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REGIOSELECTIVE DMAD-INSERTION REACTION OF SILYL DIENOL ETHER OF γ-PYRONE UNDER CATALYST- AND HEATING-FREE CONDITIONS

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Abstract – The reaction of silyl dienol ether of γ-pyrone with dimethyl acetylenedicarboxylate (DMAD) gives the regioselective insertion product in 66% yield. This DMAD-insertion reaction is thought to include a three-step sequence: (1) thermal [2+2]-type cycloaddition reaction of silyl dienol ether of γ-pyrone with DMAD, (2) ring-opening electrocyclic reaction of the cyclobutene skeleton, and (3) hydrolysis of the silyl dienol ether. The present reaction proceeds under mild conditions without any catalysts or heating. In addition, the [2+2]-type cycloaddition reaction proceeds regioselectively at the C3–C4 double bond in the silyl dienol ether of γ-pyrone.

Several γ-pyrone-containing polypropionates have been isolated from marine animals.[1] These compounds show valuable biological activities. γ-Pyrone-containing natural products are classified into α-alkyl-type γ-pyrones such as auripyrones A (**1**) and B (**2**), and α-methoxy-type γ-pyrones such as cyercene A (**3**)[2] (Figure 1). Previously, we achieved the total synthesis of auripyrones A (**1**) and B (**2**)[3] by using the diastereoselective aldol-type reaction of a γ-pyrone as a key step.[4] In the course of our extensive studies on the side-chain elongation reactions of an α-alkyl-type γ-pyrone, we synthesized silyl dienol ether of γ-pyrone **5** (Scheme 1).[5] In the presence of $TiCl_4$ as a Lewis acid promoter, the Mukaiyama aldol-type reaction of **5** with various aldehydes gives the corresponding adducts **6** with *anti*-aldol selectivity.

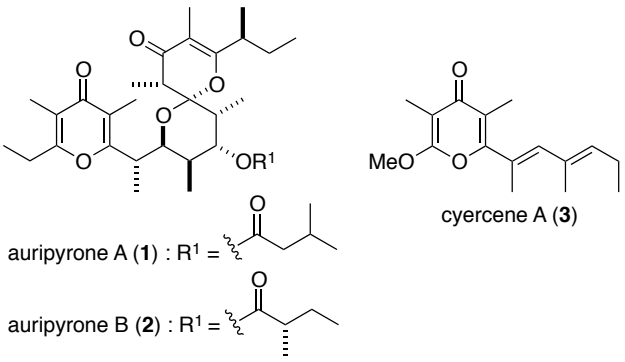
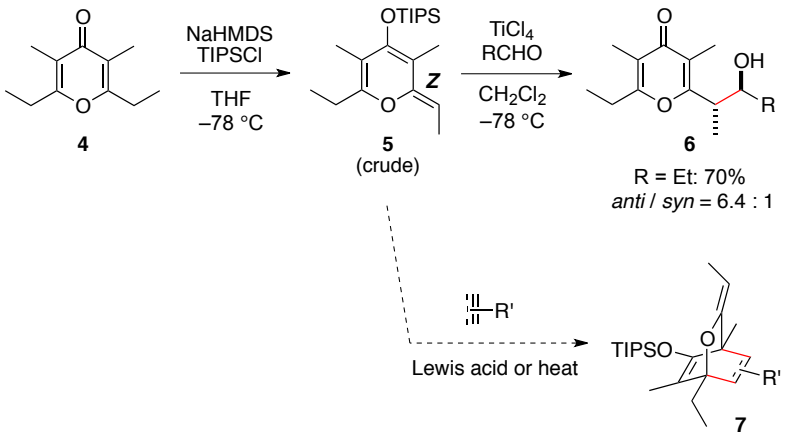


Figure 1. Structures of γ-pyrone-containing natural products

Compound **5** is considered to be not only a silyl dienol ether but also an electron-rich *s*-cis diene. So, we envisioned that **5** would react with some dienophiles to give the corresponding Diels–Alder adducts **7** in the presence of a Lewis acid catalyst or under heating conditions (Scheme 1). Thus, in this study, we examined the Diels–Alder reaction of **5** with various dienophiles. We report here our studies on the reactions of **5** with various dienophiles and our unexpected finding of the regioselective dimethyl acetylenedicarboxylate (DMAD)-insertion reaction of **5**.

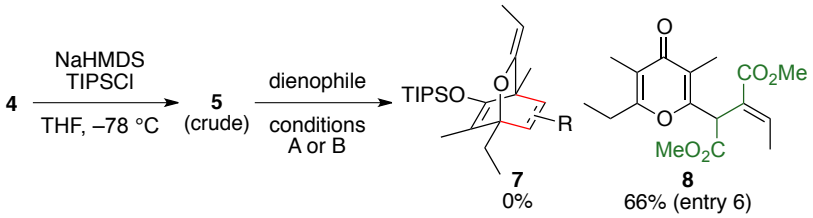


Scheme 1. Reactions of silyl dienol ether of γ-pyrone **5**: Diastereoselective aldol-type reaction with aldehydes (previous work, ref. 5) and Diels–Alder reaction with dienophiles (working hypothesis in the present study)

Our study commenced with the reaction of the silyl dienol ether of γ-pyrone **5**[6] with various dienophiles, such as maleic acid, 1,4-benzoquinone, and DMAD (Table 1). Since the Mukaiyama aldol-type reaction of **5** was most efficiently promoted by $TiCl_4$ as a Lewis acid, we carried out the Diels–Alder reaction of **5** in the presence of $TiCl_4$ (1.1 equiv) at –78 °C (condition A, entries 1–3).[5] However, the desired Diels–Alder adducts **7** were not obtained under these conditions, and γ-pyrone **4** was recovered. We next examined the Diels–Alder reaction of **5** in the absence of $TiCl_4$ at ambient temperature (condition B,

entries 4–6). The reaction with maleic acid and 1,4-benzoquinone also did not give adducts **7**, and γ-pyrone **4** was recovered (entries 4 and 5). In contrast, very interestingly, the reaction with DMAD gave diester **8** in 66% yield as a single isomer, although the Diels–Alder adduct **7** was not obtained (entry 6). The structure of diester **8** was determined by an analysis of 2D NMR (COSY and HMBC) (Figure 2). Thus, the structure of **8** suggested that DMAD was inserted at the ethylidene portion of **5**. To confirm the structure of **8**, two ester groups were hydrolyzed under basic conditions to give mono carboxylic acid **9** as crystals (Scheme 2). The structure of mono carboxylic acid **9** was established by X-ray crystallographic analysis. The geometry of the carbon–carbon double bond in the side chain was determined to be *E*.

Table 1. Investigation of Diels–Alder reaction of silyl dienol ether of γ-pyrone **5**



entry	dienophile (4.0 equiv)	conditions[a]	results
1	maleic anhydride	A	recovery of **4**
2	1,4-benzoquinone	A	recovery of **4**
3	DMAD	A	recovery of **4**
4	maleic anhydride	B	recovery of **4**
5	1,4-benzoquinone	B	recovery of **4**
6	DMAD	B	**8**, 66%
7	methyl propiolate	B	recovery of **4**
8	methyl but-2-ynoate	B	recovery of **4**
9	methyl 4-chlorobut-2-ynoate	B	decomposition

[a] condition A: $TiCl_4$ (1.1 equiv), CH_2Cl_2, –78 °C
condition B: benzene, rt

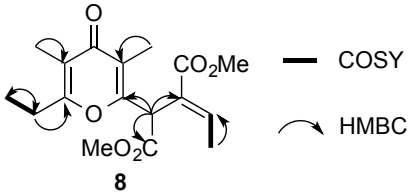
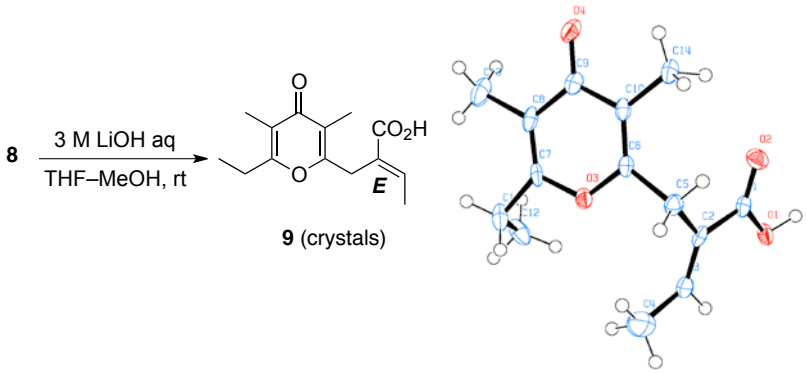
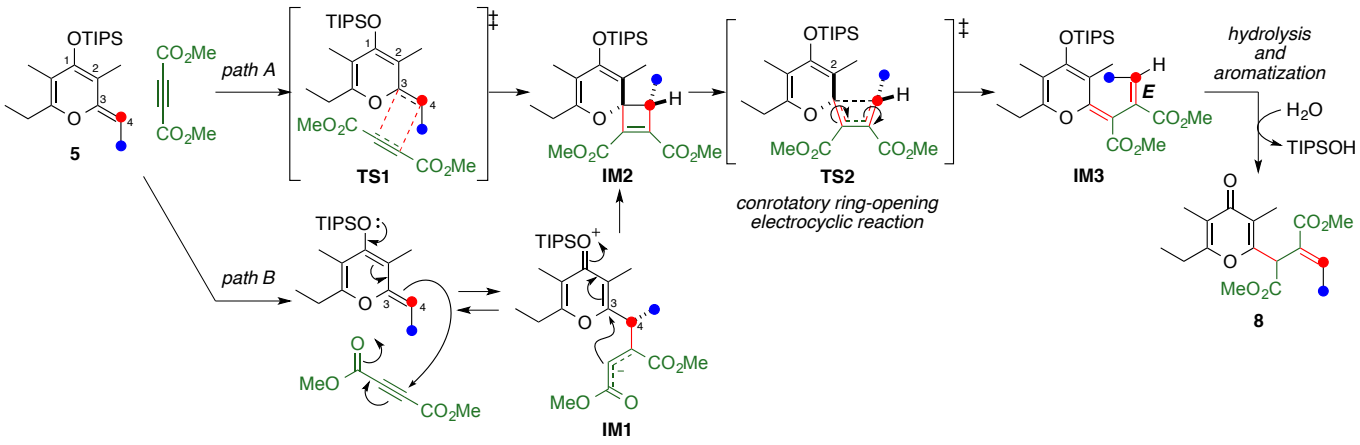


Figure 2. Structure determination of compound **8**



Scheme 2. Hydrolysis of diester **8** and X-ray single-crystal structure of carboxylic acid **9** (CCDC 1572629)

Based on these experimental results, we propose here a mechanism for the present DMAD-insertion reaction, as follows (Scheme 3). It is conceivable that cyclobutene **IM2** is generated as an intermediate in the reaction of **5** with DMAD. For this step, two reaction pathways are proposed: thermal concerted [2+2] cycloaddition reaction of the C3–C4 double bond of **5** with DMAD (path A) and conjugate addition of silyl dienol ether **5** toward DMAD followed by cyclization (path B). To get further insight into the reaction mechanism, we carried out DFT calculations (see the Supporting Information). As a result, transition state of path A (**TS1**) could not be found. In contrast, calculation results strongly suggest that this reaction proceeded through path B.[7] The first step is nucleophilic addition of **5** to DMAD to give **IM1**. Subsequent intramolecular nucleophilic attack would afford **IM2** stereoselectivity. It is probably because the cyclization would proceed before the rotation of γ-pyrone moiety due to the small activation energy from **IM1** to **IM2**. Since the cyclobutene moiety of **IM2** was highly labile, thermal ring-opening electrocyclic reaction of the cyclobutene skeleton[8] of **IM2** should occur immediately to give diester **8**, after hydrolysis of the silyl dienol ether moiety of the ring-opening product.



Scheme 3. Proposed mechanism of the DMAD-insertion reaction of **5**

The *E* geometry of **8** should be attributed to the conrotatory mode of the ring-opening electrocyclic reaction, which proceeded while avoiding steric repulsion between the C2-methyl group and a methoxycarbonyl group. The data of DFT calculations also supported the formation of the *E* isomer.

Several examples of the thermal [2+2]-type cycloaddition reaction of alkenes with electron-deficient alkynes such as DMAD have been reported.[9,10] However, most of these reactions require heating conditions even in the presence of a Lewis acid catalyst. Compared to these reactions, the present [2+2]-type cycloaddition reaction of **5** was highly reactive and did not require any catalysts or heating. This high reactivity can be attributed to the high electron-rich nature and instability of **5**. In addition, the present [2+2]-type cycloaddition reaction proceeded regioselectively at the C3–C4 double bond in the silyl dienol ether. To the best of our knowledge, there are no previous examples of the [2+2]-type cycloaddition reaction of a C3–C4 double bond in silyl dienol ether with an alkyne.

In contrast to most previously reported [2+2]-type cycloaddition reactions of alkenes with electron-deficient alkynes, the present [2+2]-type cycloaddition was accompanied by a rapid ring-opening electrocyclic reaction.[11] We presume that aromatization of **IM2** to the γ-pyrone skeleton, as well as the electron-donating nature of the silyl enol ether moiety, is a driving force of the rapid ring-opening reaction.

We next examined the reaction of **5** with other electron-deficient alkynes, such as methyl propiolate, methyl but-2-ynoate, and methyl 4-chlorobut-2-ynoate (Table 1, entries 7–9), under the same conditions as in entry 6. However, the desired alkyne-insertion products were not obtained. Unfortunately, the present catalyst- and heating-free [2+2]-type cycloaddition reaction of **5** was highly substrate-specific.

In conclusion, we have discovered a regioselective DMAD-insertion reaction of silyl dienol ether of γ-pyrone **5**. The regioselective [2+2]-type cycloaddition reaction of **5** with DMAD, followed by a ring-opening electrocyclic reaction and hydrolysis, proceeds under mild reaction conditions without any catalysts or heating. In addition, the present [2+2]-type cycloaddition reaction proceeds regioselectively at the C3–C4 double bond of the silyl dienol ether. The present catalyst- and heating-free regioselective DMAD-insertion reaction is a new potential tool for the side-chain elongation of α-alkyl-type γ-pyrones. However, the substrates are currently limited to **5** and DMAD. The substrate generality of this unique regioselective alkyne-insertion reaction is currently being evaluated by our group.

EXPERIMENTAL

General method: All chemicals were used as obtained from commercial supplies unless otherwise noted. Anhydrous benzene, CH_2Cl_2, MeOH, and THF were purchased from Wako Pure Chemical Industries Ltd. and used without further drying. TLC analysis was conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Column chromatography was performed with silica gel (E. Merck, Silica gel

60 or Fuji Silysia BW-820MH). Melting point was measured on a J-SCIENCE RFS-10 micro melting point apparatus and are uncorrected. IR spectra were recorded on a HORIBA FT/IR-720 plus spectrometer and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were measured on a Varian Mercury 300 (300 MHz) or a Varian NMR System 600 (600 MHz) spectrometer. The ^1H and ^{13}C NMR chemical shifts (δ) were reported in parts per million (ppm) downfield relative to $CDCl_3$ (δ_H = 7.26 and δ_C = 77.0). *J* values are given in Hz. The following abbreviations are used for spin multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, and br = broad). High resolution ESI (electrospray ionization)/TOF (time-of-flight) mass spectra were recorded on an Agilent Technologies G6520 QTOF LC/MS spectrometer.

Dimethyl (*E*)-2-(6-ethyl-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)-3-ethylidenesuccinate (8). To a stirred solution of triisopropylsilyl chloride (0.570 mL, 2.56 mmol) in hexane (2.0 mL) was added triethylamine (0.370 mL, 2.66 mmol) at room temperature. The mixture was centrifuged at 1000 rpm at room temperature for 30 min, and the supernatant was used as 1.0 M solution in hexane of triisopropylsilyl chloride.

To a stirred solution of 2,6-diethyl-3,5-dimethyl-4-pyrone (**4**) (319 mg, 1.77 mmol) in THF (9.0 mL) was added NaHMDS (1.0 M solution in THF, 2.0 mL, 2.0 mmol) at –78 °C. After the mixture was stirred at –78 °C for 1 h, the solution of the above-mentioned triisopropylsilyl chloride (1.0 M solution in hexane, 2.0 mL, 2.0 mmol) was added. After being stirred at –78 °C for 30 min, the resultant mixture was allowed to 0 °C, concentrated in vacuo to give triisopropylsilyl enol ether **5** as a yellow solid, which was used for the next reaction without purification.

To a stirred solution of crude triisopropylsilyl enol ether **5** in benzene (7.2 mL) was added DMAD (1.2 mL, 7.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h, diluted with 1 M aqueous HCl (20 mL), and extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (41 g, hexane–EtOAc 10 : 1 → 5 : 1 → 5 : 2 → 1 : 1) to give diester **8** (374 mg, 66%) as a yellow oil; R_f = 0.33 (*n*-hexane : EtOAc = 1 : 1); IR (neat) 3018, 2954, 2881, 1743, 1655, 1599, 1508, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (q, *J* = 7.2 Hz, 1H), 5.12 (s, 1H), 3.76 (s, 6H), 2.65–2.48 (m, 2H), 1.98 (s, 3H), 1.94 (s, 3H), 1.84 (d, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.4, 169.0, 166.4, 164.4, 156.7, 142.7, 127.3, 120.6, 118.2, 52.6, 52.1, 45.3, 24.6, 14.9, 11.0, 9.6, 9.4; HRMS (ESI) *m/z* 323.1499, calcd for $C_{17}H_{23}O_6$ $[M+H]^+$ 323.1495.

(*E*)-2-((6-Ethyl-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)methyl)but-2-enoic acid (9). To a stirred solution of diester **8** (200 mg, 0.620 mmol) in THF (2.3 mL) and MeOH (1.1 mL) was added 3 M aqueous LiOH (1.2 mL, 3.6 mmol) in room temperature. After the mixture was stirred at room temperature for 1 h, the resultant solution was acidified with 1 M aqueous HCl (10 mL), and extracted with EtOAc (20 mL × 3).

The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (2.1 g, hexane–EtOAc (with 1% Et_3N) 1 : 4 → 1 : 10 → $CHCl_3$–MeOH (with 1% Et_3N) 30 : 1 → 10 : 1 → 5 : 1 → 1 : 1) to give mono carboxylic acid **9** (67.9 mg, 44%) as a colorless solid. X-Ray analytical sample of **9** was prepared by recrystallization from hexane; R_f = 0.56 ($CHCl_3$: MeOH = 5 : 1); mp = 141–144 °C; IR (neat) 3018, 2976, 2881, 1695, 1648, 1593, 1508, 1465, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 7.22 (q, J = 7.2 Hz, 1H), 3.65 (s, 2H), 2.52 (q, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 171.4, 164.6, 160.3, 142.9, 127.4, 119.1, 118.0, 28.1, 24.7, 15.0, 11.2, 9.8, 9.5; HRMS (ESI) *m/z* 251.1284, calcd for $C_{14}H_{19}O_4$ $[M+H]^+$ 251.1283.

X-Ray crystallographic data of mono carboxylic acid 9.

$C_{14}H_{18}O_4$, M = 250.29, monoclinic, a = 10.185(9), b = 8.107(7), c = 16.777(15) Å, β = 106.629(11)°, V = 1327(2) $Å^3$, calculated density is 1.252 g/cm^3, T = 100(1) K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) = 0.0909 mm^{-1}, 20779 reflections measured, 3033 unique (R_{int} = 0.1378) which were used in all calculations. The final R_1 = 0.1701 ($I > 2\sigma(I)$, 2664 reflections) and Rw = 0.2228 (all data).

X-Ray data for mono carboxylic acid **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1572629. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

ACKNOWLEDGEMENTS

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