56%) as a colorless oil: $[\alpha]_D^{20}=+28.5$ (*c* 0.77, $CHCl_3$); IR (film) 2927, 1780, 1749, 1714, 1639 cm^{-1}; δ_H 8.04 (2H, d, *J*=8.3 Hz), 7.59 (1H, m), 7.46 (2H, dd, *J*=7.8 Hz), 6.40–6.28 (2H, complex), 5.89 (1H, d, *J*=1.5 Hz), 5.74 (1H, dd, *J*=6.8, 14.2 Hz), 5.61 (1H, dd, *J*=6.8, 13.2 Hz), 5.30 (1H, m), 5.19 (1H, d, *J*=10.3 Hz), 4.75 (2H, d, *J*=1.5 Hz), 2.54–2.50 (2H, complex), 2.18–2.01 (2H, complex); δ_C 168.8, 165.5, 135.4, 134.0, 133.2, 130.0, 129.8, 129.5, 128.4, 119.4, 115.7, 73.5, 73.0, 31.9, 24.5. HRMS calcd for $C_{18}H_{18}O_4$ ($[M]^+$) *m*/*z* 298.1205, found 298.1167.

3.1.9. (1*R*,5*S*,9*R*,10*S*)-10-Triisopropylsilyloxy-3-oxatricyclo[7.3.0.0^{1,5}]dodec-7-ene-4-one (10a), (1*R*,5*S*,9*S*,10*S*)-10-triisopropylsilyloxy-3-oxatricyclo[7.3.0.0^{1,5}]dodec-7-ene-4-one (11a), (1*S*,5*R*,9*S*,10*S*)-10-triisopropylsilyloxy-3-oxatricyclo[7.3.0.0^{1,5}]dodec-7-ene-4-one (12a). A solution of **9a** (372 mg, 1.06 mmol) in dry toluene (7 mL) was heated at 165°C for 32 h in a sealed tube. After being cooled to room temperature, the tube was opened, and mixture was concentrated in vacuo. Analysis of the crude product by ^1H NMR spectroscopy indicated that the TIPS ether **10a**, **11a**, **12a** were present in the ratio of 55:19:26. The crude products were purified by column chromatography on silica-gel (hexane–EtOAc, 10:1) to give **10a**, **11a**, and **12a** (334 mg, 90%) as diastereomeric mixture. A part of the mixture was submitted to chromatographic separation to obtain the following data.

Compound **10a**. $[\alpha]_D^{22}=+9.1$ (*c* 1.00, $CHCl_3$); mp 104–105°C (toluene–MeOH); IR (disk) 2943, 2866, 1755 cm^{-1}; δ_H 6.20 (1H, m), 5.97 (1H, m), 4.53 (1H, t, *J*=5.0 Hz), 4.22 (1H, dd, *J*=2.0, 9.9 Hz), 3.98 (1H, d, *J*=9.9 Hz), 2.67 (1H, dd, *J*=3.0, 10.2 Hz), 2.43 (1H, m), 2.36–2.30 (2H, complex), 2.16 (1H, m), 2.07 (1H, bs), 1.83 (1H, m), 1.53 (1H, m), 1.06 (21H, bs); δ_C 180.9, 129.0, 127.7, 76.5, 71.7, 51.6, 49.0, 43.7, 36.4, 35.6, 26.4, 18.2, 18.1, 12.3. HRMS calcd for $C_{17}H_{27}O_3Si$ ($[M-C_3H_7]^+$) *m*/*z* 307.1729, found 307.1727.

Compound **11a**. δ_H 5.73 (1H, m), 5.58 (1H, m), 4.45 (1H, d, *J*=8.2 Hz), 4.14 (1H, bs), 4.01 (1H, d, *J*=8.2 Hz), 2.55–2.54 (2H, complex), 2.45 (1H, bs), 2.25 (1H, m), 2.04 (1H, m), 1.79–1.68 (3H, complex), 1.06 (21H, bs); δ_C 180.0, 127.8, 125.1, 80.0, 78.6, 50.7, 46.7, 43.1, 33.7, 31.5, 20.6, 18.1, 12.1.

Compound **12a**. δ_H 6.13 (1H, m), 5.98 (1H, m), 4.03 (1H, m), 3.92 (1H, d, *J*=8.8 Hz), 3.82 (1H, d, *J*=8.8 Hz), 2.70 (1H, dd, J=3.4, 9.4 Hz), 2.44–2.41 (2H, complex), 2.26 (1H, m), 1.92 (1H, m), 1.86–1.75 (2H, complex), 1.07 (21H, bs); δ_C 180.5, 129.6, 128.3, 75.4, 73.2, 51.0, 49.5, 43.8, 34.3, 32.6, 26.4, 18.1, 12.3.

3.2. Intramolecular Diels–Alder reaction of 9b–9e

A solution of substrate in dry toluene (0.15 M) was heated at 165°C for 32 h in a sealed tube. After being cooled to room temperature, the tube was opened, and the mixture was concentrated in vacuo. Purification by column

chromatography on silica-gel to give the tricyclic compound as diastereomeric mixture. Protecting groups were removed by aqueous HCl or K_2CO_3 in MeOH, and the resulting alcohols were treated with TIPSOTf and 2,6-lutidine to give a crude mixture, which was spectroscopically analyzed to determine a ratio of **10**, **11**, and **12**.

3.2.1. (1*S*,5*S*)-3-Oxatricyclo[7.3.0.0^{1,5}]dodec-8-ene-4,10-dione (4a). To a solution of **10a** (9.3 mg, 0.027 mmol) in THF (0.5 mL) was added 6 M HCl (0.5 mL). The resulting solution was stirred at room temperature for 12 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ at 0°C, then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 1:2) to give alcohol (4.9 mg, 95%) as a colorless oil: δ_H 6.13 (1H, dt, J=2.8, 9.6 Hz), 6.02 (1H, m), 4.47 (1H, t, J=5.2 Hz), 4.20 (1H, dd, J=1.8, 10.0 Hz), 4.01 (1H, d, J=10.0 Hz), 2.69 (1H, dd, J=3.8, 9.4 Hz), 2.45 (1H, m), 2.35 (1H, m), 2.19 (1H, m), 2.15 (1H, bs), 1.86–1.70 (2H, complex), 1.51 (1H, m).

To a solution of above alcohol (4.9 mg, 0.025 mmol) in DMSO (0.2 mL) and Et_3N (0.2 mL) was added SO_3·py (50 mg, 0.31 mmol). The resulting solution was stirred at room temperature for 4 h. The mixture was quenched by the addition of saturated aqueous NH_4Cl at 0°C, then resulting slurry was partitioned between EtOAc and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica-gel (hexane–EtOAc, 1:2) to give **4a** (4.6 mg, 95%) as a colorless oil: $[\alpha]_D^{24}=-5.4$ (c 0.26, $CHCl_3$); IR (film) 2950, 1772, 1720, 1651 cm^{-1}; δ_H 6.90 (1H, t, J=4.4 Hz), 4.28 (1H, d, J=9.2 Hz), 4.13 (1H, dd, J=1.0, 9.2 Hz), 2.54 (1H, dd, J=5.2, 8.8 Hz), 2.43–2.40 (2H, complex), 2.39–2.31 (3H, complex), 2.02 (1H, m), 1.92 (1H, m), 1.69 (1H, m); δ_C 203.2, 177.9, 139.2, 134.5, 76.3, 46.3, 43.6, 35.6, 32.8, 23.7, 21.4. HRMS calcd for $C_{11}H_{12}O_3$ ([M]$^+$) m/z 192.0786, found 192.0781.

3.2.2. (1*R*,5*R*)-3-Oxatricyclo[7.3.0.0^{1,5}]dodec-8-ene-4,10-dione (4b). $[\alpha]_D^{22}=+4.6$ ($CHCl_3$), its spectroscopic data was superimposable to those of **4a**.

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9. Lewis acid-promoted conditions ($TiCl_4$, Et_2AlCl) were unsuccessful, and further elaboration to optimize the reaction is in progress.
10. Since **10** and **11** would be converted into the same **4a**, a product ratio of the Diels–Alder reaction could be assessed as a sum of **10** and **11** versus **12** (**10**+**11**:**12**=64:36–76:24).
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12. A possibility of electrostatic effect by the polaritic hydroxyl group is also considered.