Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c0xx00000x

Article

www.rsc.org/xxxxxx

Preparation of Cycloheptane Ring by Nucleophilic Cyclopropanation of 1,2-Diketones with Bis(iodozincio)methane

Ryosuke Haraguchi, Yoshiaki Takada, Seijiro Matsubara*

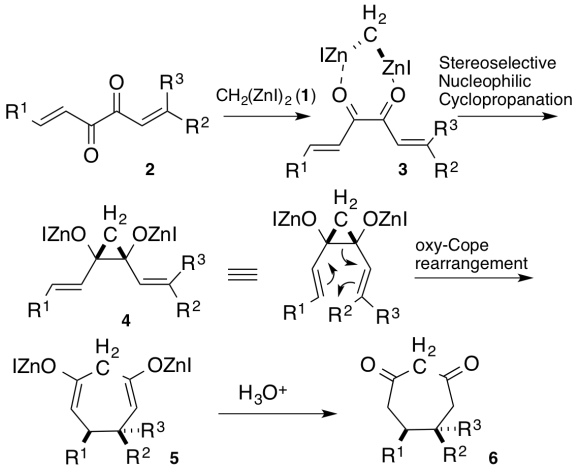
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The nucleophilic cyclopropanation of hexa-1,5-diene-3,4-diones with bis(iodozincio)methane afforded the Zn alkoxides of *cis*-dialkenylcyclopropane-1,2-diols stereoselectively. The subsequent oxy-Cope rearrangement afforded the corresponding Zn alkoxides of 5,6-dialkylcyclohepta-3,7-diene-1,3-diols .

Introduction

The Cope rearrangement of *cis*-divinylcyclopropanes has been recognized as an efficient route to synthesize cycloheptane rings. The disadvantageous entropic factor for a seven-membered ring construction is overcome by coming close of both ends caused from the rigid configuration of cyclopropane.[1] The difficulty in the stereoselective preparation of the *cis*-isomer of the substrate, however, often makes the transformation less valuable. Although some practical methods have been developed for the preparation of the *cis*-isomers,[2] most of the methods afforded the *trans*-isomers that required a temperature of >100 °C to perform the Cope rearrangement.[3] Thus, a direct route to synthesize *cis*-isomers stereoselectively is desirable in order to construct cycloheptane rings easily. During our studies on bis(iodozincio)methane (**1**),[4] we found that the nucleophilic cyclopropanation of 1,2-diketones afforded *cis*-cyclopropane-1,2-diols stereoselectively.[5] The mechanism of the reaction was elucidated by a computational method; the *cis*-selectivity was attributed to the face–to–face coordination of **1** with the diketones.[6] We envisioned that the reaction of 1,6-dialkylhexa-1,5-diene-3,4-diones **2** with **1** would afford the Zn alkoxides of *cis*-divinylcyclopropane-1,2-diols **4**, via the face-to-face coordination **3**, thus facilitating the oxy-Cope rearrangement of **4** to **5**, with the additional acceleration by the alkoxide groups (Scheme 1).[7]



Scheme 1. Synthesis of Cycloheptane Ring **5** by Nucleophilic Cyclopropanation of 1,2-Diketone **2**

Results and Discussion

1. As one-pot reaction

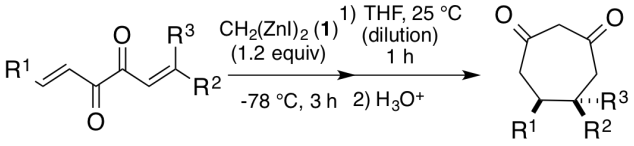
The reaction of (*1E,5E*)-1,6-diphenylhexa-1,5-diene-3,4-dione (R^1, R^2 = Ph, R^3 = H, **2a**) with dizinc **1** at –20 °C, however, afforded a complex mixture, even though it contained a small amount of the desired cycloheptane-1,3-dione **6a** after the hydrolysis. The main byproduct was the adduct of an enolate **5a** with the substrate **2a**. This result indicates that the first reaction, i.e., the cyclopropanation of **2a** with **1** should be completed before the start of Cope rearrangement to prevent the side reactions of the rearranged product **5** with substrate **2**. For this purpose, we reacted diketone **2** with **1** at the lower temperatures, which do not allow Cope-rearrangement, for an appropriate period, until the complete conversion of **2**; the resulting mixture was warmed up to promote the subsequent Cope-rearrangement. In fact, the reaction of **2a** with **1** for 3 h at –78 °C, followed by warming up the resulting mixture to 25 °C afforded the seven-membered ring **6a** in 78% yield.[8] Moreover, instead of the simple heating

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyotodaigaku-Katsura, Nishikyo, Kyotp 615-8510, Japan Fax +81(75)3832438; E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

to 25 °C, the addition of THF (25 °C) to the reaction mixture afforded **6a** in 84% yield, because the dilution suppressed the intermolecular side reactions without affecting the rate of intramolecular rearrangement reaction. Some examples of the preparation of cycloheptane-1,3-diones are shown in Table 1. Various cycloheptane-1,3-diones substituted with two *cis*-aryl groups **6** were prepared and isolated in good yields (Table 1, entries 1–4). The presence of an electron-withdrawing group on the benzene ring resulted in a low yield (entry 5). The presence of bulky group such as 1-naphthyl also resulted in a low yield (entry 7). The presence of alkyl groups as the substituents (R^1, R^2, and R^3) did not hinder the reaction (Tabke 1, entries 8–11). These transformations were stereospecific. As shown in entries 8 and 9, the *cis*- and *trans*-isomers were obtained specifically depending on the *E,Z*-configuration of the substrate.

Table 1. Preparation of Cycloheptane-1,3-diones[a]

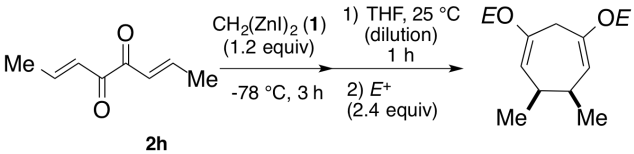


2 **6**

entry	2	R¹	R²	R³	**6** (yield %)[b,c]
1	**2a**	Ph	Ph	H	**6a** (84%)
2	**2b**	4-Me-C_6H_4	4-Me-C_6H_4	H	**6b** (93%)
3	**2c**	4-MeO-C_6H_4	4-MeO-C_6H_4	H	**6c** (98%)
4	**2d**	4- *t*-Bu -C_6H_4	4- *t*-Bu -C_6H_4	H	**6d** (96%)
5	**2e**	4-F-C_6H_4	4-F-C_6H_4	H	**6e** (47%)
6	**2f**	2-Furyl	2-Furyl	H	**6f** (78%)
7	**2g**	1-Naphthyl	1-Naphthyl	H	**6g** (41%)
8	**2h**	Me	Me	H	**6h** (99%)
9	**2i**	Me	H	Me	**6i** (65%)
10	**2j**	Me	Ph	H	**6j** (88 %)
11	**2k**	Me	Me	Me	**6k** (86%)

[a]The reaction was performed with the following scale: **1** (1.2 mmol, 0.35 M THF solution), **2** (1.0 mmol, 0.35 M in THF). After 3 h at –78 °C, 10 mL of THF (25 °C) was added in one portion. [b]Isolated yields. [c]The diastereomer was not detected.

The Zn-enolate intermediate **5** in Scheme 1 was able to be trapped with chlorotrimethylsilane (TMSCl) or acetic anhydride (Ac_2O). As shown in Scheme 2, after the treatment of **2h** with dizinc **1** at –78 °C for 3 h and at 25 °C for 1 h with additional THF, TMSCl was added. The corresponding silyl enol ether **7** was obtained in 96% isolated yield. Instead of TMSCl, the addition of Ac_2O afforded the corresponding enol acetate **8** in 82% isolated yield.



2h

E^+ = Me_3SiCl **7** (96%)
= Ac_2O **8** (82%)

Scheme 2. Trapping of Zn-enolate Intermediate from **2h** with Electrophiles

2. In a Microflow reactor

This [6+1] transformation contains two reactions, that is, the nucleophilic cyclopropanation of 1,2-diketone and the oxy-Cope rearrangement of *cis*-1,2-divinylcyclopropane-1,2-diol. As the activation energy for the first step is smaller than the second one, the first reaction can be completed before the second reaction proceeds at -78 °C. Otherwise, the formed zinc enolate **5** reacts with the diketone **2**. Therefore, careful temperature control made the entire transformation proceed reasonably to obtain the 7-membered product in good yields. In other words, two reactions were differentiated by the reaction temperature.

Instead of the temperature control, it is possible to differentiate the two reactions with space. The microflow system (space integration)[9] may improve the problem arising from a preemptive start of the second reaction, because it can supply a minimum amount of the substrate to be consumed at the micromixer spontaneously.[10] Thus, as shown in Figure 1, we constructed a microflow system consisting of two T-shaped SUS micromixers (**M1** and **M2**, Φ = 0.5 mm) and SUS microtube reactors (**R1**, Φ = 1.0 mm).[11] A THF solution of **1** (0.16 M, 3.92 mL/min) and a THF or CH_2Cl_2 solution of 1,2-diketone (0.09 M, 3.92 mL/min) were introduced by a syringe pump; after passage through a reactor **R1**, the enolate **5** and the excess amount of **1** were quenched with methanol in **M2**. The residence time was optimized by varying the length of the microtube reactor (See, the Supporting Information). In the flow system, that of 6 seconds (1-m length, Φ = 1.0 mm, SUS microtube reactor (**R1**)) afforded the products in good yields continuously. In this case, the residence time of the reaction mixture of **1** and **2** in **R1** was 6 s. The period was calculated from the flow late (3.92 × 2 mL/min) and the inner volume of **R1**. The results are summarized in Table 2.

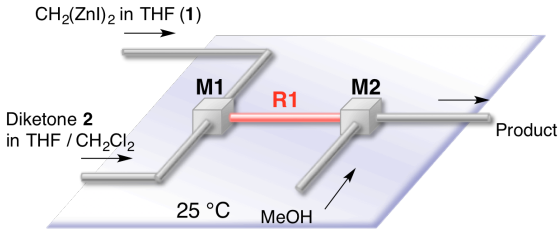


Figure 1. Microflow system for the preparation of cycloheptane-1,3-dione

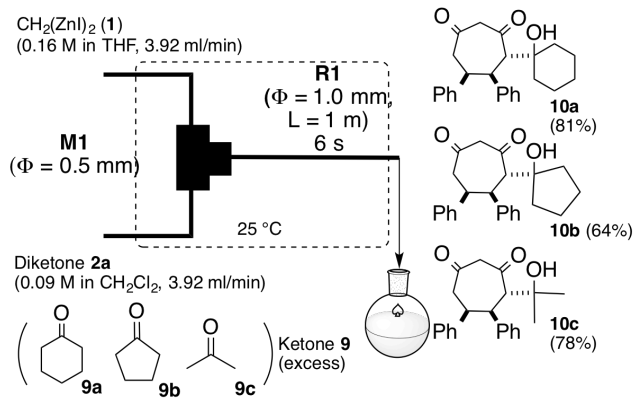
Table 2. Preparation of Cycloheptane-1,3-diones Using a Microflow System[a]

entry	2	R¹	R²	R³	**6** (yield %)[b,c]
1	**2a**	Ph	Ph	H	**6a** (>99%)
2	**2b**	4-Me-C_6H_4	4-Me-C_6H_4	H	**6b** (>99%)
3	**2c**	4-MeO-C_6H_4	4-MeO-C_6H_4	H	**6c** (92%)
4	**2d**	4-*t*-Bu-C_6H_4	4-*t*-Bu-C_6H_4	H	**6d** (81%)
5[b]	**2e**	4-F-C_6H_4	4-F-C_6H_4	H	**6e** (82%)
6[b]	**2f**	2-Furyl	2-Furyl	H	**6f** (77%)
7	**2h**	Me	Me	H	**6h** (70%)

[a]The reaction was performed using the microflow system shown in Figure 2: T-shaped SUS micromixer: **M1** (inner diameter: 0.5 mm) and **M2** (inner diameter: 0.5 mm), SUS microtube reactor: **R1** (ϕ = 1.0 mm, length = 1 m), a solution of **1**: 3.92 mL/min, 0.16 M; a solution of **2** in CH_2Cl_2: 3.92 mL/min, 0.09 M; methanol: 7.25 mL/min. [b]THF was used as the solvent for the solution of **2** instead of CH_2Cl_2.

As shown in Table 2, the products were obtained in reasonable yields at 25 °C for 6 s continuously. Except entries 5 and 6, dichloromethane was used as the solvent to prepare the solution of diketones **2**, because the corresponding diketones except **2e** and **2f** were not very soluble to THF. Notably, the microflow system allowed us to use dichloromethane as a cosolvent for reactions using a fairly basic dizinc reagent **1**. Moreover, dichloromethane is difficult to use as a cosolvent in a batch reaction, because the monomeric structural of dizinc **1** in THF is changed into polymethylenezinc form thorugh the Schlenk equilibrium by the addition of any other less polar solvent such as dichloromethane. The polymeric structure often loses the nucleophilicity.[12]

In the microflow system shown in Figure 1, Zn- enolate **5** and an excess amount of dizinc **1** was protonated with methanol in **M2**. Subsequently, instead of protonation, the resulting reaction mixture via **R1** was introduced to a THF solution of ketones **9a-c** as shown in Scheme 3. Although dienolate **5** was treated with an excess amount of ketone, **5** reacted with only one molar equivalent of ketone to afford the corresponding aldol adducts **10a-c** diastereoselectively.[13]



Scheme 3. Reaction of Intermediary Zinc-enolates **5a** with Ketones **9**

Conclusion

In conclusion, the reaction of bis(iodozincio)methane **1** with divinyl-1,2-diketones **2** afforded cycloheptane-1,3-diones **6** efficiently via a reactive *cis*-divinylcyclopropane derivative as the key-intermediate. Bis(iodozincio)methane was found to be a unique reagent to perform a nucleophilic cyclopropanation reaction with *vicinal* electrophiles such as 1,2-diketone, and affords reactive cyclopropanol derivatives efficiently.[14]Although classical batch reactions required a careful temperature control to suppress the side-reactions of the product with the starting substrate, the microflow system removed the reactive product from the reaction site continuously, thus improving the yield of the desired product.

Experimental Section

Nuclear magnetic resonance spectra were taken on Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane for ^{1}H NMR as an internal standard (δ = 0 ppm), $CDCl_3$ for ^{13}C NMR as an internal standard (δ = 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were obtained with a Thermo Fisher SCIENTIFIC EXACTIVE (ESI, APCI). Infrared (IR) spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Melting points were determined using a YANAKO MP-500D. TLC analyses were performed by means of Merck Kieselgel 60 F254 (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and an aqueous vanillin solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–100 μm).

Unless otherwise noted, commercially available reagents were used without purification. Tetrahydrofuran, Dehydrated stabilizer free —Super— was purchased from Kanto Chemical Co., stored under argon, and used as it is. Zinc powder was used after washing with 10% HCl according to the reported procedure.[15]

Preparation of bis(iodozincio)methane (1)

A mixture of pure zinc dust (150 mmol), diiodomethane (1.0 mmol), and $PbCl_2$ (0.005 mmol) in THF (5.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. When pyrometallurgy zinc dust was used instead of pure zinc, it was not necessary to add $PbCl_2$. Both pure zinc and pyrometallurgy zinc are commercially available. Diiodomethane (50 mmol) in THF (45 mL) was added dropwise to the mixture over 30 min at 0 °C with vigorous stirring. The mixture was then stirred for 4 h at 25 °C. After the stirring was stopped, the reaction vessel was allowed to stand undisturbed for several hours. Excess zinc was separated by sedimentation. ^{1}H NMR spectra of the obtained supernatant showed a broad singlet at –1.2 ppm at 0 °C, which corresponded to the methylene proton of **1**. The supernatant was used in further reactions as a solution of **1** in THF (0.1–0.5 M). The concentration of **1** was estimated by ^{1}H NMR analysis using 2,2,3,3-tetramethylbutane as an internal standard. Bis(iodozincio)methane in THF can be kept for at least a month in a sealed reaction vessel.

(*1E,5E*)-1,6-diphenylhexa-1,5-diene-3,4-dione (2a) (CAS RN [126201-33-0]).

Yellow solid. mp. 163.2–164.6 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.5 Hz, 2H), 7.69—7.64 (m, 4H), 7.48 (d, *J* = 16.5 Hz, 2H), 7.46—7.41 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 147.8, 134.5, 131.3, 129.04, 128.95, 119.7. IR (KBr) 1706, 1669, 1607, 1595, 1574, 1449, 1032, 1001, 988, 755, 722, 698, 688, 557, 434 cm^{-1}.

(*1E,5E*)-1,6-Bis(4-methylphenyl)hexa-1,5-diene-3,4-dione (2b) (CAS RN [263249-11-2]).

Yellow solid. mp. 182.5–185.3 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 16.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 16.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 4H), 2.40 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.9, 142.1, 131.8, 129.8, 129.0, 118.9, 21.6. IR

(KBr) 1669, 1595, 1560, 1512, 1307, 1328, 1295, 1183, 993, 806, 684, 428 cm^{-1}.

(*1E,5E*)-1,6-Bis(4-methoxyphenyl)hexa-1,5-diene-3,4-dione (2c) (CAS RN [263249-10-1]).

Orange solid. mp. 167.0–171.6 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 16.0 Hz, 2H), 7.62 (dt, *J* = 9.0, 2.5 Hz, 4H), 7.33 (d, *J* = 16.0 Hz, 2H), 6.94 (dt, *J* = 9.0, 2.5 Hz, 4H), 3.86 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 162.4, 147.5, 130.9, 127.3, 117.7, 114.5, 55.5. IR (KBr) 1680, 1671, 1593, 1568, 1509, 1421, 1282, 1253, 1175, 1030, 996, 816, 790, 552 cm^{-1}.

(*1E,5E*)-1,6-Bis(4-tert-butylphenyl)hexa-1,5-diene-3,4-dione (2d).

Yellow solid. mp. 164.8–166.2 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.0 Hz, 2H), 7.62—7.58 (m, 4H), 7.46—7.43 (m, 4H), 7.43 (d, *J* = 16.0 Hz, 2H), 1.34 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 155.2, 147.8, 131.8, 128.9, 126.1, 119.1, 35.1, 31.1. IR (KBr) 2960, 1669, 1592, 1560, 993, 822, 746, 646 cm^{-1}. HRMS Calcd for $C_{26}H_{30}O_2$: M^+ 374.2246. Found: *m/z* 374.2248.

(*1E,5E*)-1,6-Bis(4-fluorophenyl)hexa-1,5-diene-3,4-dione (2e).

Yellow solid. mp. 184.7–187.0 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 16.5 Hz, 2H), 7.68—7.64 (m, 4H), 7.43 (d, *J* = 16.5 Hz, 2H), 7.15—7.10 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 164.6 (d, *J* = 253.4 Hz), 146.4, 131.0 (d, *J* = 8.7 Hz), 130.7, 119.2, 116.3 (d, *J* = 22.1 Hz). IR (KBr) 1675, 1617, 1599, 1589, 1507, 1245, 1161, 995, 815, 695, 523, 440 cm^{-1}. HRMS Calcd for $C_{18}H_{12}F_2O_2$: M^+ 298.0805. Found: *m/z* 298.0805.

(*1E,5E*)-1,6-difurylhexa-1,5-diene-3,4-dione (2f) (CAS RN [1190209-38-1]).

Brown solid. mp. 156.3–158.9 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 15.5 Hz, 2H), 7.57 (ddd, *J* = 1.5, 0.5, 0.5 Hz, 2H), 7.31 (d, *J* = 15.5 Hz, 2H), 6.80 (ddd, *J* = 3.5, 0.5, 0.5 Hz, 2H), 6.53 (dd, *J* = 3.5, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 151.5, 146.0, 133.0, 117.6, 117.4, 113.0. IR (KBr) 1666, 1592, 1548, 1267, 999, 750, 641 cm^{-1}.

(*1E,5E*)-1,6-Di(naphthalen-1-yl)hexa-1,5-diene-3,4-dione (2g) (CAS RN [1192343-59-1]).

orange solid. mp. 184.3–185.7 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.82 (d, *J* = 16.0 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 6.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.93—7.89 (m, 2H), 7.67 (d, *J* = 16.0 Hz, 2H), 7.65—7.61 (m, 2H), 7.59—7.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) d 188.8, 144.4, 133.8, 131.85, 131.79, 131.57, 128.9, 127.3, 126.4, 125.8, 125.5, 123.2, 121.9. IR (KBr) 1669, 1594, 1585, 1569, 1347, 998, 982, 799, 770, 689, 592 cm^{-1}.

(*2E,6E*)-octa-2,6-diene-4,5-dione (2h) (CAS RN [55409-19-3]).

Yellow solid. mp. 43.6–46.0 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dq, *J* = 7.0, 19.5 Hz, 2H), 6.61 (dq, *J* = 16.0, 1.5 Hz, 2H), 1.98 (dd, *J* = 7.0, 1.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 149.5, 126.5, 19.0; IR (KBr) 1670, 1598, 1437, 1284, 1024, 993, 966, 895, 738, 684 cm^{-1}.

(*2Z,6E*)-Octa-2,6-diene-4,5-dione (2i).

Orange liquid. Rf: 0.61 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dq, *J* = 16.0, 7.0 Hz, 1H), 6.82 (dq, *J* = 11.5, 1.5 Hz, 1H), 6.77 (dq, *J* = 16.0, 2.0 Hz, 1H), 6.60 (dq, *J* = 15.5, 7.5 Hz, 1H), 2.21 (dd, *J* = 7.5, 1.5 Hz, 3H), 1.99 (dd, *J* = 7.0, 2.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 188.9, 149.4, 149.0, 125.1, 122.0, 19.0, 16.6. IR (neat) 2983, 2941, 1717, 1447. 1377, 1260, 1046, 971 cm^{-1}. HRMS Calcd for $C_8H_{10}O_2$: M^+ 138.0681. Found: *m/z* 138.0681.

(*1E,5E*)-1-Phenylhepta-1,5-diene-3,4-dione (2j).

Orange solid. mp. 68.5–71.8 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 16.0 Hz, 1H), 7.64—7.61 (m, 2H), 7.46—7.39 (m, 3H), 7.33 (d, *J* = 16.0 Hz, 1H), 7.19 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.77 (dq, *J* = 15.5, 1.5 Hz, 1H), 2.01 (dd, *J* = 6.5, 1.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.8, 189.6, 149.6, 147.7, 134.3, 131.3, 129.0, 128.9, 126.0, 120.1, 19.1. IR (KBr) 2968, 2936, 1689, 1597, 1449, 1206, 974, 698 cm^{-1}. HRMS Calcd for $C_{13}H_{12}O_2$: M^+ 200.0837. Found: *m/z* 200.0842.

(*E*)-2-methylocta-2,6-diene-4,5-dione (2k).

Orange liquid. Rf 0.71 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (dq, *J* = 16.0, 7.0 Hz, 1H), 6.78 (dq, *J* = 16.0, 1.5 Hz, 1H), 6.72 (qq, *J* = 1.5, 1.0 Hz, 1H), 2.26 (d, *J* = 1.0 Hz, 3H), 2.01 (d, *J* = 1.5 Hz, 3H), 1.98 (dd, *J* = 7.0, 1.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 189.2, 163.1, 148.6, 125.3, 118.1, 28.5, 21.6, 19.0. IR (neat) 2977, 2941, 2915, 1674, 1619, 1442, 1377, 1312, 1010, 972, 743 cm^{-1}. HRMS Calcd for $C_9H_{12}O_2$: M^+ 152.0837. Found: *m/z* 152.0836.

Preparation of (5*R*,6S)-5,6-diphenylcycloheptane-1,3-dione (6a) (CAS RN [222629-92-7]). (General procedure for one-pot synthesis of 6).**

To a solution of diketone **2a** (1.0 mmol) in THF (5.0 ml), dizinc **1** (1.2 mmol, 0.35 M in THF) was added dropwise at -78 °C under Ar. After being stirred for 3 h at -78 °C, the mixture was diluted with THF (10 ml, 25 °C). The resulting mixture was stirred at 25 °C for 1 h, and poured into sat. NH_4Cl_{aq} (10 ml). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Purification by silica gel column chromatography (hexane/ethyl acetate) gave the title compound in 84% yield (233 mg).

White solid. mp. 106.7–112.8 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18—7.10 (m, 6H), 6.74—6.69 (m, 4H), 3.95 (d, *J* = 17.5 Hz, 1H), 3.74—3.67 (m, 2H), 3.57 (d, *J* = 17.5 Hz, 1H), 3.22 (dd, *J* = 15.5, 11.0 Hz, 2H), 2.79 (dd, *J* = 15.5, 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 139.3, 128.2, 128.1, 127.1, 58.2, 46.2, 45.8. IR (KBr) 3060, 3030, 2969, 2889, 1710, 1600, 1491, 1452, 1383, 1284, 1255, 1240, 1220, 1133, 1076, 806, 755, 738, 712, 537, 462cm^{-1}.

(5*R*,6S)-5,6-Bis(4-methylphenyl)cycloheptane-1,3-dione (6b).**

Yellow solid. mp.129.2–131.3 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 8.0 Hz, 4H), 6.62 (d, *J* = 8.0 Hz, 4H), 3.95 (d, *J* = 17.0 Hz, 1H), 3.69—3.62 (m, 2H), 3.55 (d, *J* = 17.0 Hz, 1H), 3.17 (dd, *J* = 15.5, 11.0 Hz, 2H), 2.76 (dd, *J* = 15.0, 5.0 Hz, 2H), 2.27 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 136.6, 136.3, 128.8, 128.2, 58.3, 46.1, 45.8, 20.9. IR (KBr) 3024, 2954, 1715, 1513, 1248, 1196, 1019, 806, 480 cm^{-1}. HRMS Calcd for $C_{21}H_{22}O_2$: M^+ 306.1620. Found: *m/z* 306.1625.

(*5R*,6S)-5,6-Bis(4-methoxyphenyl)cycloheptane-1,3-dione (6c).**

Yellow solid. mp. 105.1–106.2 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71—6.67 (m, 4H), 6.66—6.62 (m, 4H), 3.93 (d, *J* = 17.0 Hz, 1H), 3.75 (s, 6H), 3.65—3.59 (m, 1H), 3.54 (d, *J* = 17.0 Hz, 1H), 3.14 (d, *J* = 15.0, 11.0 Hz, 2H), 2.75 (dd, *J* = 15.0, 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 158.4, 131.4, 129.2, 113.4, 58.2, 55.1, 46.1, 45.5. IR (KBr) 2958, 1697, 1611, 1511, 1250, 1178, 1028, 839, 779, 541 cm^{-1}. HRMS Calcd for $C_{21}H_{22}O_4$: M^+ 338.1518. Found: *m/z* 338.1521.

(*5R*,6S)-5,6-Bis(4-fluorophenyl)cycloheptane-1,3-dione (6d).**

White solid. mp. 165.7–169.8 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88—6.83 (m, 4H), 6.71—6.66 (m, 4H), 3.92 (d, *J* = 17.0 Hz, 1H), 3.70—3.63 (m, 2H), 3.57 (d, *J* = 17.0 Hz, 1H), 3.14 (dd, *J* = 15.0, 11.0 Hz, 2H), 2.77 (dd, *J* = 15.0, 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 161.9 (d, *J* = 246.6 Hz), 134.8, 129.7 (d, *J* = 8.2 Hz), 115.4 (d, *J* = 21.1 Hz), 58.1, 45.8, 45.5. IR (KBr) 1722, 1696, 1603, 1511, 1224, 1159, 843, 812, 789, 514cm^{-1}. HRMS Calcd for $C_{19}H_{16}F_2O_2$: M^+ 314.1118. Found: *m/z* 314.1115.

(*5R*,6S)-5,6-Di(naphthalen-1-yl)cycloheptane-1,3-dione (6e).**

White solid. mp. 67.5–69.8 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69—7.65 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.33—7.29 (m, 2H), 7.11—7.03 (m, 4H), 6.80—6.75 (m, 2H), 4.88—4.81 (m, 2H), 4.15 (d, *J* = 17.5 Hz, 1H), 3.73 (d, *J* = 17.5 Hz, 1H), 3.52 (dd, *J* = 15.5, 11.5 Hz, 2H), 2.89 (dd, *J* = 15.5, 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 135.0, 133.5, 131.9, 128.7, 127.6, 125.9, 125.3, 124.51, 124.45, 121.9, 58.5, 46.3, 38.2. IR (KBr) 3050, 2926, 2364, 2343, 1696, 1598, 1507, 1396, 1259, 778 cm^{-1}. HRMS Calcd for $C_{27}H_{22}O_2$: M^+ 378.1620. Found: *m/z* 378.1621.

(*5R*,6S)-5,6-Di(furan-2-yl)cycloheptane-1,3-dione (6f).**

Yellow solid. mp. 85.5–87.6 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 2.0, 1.0 Hz, 2H), 6.23 (dd, *J* = 3.0, 2.0 Hz, 2H), 5.84 (ddd, *J* = 3.0, 1.0, 1.0 Hz, 2H), 3.93—3.88 (m, 2H), 3.89 (d, *J* = 15.0 Hz, 1H), 3.72 (d, *J* = 15.0 Hz, 1H), 3.05 (dd, *J* = 15.0, 9.5 Hz, 2H), 2.91 (dd, *J* = 15.0, 4.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 153.4, 141.9, 110.2, 106.9, 59.9, 45.5, 38.9. IR (KBr) 3150, 3119, 1719, 1503, 1206, 1006, 942, 748 cm^{-1}. HRMS Calcd for $C_{15}H_{14}O_4$: M^+ 258.0892. Found: *m/z* 258.0891.

(*5R*,6S)-5,6-Bis(4-tert-butylphenyl)cycloheptane-1,3-dione (6g).**

White solid. mp. 125.1–126.8 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13—7.09 (m, 4H), 6.64—6.60 (m, 4H), 3.95 (d, *J* = 17.0 Hz, 1H), 3.69—3.63 (m, 2H), 3.56 (d, *J* = 17.0 Hz, 1H), 3.19 (dd, *J* = 15.0, 11.0 Hz, 2H), 2.78 (dd, *J* = 15.0, 4.5 Hz, 2H), 1.25 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 150.0, 136.4, 127.8, 124.8, 58.4, 45.9, 45.7, 34.3, 31.3. IR (KBr) 2961, 2360, 1730, 1700, 1509, 853 cm^{-1}. HRMS Calcd for $C_{27}H_{34}O_2$: M^+ 390.2559. Found: *m/z* 390.2552.

(*5R*,6S)-5,6-Dimethylcycloheptane-1,3-dione (6h)**

Colorless liquid. Rf 0.33 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (d, *J* = 15.5 Hz, 1H), 3.35 (d, *J* = 15.5 Hz, 1H), 2.51 (dd, *J* = 14.0, 4.5 Hz, 2H), 2.47 (dd, *J* = 14.0, 8.5 Hz, 2H), 2.33—2.24 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 59.7, 48.7, 34.9, 16.5. IR (neat) 2964, 2364, 1701, 1254, 1199, 1099 cm^{-1}. HRMS Calcd for $C_9H_{14}O_2$: M^+ 154.0994. Found: *m/z* 154.0998.

(*5S*,6S)-5,6-Dimethylcycloheptane-1,3-dione (6i).**

Colorless liquid. Rf 0.29 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.43 (s, 2H), 2.59 (dd, *J* = 14.0, 3.0 Hz, 2H), 2.44 (dd, *J* = 14.0, 8.5 Hz, 2H), 1.87—1.77 (m, 2H), 1.09 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 59.1, 50.0, 38.0, 20.7. IR (neat) 2963, 2360, 1698, 1611, 1459, 1388, 1252 cm^{-1}. HRMS Calcd for $C_9H_{14}O_2$: M^+ 154.0994. Found: *m/z* 154.0990.

(*5S*,6R)-5-Methyl-6-phenylcycloheptane-1,3-dione (6j).**

colorless liquid. Rf 0.28 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35—7.31 (m, 2H), 7.28—7.23 (m, 1H), 7.15—7.11 (m, 2H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.51 (ddd, *J* = 12.5, 4.0, 4.0 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 12.5 Hz, 1H), 2.75 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.72 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.56 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.52—2.44 (m, 1H), 0.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 204.3, 141.6, 128.6, 127.6, 127.0, 59.0, 49.9, 45.9, 45.9, 44.3, 35.5. IR (neat) 2963, 2360, 1716, 1695, 1452, 1387, 1257, 1202, 1149, 744, 703 cm^{-1}. HRMS Calcd for $C_{14}H_{16}O_2$: M^+ 216.1150. Found: *m/z* 216.1145.

5,5,6-Trimethylcycloheptane-1,3-dione (6k).

Colorless liquid. Rf 0.36 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (d, *J* = 17.5 Hz, 1H), 3.33 (d, *J* = 17.5 Hz, 1H), 2.60 (dd, *J* = 16.0, 11.5 Hz, 1H), 2.51 (d, *J* = 12.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.32 (d, *J* = 12.0 Hz, 1H), 2.03 (ddq, *J* = 11.5, 7.0, 3.0 Hz, 1H), 1.09 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 204.3, 58.5, 56.3, 47.7, 39.7, 37.3, 28.5, 22.3, 16.5. IR (neat) 2966, 2362, 1695, 1469, 1395, 1304, 1267, 1196, 1135 cm^{-1}. HRMS Calcd for $C_{10}H_{16}O_2$: M^+ 168.1150. Found: *m/z* 168.1147.

Preparation of ((*5R*,6S)-5,6-dimethylcyclohepta-3,7-diene-1,3-diyl)bis(oxy)bis(trimethylsilane) (7).**

To a solution of diketone **2a** (1.0 mmol) in THF (1.0 ml), dizinc **1** (1.2 mmol, 0.35 M in THF) was added dropwise at -78 °C under Ar. After being stirred for 3 h at -78 °C, the mixture was diluted with THF (10 ml, room temperature). The resulting mixture was stirred at 25 °C for 1 h. To the resulting mixture, chlorortrimethylsilane (2.4 mmol) was added at 0 °C. The resulting mixture was stirred for 1 h at 25 °C, and poured into sat. NH_4Claq (10 ml). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Purification by silica gel column chromatography (hexane/ethyl acetate) gave the title compound in 96% yield. Instead of treatment of the reaction mixture with chlorotrimethylsilane, an addition of acetic anhydride gave **8**.

Colorless liquid. Rf 0.56 (Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 6.0, 2.0 Hz, 2H), 3.28 (dtt, *J* = 19.5, 2.0,2.0 Hz, 1H), 2.44 (d, *J* = 19.5 Hz, 1H), 2.42—2.35 (m, 2H), 0.948 (d, *J* = 7.0 Hz, 6H), 0.18 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 113.7, 40.6, 34.6, 17.5, 0.2. IR (neat) 2961, 2874, 1669, 1253, 1198, 1173, 1147, 962, 846, 752 cm^{-1}. HRMS Calcd for $C_{15}H_{30}O_2Si_2$: M^+

298.1784. Found: *m/z* 298.1782.

(*5R*,6S)-5,6-dimethylcyclohepta-3,7-diene-1,3-diyl diacetate (8)**

Colorless liquid. Rf 0.53 (Hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (dd, *J* = 6.5, 2.0 Hz, 2H), 3.74 (dtt, *J* = 19.5, 2.0, 2.0 Hz, 1H), 2.65—2.55 (m, 2H), 2.55 (d, *J* = 19.5 Hz, 1H), 2.01 (s, 6H), 1.04 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 143.7, 123.0, 35.1, 34.2, 20.9, 16.7. IR (neat) 2967, 2876, 1755, 1693, 1370, 1225, 1134, 1092, 1061, 1020, 900 cm^{-1}. HRMS Calcd for $C_{13}H_{18}O_4$: M^+ 238.1205. Found: *m/z* 238.1215.

Reaction in a microreactor.

Stainless steel (SUS304) T-shaped micromixer with inner diameter of 0.5 mm was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactor with inner diameter of 1.0 mm was purchased from GL Sciences and was cut unto appropriate length (**R1** = 1 m). The micromixers and microtubes reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. The flow microreactor was dipped in the bath to control the temperature. Solutions were continuously introduced to the flow microreactor using syringe pumps, Harvard Model 11. After a steady state was reached, the product solution was collected for 90 sec. When the collection time was longer, the product solution can be obtained in a preparative scale. As shown in Figure 1, a flow microreactor consisting two T-shaped micromixers (**M1** and **M2**, Φ = 0.5 mm) and one microtube reactor (**R1**, Φ = 1.0 mm) was used. To **M1**, bis(iodozincio)methane (**1**, 0.16 M solution in THF) was introduced by a syringe pump with a rate of 3.92 mL/min. The syringe pump and **M1** was connecter with a Teflon tube (Φ = 1.0 mm). To **M1**, a solution of **2** (0.09 M solution in dichloromethane for **2a**,**b,c,d,h** and in THF for **2e,f**) was introduced by a syringe pump with a rate of 3.92 mL/min. The syringe pump and **M1** was also connecter with a Teflon tube (Φ = 1.0 mm). The mixture was passed through **R1** (Φ = 1.0 mm) and was mixed with methanol (7.84 mL/min) in **M2**. The resulting mixture was poured into 1M HClaq. The product was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Purification by silica gel column chromatography (hexane/ethyl acetate) gave the cycloheptane derivatives **6**.

Instead of quenching, the product flow from **R1** was poured into a solution of a ketone (3.0 mmol) in THF 10 mL at 25 °C. The addition from **R1** was continued for 3 min (The amount of the substrate was 1.06 mmol (0.09 M x 3.92 mL/min x 3 min)). After the addition, the resulting mixture was stirred for 30 min, and poured into sat. NH_4Claq (10 ml). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Purification by silica gel column chromatography (hexane/ethyl acetate) gave the adduct **10**.

Preparation of (*5S*,6S)-4-(1–hydroxycyclohexyl)-5,6-diphenylcycloheptane-1,3-dione (10a)**.

Yellow solid. mp. 175.2–175.8 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.11–7.19 (m, 6H), 6.70 (d, *J* = 6.5 Hz, 2H), 6.64–6.65 (m, 2H), 3.81 (m, 4H), 3.60 (d, *J* = 17.5 Hz, 1H), 3.37 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.11 (dd, *J* = 17.5, 15.0 Hz, 1H), 2.61 (dd, *J* = 17.5, 4.0 Hz 1H), 1.63–1.72 (m, 2H) 1.24–1.46 (m, 4H), 1.15 (d, *J* = 16 Hz, 1H), 0.98–1.07 (m, 2H) 0.47 (t, 11.5 Hz 1H). ^{13}C NMR ($CDCl_3$) δ 211.3, 205.3, 140.6, 137.7, 129.5, 128.0, 127.9, 127.8, 127.0, 126.8, 77.2, 73.8, 60.9, 49.3, 43.8, 43.8, 37.5, 35.9, 25.4, 21.8, 21.1. IR (KBr) 3510.6, 2960.9, 2938.7, 2852.8, 1692.6, 1495.9, 1457.3, 1398.5, 1380.1, 1359.9, 1282.7, 1175.7, 1156.4, 1139.0, 1076.3, 982.8, 845.8, 765.8, 708.9. cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{28}O_3Cl$: $[M+Cl]^-$, 411.1721. Found: *m/z* 411.1736.

(*5S*,6S)-4-(1–hydroxycyclopentyl)-5,6-diphenylcycloheptane-1,3-dione (10b).**

Yellow solid. mp. 185.0–185.5 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.10–7.16 (m, 6H), 6.73 (d, *J* = 6.5 Hz, 2H), 6.66–6.64 (m, 2H), 3.89 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.77–3.84 (m, 2H), 3.59 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.46 (d, *J* = 2.5 Hz, 1H), 3.28 (dd, *J* = 9.0, 2.0 Hz, 1H) 3.21 (ddd, *J* = 17.5, 15.5, 1.0 Hz, 1H), 2.64 (ddd, *J* = 17.5, 4.0, 1.0 Hz, 1H), 1.84–1.89 (m, 1H) 1.71–1.78 (m, 1H) 1.24–1.59 (m, 4H) 0.93–0.97 (m, 1H) 0.41–0.47 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 210.5, 205.6, 140.6, 137.6, 129.6, 128.0, 127.9, 127.8, 127.0, 127.0, 82.7, 77.2, 61.7, 59.5, 50.4, 43.9, 41.0, 38.3, 23.4, 22.3 . IR (KBr) 3525.1, 2974.4, 2924.2, 2869.2, 1714.8, 1693.6, 1493.9, 1456.3, 1382.1, 1266.3, 1456.3, 1382.1, 1266.3, 1232.6, 1139.0, 1096.6, 1003.0, 767.7, 708.9. cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{26}O_3Cl$: $[M+Cl]^-$, 397.1565. Found: *m/z* 397.1579.

(*5S*,6S)-4–(2–hydroxypropan-2-yl)-5,6-diphenylcycloheptane-1,3-dione (10c).**

Yellow solid. mp. 111.2–112.0 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.11–7.18 (m, 6H), 6.67 (d, *J* = 7.0 Hz, 2H), 6.65–6.63 (m, 2H), 3.86–3.80 (m, 3H), 3.75 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.61 (dd, *J* = 18.0, 1.0Hz, 1H), 3.35 (dd, *J* =9.0, 2.0 Hz, 1H), 3.14 (ddd, *J* =18.0, 14.0, 1.0 Hz, 1H), 2.62 (ddd, *J* = 18.0, 3.5, 1.0 Hz, 1H) 1.20 (s, 3H) 0.64 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 210.9, 205.3, 140.5, 137.7, 129.4, 128.0, 128.0, 127.9, 127.1, 126.9, 72.4, 61.2, 60.4, 50.2, 43.9, 43.8, 30.2, 28.5 . IR (KBr) 3500.6, 2974.4, 1721.5, 1689.7, 1495.9, 1455.4, 1392.7, 1380.1, 1362.8, 1235.5, 1197.9, 1158.3, 1136.1, 1095.6, 1078.3, 958.7, 767.7, 704.1. cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{24}O_3Cl$: $[M+Cl]^-$, 371.1408. Found: *m/z* 371.1422.

Notes and references

1. H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203; D. A. Foley and A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131; G. A. Molander, *Acc. Chem. Res.* **1998**, *31*, 603; Y. Ni and J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 11162.
2. H. Lebel, J. F. Marcoux, C. Molinaro, and A. B. Charette, *Chem. Rev.* **2003**, *103*, 977; K. Takeda, M. Takeda, A. Nakajima, and E. Yoshii, *J. Am. Chem. Soc.* **1995**, *117*, 6400; V. Vuligonda, M. E. Garst, and R. A. S. Chandraratna, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 589; N. J. Wallock and W. A. Donaldson, *Org. Lett*. **2005**, *7*, 2047; S. Pantke-Böcker, G. Pohnert, I. Fischer-Lui, W. Boland, and A. F. Peters, *Tetrahedron*, **1991**, *51*, 7927; J. P. Olson and H. M. L. Davies, *Org. Lett.* **2008**, *10*, 573.
3. P. A. Wender and M. P. Filosa, *J. Org. Chem.* **1976**, *41*, 3490; H. M. L. Davies, T. J. Clark, and H. D. Smith, *J. Org. Chem.* **1991**, *56*, 3817; H. M. Davies and D. B. Doan, *J. Org. Chem.* **1999**, *64*, 8501; J. E. Baldwin and K. E. Gilbert, *J. Am. Chem. Soc.* **1976**, *98*, 8283.

4. M. Sada, S. Komagawa, M. Uchiyama, M. Kobata, T. Mizuno, K. Utimoto, K. Oshima, and S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 17452; M. Sada and S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 432; R. Haraguchi and S. Matsubara, *Org. Lett.* **2013**, *15*, 3378.
5. K. Ukai, K. Oshima, and S. Matsubara, *J. Am. Chem. Soc.* **2000**, *122*, 12047; K. Nomura, K. Asano, T. Kurahashi, and S. Matsubara, *Heterocycles* **2008**, *76*, 1381.
6. S. Matsubara, K. Ukai, H. Fushimi, Y. Yokota, H. Yoshino, K. Oshima, K. Omoto, A. Ogawa, Y. Hioki, and H. Fujimoto, *Tetrahedron* **2002**, *58*, 8255.
7. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765.
8. Y. Takada, K. Nomura, and S. Matsubara, *Org. Lett.* **2010**, *12*, 5204.
9. S. Suga, D. Yamada, and J. Yoshida, *Chem. Lett.* **2010**, *39*, 404; J. Yoshida, K. Saito, T. Nokami, and A. Nagaki, *Synlett* **2011**, 1189.
10. R. Haraguchi, Y. Takada, and S. Matsubara, *Chem. Lett.* **2012**, *41*, 628.
11. H. Wakami and J. Yoshida, J. *Org. Proc. Res. Dev.* **2005**, *9*, 787.
12. S. Matsubara, H. Yoshino, Y. Yamamoto, K. Oshima, H. Matsuoka, K. Matsumoto, K. Ishikawa, and E. Matsubara, *J. Organomet. Chem.* **2005**, *690*, 5546.
13. The structure of **10a** was determined by a single crystal X-ray analysis (see ref 10). The structure of the other products **10b**,**c** was determined by analogy of the structure of **10a**.
14. K. Nomura and S. Matsubara, *Chem.—Eur. J.* **2010**, *16*, 703; K. Nomura and S. Matsubara, *Chem.—Asian. J.* **2010**, *5*, 147.