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PAPER

A tandem reaction of organozinc reagent prepared from palladium-catalyzed umpolung method: diastereoselective formation of cyclohexene derivatives bearing three adjacent stereocenters†

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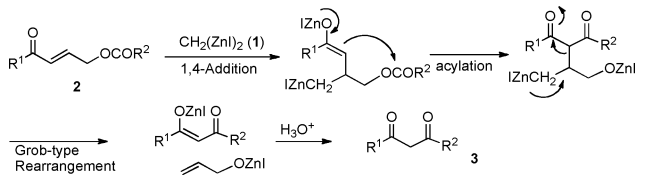
In the presence of a palladium catalyst, treatment of γ-acyloxy-α,β-unsaturated ketone with bis(iodozincio)methane caused umpolung of π-allylpalladium to give a zinc dienolate. Thus formed zinc species afforded a cyclohexene derivative *via* a self-condesation reaction. It is noteworthy that the three adjacent stereogenic centers were created in a single process with quite high diastereoselectivity.

Introduction

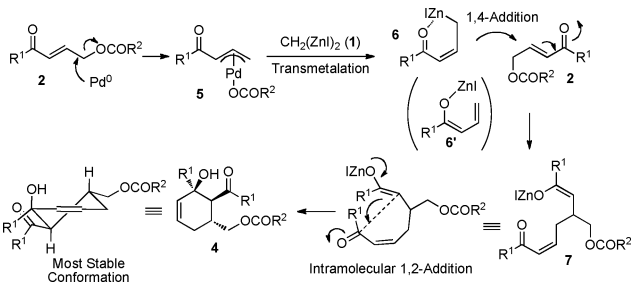
A tandem reaction is one of the most efficient reactions in organic syntheses.[1] It enables one to construct plural bonds and stereocenters in a single process, and therefore it is often applied to the formation of structurally complex compounds. However, there still has been a significant challenge to succeed in a stereoselective construction of multiple stereocenters, in particular, adjacent stereocenters containing a highly substituted carbon atom such as a tertiary alcohol, which are often found as key units in complex natural products.[2]

In the course of our study on bis(iodozincio)methane (**1**),[3] we recently reported a novel tandem reaction using the *gem*-dizinc **1** as a nucleophile to γ-acyloxy-α,β-unsaturated ketone **2**[4] to afford a 1,3-diketone **3** efficiently *via* three sequential steps (Scheme 1).[5] In this reaction, the acyloxy group in the substrate was used as an electrophilic moiety for the intramolecular tandem reaction.



Scheme 1 Tandem reactions of γ-acyloxyenone **2** with dizinc **1**.

As another possibility of bis(iodozincio)methane (**1**), the dizinc **1** could be an efficient reagent for umpolung of π-allylpalladium species.[6] When this umpolung method is applied to γ-acyloxy-α,β-unsaturated ketone **2**, an allylic zinc reagent bearing a ketone group would be prepared and it would perform another type of tandem reaction. In fact, in the presence of a palladium catalyst, the reaction product dramatically changed, and a cyclohexene derivative **4** was obtained *via* a self-condensation reaction[7] with high diastereoselectivity (Scheme 2). This reaction would be an efficient method to create adjacent multiple stereocenters in a single operation.[8] While umpolung of a simple allylic acetate with palladium catalyst and diethylzinc was developed and shown to be useful for C–C bond–forming reactions by Tamaru, umpolung of γ-acylallylic acetate has not been shown.



Scheme 2 Umpolung of γ-acyloxyenone **2** with dizinc **1**.

The active species **6**, an allylic zinc reagent bearing a ketone group, would be in equilibrium with a zinc dienolate **6′**.[9] Although an enone has been frequently used as Michael accepter, its alternative use as dienol has not attracted much attention except for the vinylogous aldol reaction.[10] Especially, it has been a challenging subject to perform a reaction of the dienolate with unsaturated ketones, since there are many possible adducts and in most reported cases cyclized products were obtained only as by-products.[11] Encouraged by this fact, we decided to examine this reaction in detail.

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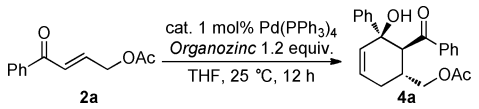
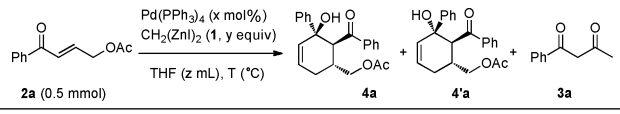
Table 1 Screening of organozinc reagents in the palladium-catalyzed cyclization reaction[a]



Entry	*Organozinc*	Product[b]		Recovery[b]
1	$CH_2(ZnI)_2$	**4a**	67%	—
2	MeZnI		—	82%
3	Me_2Zn	**4a**	8.9%	89%
4	Et_2Zn	**4a**	34%	—
5	Me_3ZnLi	Complex mixture		—
6	$^tBu_3ZnLi$	Complex mixture		—
7	$^tBu_4ZnLi_2$	Complex mixture		—

[a] To a solution of **2a** (1.0 equiv) and $Pd(PPh_3)_4$ (1 mol%) in THF (2 mL), organozinc reagent (1.2 equiv) was added dropwise at 25 °C, and whole was stirred for 12 h. [b] The yields were determined by ^1H NMR using bromoform as an internal standard.

Table 2 Optimization of the reaction conditions[a]



Entry	x (mol%)	y (equiv.)	z (mL)	*T*/°C	**4a** (%)[b]	**4′a** (%)[b]	**3a** (%)[b]
1	1	1.2	2	25	67	4.4	11
2	1	1.2	10	25	68	4.0	21
3	1	1.2	2	0	60	2.7	6.6
4	10	1.2	2	25	52	2.2	—
5	5	1.2	5	25	72	3.7	1.8
6	3	1.2	5	25	77	4.8	7.7
7	**3**	**1.0**	**5**	**25**	**77**	**5.5**	**5.5**
8	3	1.0	5	0	61	4.4	1.6

[a] To a solution of **2a** (1.0 equiv.) and $Pd(PPh_3)_4$ in THF, **1** was added dropwise, and whole was stirred for 1–12 h. [b] The yields were determined by ^1H NMR using bromoform as an internal standard.

Results and discussion

Treatment of γ-acylallylic acetate with various organozinc ragents in the presence of palladium catalyst was examined as shown in Table 1. A reaction of (*E*)-4-acetoxy-1-phenyl-2-buten-1-one (**2a**, 0.5 mmol) with **1** (0.6 mmol, 0.5 M in THF) in the presence of $Pd(PPh_3)_4$ (1 mol%) in THF at 25 °C for 12 h gave a cyclic product **4a** in 67% yield (entry 1, Table 1). Methylzinc iodide and dimethylzinc did not afford the product **4a** efficiently; most of the starting material was recovered (entries 2, 3). In comparison, diethylzinc gave **4a**, but in a lower yield than in the case of using **1**, with a lot of by-products (entry 4). Using ate complexes, the reactions resulted in complex mixtures, probably because of the higher nucleophilicity (Entries 5–7).[12] From these results, the *gem*-dizinc **1** was shown to be a specific reagent for this reaction.

To optimize the reaction conditions, we examined the reaction using dizinc **1** with various conditions. The results are listed in Table 2. A smaller amount of palladium catalyst lead to a more formation of 1,3-diketone **3a** (entry 1), because by-product **3a** was formed *via* a tandem reaction initiated by a direct nucleophilic attack of **1** to **2a** without Pd catalyst as shown in Scheme 1. Lowering the reaction temperature to 0 °C evidently prevented the formation of **3a**, but the yield of **4a** was still unsatisfying (entries 3, 8). Increasing the catalyst loading to 3 mol% gave the improved yield of **4a** (entries 4–7), and we set the condition of entry 7 as the optimal. It is notable that the only two diastereomers were generated in this reaction even though the cyclic product **4a** contained three stereogenic centers, and its diastereoselectivity was quite high (**4a**:**4′a** = 14 : 1, entry 7).

The structure of ((*1R**,5*R**,6*S**)-6-benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)methyl acetate (**4a**) was determined by X-ray crystallographic analysis (Fig. 1). The structure of the obtained diastereomer, ((*1R**,5*S**,6*S**)-6-benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)methyl acetate (**4′a**), was estimated by ^1H NMR analysis. Both coupling constants between the protons on C5 and C6 in **4a** and **4′a** were 12 Hz, those are typical for diaxial protons.

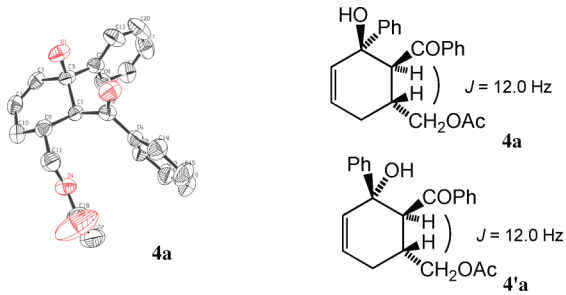
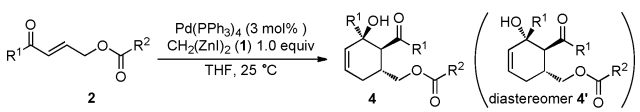


Fig. 1 ORTEP of **4a** (Triclinic, a = 6.0102(6), b = 10.0194(9), c = 15.9053(15) Å, β = 83.245(2)°, V = 914.94(15) Å^3, Z = 2, ρ_c = 1.272 Mg m^{-3}, λ(Mo$_{K\alpha}$) = 0.71073 Å, T = 296 K, θ_{max} = 27.0°,, R = 0.0150 for 3892 reflections ($I > 2\delta(I)$).

Under the optimal conditions, we treated various γ-acyloxy-α,β-unsaturated ketones **2** with the dizinc **1**, and the results are listed in Table 3. This reaction proceeded efficiently in every case, and afforded the corresponding cyclohexene derivative **4** with high diastereoselectivity. The excellent selectivity was observed especially in the case that R^1 was 2-naphthyl or *p*-bromophenyl group (entries 2, 5). Not only acetate but also benzoate or

Table 3 Diastereoselective formation of a cyclohexene derivative **4** *via* the tandem reaction[a]



Entry	R^1	R^2		**4** + **4′** (%)[b]		dr
1	Ph	Me	**2a**	83	**4a**	14/1
2	2-Naphthyl	Me	**2b**	74	**4b**	33/1
3	*p*-Tolyl	Me	**2c**	72	**4c**	9.0/1
4	*p*-$MeOC_6H_4$	Me	**2d**	67	**4d**	3.5/1
5	*p*-BrC_6H_4	Me	**2e**	82	**4e**	33/1
6	$PhCH_2CH_2$	Me	**2f**	72	**4f**	2.1/1
7	Ph	^{i}Pr	**2g**	78	**4g**	16/1
8	Ph	Ph	**2h**	81	**4h**	14/1

[a] To a solution of **2** (1.0 equiv) and $Pd(PPh_3)_4$ (3 mol%) in THF (5 mL), bis(iodozincio)methane (**1**, 1.0 equiv) was added dropwise at 25 °C, and whole was stirred for 1.5–6 h. [b] The yields were determined by ^1H NMR analyses. All of the products were isolated by silica gel column chromatography for the identification.

isopropanoate was applicable to this reaction to afford the product **4** with high selectivity (entries 7, 8). As this reaction should proceed under a relatively mild condition, it could tolerate many functional groups such as esters and tertiary alcohols in the products.

The plausible reaction pathway was shown in Scheme 2. Oxidative addition of γ-acyloxy-α,β-unsaturated ketone **2** to palladium(0) forms the π-allylpalladium species **5**. Transmetalation between **5** and bis(iodozincio)methane (**1**)[6b] gives the active zinc species **6** or **6′**, which attacks the enone **2** in a 1,4-manner to afford a zinc enolate **7** bearing an electrophilic site. Then the formed enolate attacks the enone unit intramolecularly in a 1,2-manner in turn, and gives the cyclohexene derivative **4**. This major product **4** has the most stable conformation, in which all large substituents occupy equatorial positions. The cyclization to **4** shoud be reversible. In order to achieve this reaction efficiently, an organozinc reagent should perform a transmetalation prior to its direct nucleophilic attack to the substrate. The dianionic character of *gem*-dizinc **1** would promote the umpolung step; thus, the dizinc **1** was the most suitable reagent for this reaction which has ideal reactivity.

Experimental section

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 is not necessary to add $PbCl_2$. Both of pure zinc and pyrometallurgy zinc are commercially available. To the mixture, diiodomethane (50 mmol) in THF (45 mL) was added dropwise over 30 min at 0 °C with vigorous stirring. The mixture was 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 for the further reaction as a solution of **1** in THF (0.4–0.5 M). Bis(iodozincio)methane in THF can be kept unchanged at least for a month in a sealed reaction vessel.

Preparation of (*E*)-4-oxo-4-phenylbut-2-enyl acetate (2a)

The substrate **2a** is easily obtained by an acetylation of the corresponding γ-hydroxy-α,β-unsaturated ketone, (*E*)-4-hydroxy-1-phenylbut-2-en-1-one, which is obtained in 4 steps from benzaldehyde in 49% overall yield by our reported procedure.[1]

To a solution of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (10 mmol) in dichloromethane (10 mL), pyridine (24 mmol), acetic anhydride (12 mmol), and N,N-dimethyl-4-aminopyridine (0.5 mmol) were added subsequently and stirred for 12 h at 25 °C. A saturated aqueous solution of ammonium chloride was added to the reaction mixture, and then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. After a purification by a flash silica gel column chromatography (hexane–ethyl acetate = 5 : 1), the pure acetate **2a** was isolated in 96% yield.

General procedure for preparation of cyclohexene derivatives 4

The reaction was performed in a 20 mL round-bottomed flask filled with argon gas. Bis(iodozincio)methane (**1**, 0.5 mmol, 0.5 M in THF) was added to the solution of γ-acyloxy-α,β-unsaturated ketone (**2**, 0.5 mmol) in THF (5.0 mL) in the presence of 3 mol% of $Pd(PPh_3)_4$. Then the mixture was stirred at 25 °C for 1.5–6 h. After an addition of saturated aqueous ammonium chloride solution, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by a flash silica gel column chromatography gave the pure corresponding cyclohexene derivative **4**.

((1*R,5*R**,6*S**)-6-Benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)-methyl acetate (4a).** Yield: 77%, white solid. TLC: R_f 0.21 (hexane–ethyl acetate = 3 : 1). Mp. 135.5–136.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2H), 7.43–7.39 (m, 1H), 7.34–7.31 (m, 2H), 7.26–7.21 (m, 2H), 7.20–7.14 (m, 2H), 7.09–7.04 (m, 1H), 6.07 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H), 5.88 (ddd, J = 10.0, 2.0, 2.0 Hz, 1H), 5.17 (s, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.89 (d, J = 4.5 Hz, 2H), 3.00–2.90 (m, 1H), 2.43 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.26 (dddd, J = 18.5, 11.0, 2.0, 2.0 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 170.4, 145.9, 138.0, 133.4, 132.5, 128.3, 128.3, 128.1, 127.9, 127.0, 125.2, 73.6, 65.9, 53.3, 34.0, 29.0, 20.4. IR (KBr): 3447, 1742, 1653, 1447, 1362, 1248, 1227, 1049, 698 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 350.1518. Found: m/z 350.1517.

((1*R,5*S**,6*S**)-6-Benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)-methyl acetate (4′a).** Yield: 5.5%, colorless oil. TLC: R_f 0.32 (hexane–ethyl acetate = 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–7.96 (m, 2H), 7.61–7.55 (m, 1H), 7.50–7.43 (m, 3H), 7.40–7.33 (m, 4H), 6.01 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.79 (ddd, J = 10.0, 2.0, 2.0 Hz, 1H), 4.61 (bs, 1H), 4.27 (d, J = 5.5 Hz, 2H), 3.15 (d, J = 12.0 Hz, 1H), 3.0–2.9 (m, 1H), 2.48 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.22 (dddd, J = 18.5, 11.0, 2.5, 2.0 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 166.2, 145.6, 133.3, 132.2, 129.7, 129.5, 128.5, 128.4, 128.2, 127.2, 125.2, 73.0, 66.7, 59.8, 34.1, 33.4, 28.7. IR (neat): 3458, 3028, 2361, 1715, 1694, 1601, 1449, 1269, 1115, 1001, 764, 712, 469 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 350.1518. Found: m/z 350.1516.

((1*R,5*R**,6*S**)-6-(2-Naphthoyl)-5-hydroxy-5-(naphthalen-2-yl)-cyclohex-3-enyl)methyl acetate (4b).** Yield: 72%, white solid. TLC: R_f 0.18 (hexane–ethyl acetate = 3 : 1). Mp. 155.0–156.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 12.5, 2.0 Hz, 2H), 7.72–7.58 (m, 7H), 7.51–7.46 (m, 2H), 7.42–7.38 (m, 1H), 7.36–7.28 (m, 2H), 6.14 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.96 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 5.44 (s, 1H), 4.22 (d, J = 11.5 Hz, 1H), 3.94 (d, J = 4.5 Hz, 2H), 3.12–3.02 (m, 1H), 2.50 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.37 (dddd, J = 18.5, 11.0, 2.5, 2.5 Hz, 1H), 1.65 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 170.4, 143.2, 135.5, 135.1, 133.0, 132.5, 132.3, 131.9, 130.2, 129.4, 128.7, 128.5, 128.2, 128.1, 128.0, 127.5, 127.3, 126.7, 126.0, 125.7, 124.2, 123.6, 123.2, 74.0, 65.9, 52.9, 34.2, 29.1, 20.4. IR (KBr): 3408, 1740, 1653, 1622, 1362, 1233, 1038, 827, 748 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 450.1831. Found: m/z 450.1840.

((1*R,5*R**,6*S**)-5-Hydroxy-6-(4-methylbenzoyl)-5-*p*-tolylcyclohex-3-enyl)methyl acetate (4c).** Yield: 65%, white solid. TLC: R_f

0.31 (hexane–ethyl acetate = 3 : 1). Mp. 136.0–137.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (ddd, J = 8.0, 1.5, 1.5 Hz, 2H), 7.21 (ddd, J = 8.0, 2.0, 2.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.02 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.84 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 5.34 (s, 1H), 3.87 (d, J = 11.5 Hz, 1H), 3.86 (d, J = 5.0 Hz, 2H), 2.98–2.88 (m, 1H), 2.40 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.31 (s, 3H), 2.23 (dddd, J = 18.5, 11.0, 2.5, 2.5 Hz, 1H), 2,19 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 170.4, 144.4, 143.1, 136.3, 135.5, 132.8, 128.9, 128.7, 128.1, 127.9, 125.1, 73.5, 65.9, 52.9, 34.0, 28.9, 21.5, 20.8, 20.4. IR (KBr): 3457, 1738, 1647, 1605, 1362, 1238, 1032, 812 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 378.1831. Found: m/z 378.1827.

((1*R,5*R**,6*S**)-5-Hydroxy-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)cyclohex-3-enyl)methyl acetate (4d).** Yield: 52%, white solid. TLC: R_f 0.21 (hexane–ethyl acetate = 3 : 1). Mp. 110.0–110.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (ddd, J = 10.0, 2.5, 2.5 Hz, 2H), 7.24 (ddd, J = 10.0, 2.5, 2.5 Hz, 2H), 6.73 (ddd, J = 9.0, 2.0, 2.0 Hz, 2H), 6.70 (ddd, J = 9.0, 2.5, 2.5 Hz, 2H), 6.02 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.83 (ddd, J = 10.0, 2.0, 2.0 Hz, 1H), 5.40 (s, 1H), 3.88–3.81 (m, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 2.97–2.86 (m, 1H), 2.41 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.23 (dddd, J = 18.5, 11.0, 2.5, 2.0 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 170.5, 163.9, 158.3, 138.3, 132.8, 130.8, 130.5, 128.0, 126.3, 113.5, 113.4, 73.2, 66.0, 55.4, 55.1, 52.5, 34.0, 28.9, 20.5. IR (KBr): 3412, 2359, 1738, 1653, 1508, 1260, 1238, 1180, 1032, 847 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 410.1729. Found: m/z 410.1724.

((1*R,5*S**,6*S**)-5-Hydroxy-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)cyclohex-3-enyl)methyl acetate (4′d).** Yield: 15%, white solid. TLC: R_f 0.30 (hexane–ethyl acetate = 3 : 1). Mp. 111.0–112.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (ddd, J = 9.0, 2.5, 2.5 Hz, 2H), 7.28 (ddd, J = 10.0, 2.0, 2.0 Hz, 2H), 6.93 (ddd, J = 9.0, 2.0, 2.0 Hz, 2H), 6.87 (ddd, J = 9.0, 2.5, 2.5 Hz, 2H), 5.97 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H), 5.76 (ddd, J = 10.0, 2.5, 1.5 Hz, 1H), 4.59 (s, 1H), 4.23 (d, J = 5.0 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.10 (d, J = 12.0 Hz, 1H), 3.0–2.9 (m, 1H), 2.44 (dddd, J = 18.5, 5.0, 5.0, 1.5 Hz, 1H), 2.18 (dddd, J = 18.5, 11.5, 2.5, 2.0 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 166.0, 163.6, 158.6, 137.7, 132.4, 131.6, 128.1, 126.3, 122.0, 113.8, 113.7, 72.7, 66.4, 59.8, 55.4, 55.2, 34.3, 33.5, 28.7. IR (KBr): 3366, 2359, 1715, 1684, 1607, 1508, 1271, 1252, 1169, 1026, 770 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 410.1729. Found: m/z 410.1731.

((1*R,5*R**,6*S**)-6-(4-Bromobenzoyl)-5-(4-bromophenyl)-5-hydroxycyclohex-3-enyl)methyl acetate (4e).** Yield: 80%, white solid. TLC: R_f 0.18 (hexane–ethyl acetate = 3 : 1). Mp. 126.0–126.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.38 (m, 4H), 7.30 (ddd, J = 8.5, 2.5, 2.5 Hz, 2H), 7.19 (ddd, J = 8.5, 2.0, 2.0 Hz, 1H), 6.06 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H), 5.80 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 4.99 (s, 1H), 3.90 (dd, J = 11.5, 4.5 Hz, 1H), 3.87 (dd, J = 11.5, 4.5 Hz, 1H), 3.80 (d, J = 11.5 Hz, 1H), 2.97–2.87 (m, 1H), 2.42 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.24 (dddd, J = 18.5, 11.5, 2.5, 2.0 Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 170.2, 144.9, 136.4, 131.9, 131.8, 131.3, 129.4, 129.3, 128.7, 127.1, 121.2, 73.4, 65.7, 53.1, 34.0, 28.8, 20.5. IR (KBr): 3648, 1738, 1651, 1398, 1234, 1011, 819 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 505.9728. Found: m/z 505.9724.

((1*R,5*R**,6*S**)-5-Hydroxy-5-phenethyl-6-(3-phenylpropanoyl)-cyclohex-3-enyl)methyl acetate (4f).** Yield: 48%, colorless oil. TLC: R_f 0.18 (hexane–ethyl acetate = 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 4H), 7.21–7.16 (m, 2H), 7.16–7.12 (m, 2H), 7.12–7.08 (m, 2H), 5.88 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.77 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 3.98 (dd, J = 11.5, 4.5 Hz, 1H), 3.89 (dd, J = 11.5, 4.5 Hz, 1H), 3.86 (s, 1H), 2.97–2.88 (m, 2H), 2.87–2.77 (m, 3H), 2.73–2.59 (m, 3H), 2.25 (dddd, J = 18.5, 5.0, 5.0, 2.0 Hz, 1H), 2.04 (s, 3H), 1.95 (dddd, J = 18.5, 11.5, 2.5, 2.5 Hz, 1H), 1.80 (ddd, J = 13.5, 11.5, 5.0 Hz, 1H), 1.70 (ddd, J = 13.5, 11.5, 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 170.5, 141.6, 140.6, 130.4, 128.9, 128.5, 128.5, 128.3, 128.3, 126.2, 126.0, 71.5, 65.9, 55.2, 48.8, 43.0, 35.2, 30.6, 28.8, 28.8, 20.8. IR (neat): 3464, 2930, 1742, 1694, 1233, 1036, 700 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 406.2144. Found: m/z 406.2144.

((1*R,5*S**,6*S**)-5-Hydroxy-5-phenethyl-6-(3-phenylpropanoyl)-cyclohex-3-enyl)methyl acetate (4′f).** Yield: 23%, colorless oil. TLC: R_f 0.14 (hexane–ethyl acetate = 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 4H), 7.23–7.18 (m, 4H), 7.18–7.13 (m, 2H), 5.87 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H), 5.77 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 4.05 (dd, J = 11.5, 5.0 Hz, 1H), 3.97 (dd, J = 11.5, 5.0 Hz, 1H), 3.76 (s, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.75 (d, J = 12.0 Hz, 1H), 2.71–2.58 (m, 5H), 2.19 (dddd, J = 18.0, 5.0, 5.0, 2.0 Hz, 1H), 2.17 (s, 3H), 1.91–1.74 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 172.5, 141.7, 140.2, 130.4, 128.9, 128.6, 128.5, 128.3, 128.3, 126.4, 126.0, 71.3, 66.0, 55.7, 43.0, 35.7, 34.1, 33.1, 30.8, 30.6, 28.8. IR (neat): 3458, 2930, 1736, 1694, 1497, 1360, 1161, 700 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 406.2144. Found: m/z 406.2136.

((1*R,5*R**,6*S**)-6-Benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)-methyl isobutyrate (4g).** Yield: 75%, white solid. TLC: R_f 0.25 (hexane–ethyl acetate = 3 : 1). Mp. 107.0–107.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.42–7.37 (m, 1H), 7.35–7.30 (m, 2H), 7.24–7.19 (m, 2H), 7.19–7.14 (m, 2H), 7.09–7.04 (m, 1H), 6.07 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.88 (ddd, J = 10.0, 2.5, 2.5 Hz, 1H), 5.13 (s, 1H), 3.94 (dd, J = 11.5, 4.0 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 3.86 (dd, J = 11.5, 5.0 Hz, 1H), 3.01–2.90 (m, 1H), 2.43 (dddd, J = 18.5, 5.0, 5.0, 2.5 Hz, 1H), 2.25 (dddd, J = 18.5, 10.5, 2.5, 2.5 Hz, 1H), 2.23 (sept, J = 7.0 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 176.5, 145.9, 137.9, 133.4, 132.4, 128.4, 128.3, 128.1, 127.9, 127.0, 125.2, 73.6, 65.7, 53.5, 34.2, 33.7, 28.9, 18.8, 18.6. IR (KBr): 3428, 1734, 1651, 1449, 1339, 1244, 1152, 1055, 691 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 378.1831. Found: m/z 378.1842.

((1*R,5*R**,6*S**)-6-Benzoyl-5-hydroxy-5-phenylcyclohex-3-enyl)-methyl benzoate (4h).** Yield: 76%, white solid. TLC: R_f 0.24 (hexane–ethyl acetate = 3 : 1). Mp. 119.5–120.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2H), 7.54–7.50 (m, 1H), 7.46–7.42 (m, 2H), 7.39–7.33 (m, 4H), 7.31–7.26 (m, 1H), 7.20–7.15 (m, 2H), 7.10–7.04 (m, 3H), 6.10 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 5.91 (ddd, J = 10.0, 2.5, 2.0 Hz, 1H), 5.29 (s, 1H), 4.21 (dd, J = 11.5, 5.0 Hz, 1H), 4.11 (dd, J = 11.5, 4.5 Hz, 1H), 3.98 (d, J = 11.5 Hz, 1H), 3.16–3.07 (m, 1H), 2.54 (dddd, J = 18.5, 5.5, 5.0, 2.0 Hz, 1H), 2.35 (dddd, J = 18.5, 11.0, 2.5, 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 166.0, 145.9, 137.7, 133.4, 132.9, 132.5, 129.6, 129.5, 129.4, 128.3, 128.2, 128.1, 127.9,

127.0, 125.2, 73.7, 66.3, 53.5, 34.5, 29.1. IR (KBr): 3480, 1717, 1647, 1449, 1273, 1233, 1113, 704, 691 cm^{-1}. HRMS Calcd for $C_{20}H_{18}O_4$: M^+, 412.1675. Found: *m/z* 412.1677.

1-Phenylbutane-1,3-dione (3a): CAS RN [93-91-4]

White solid. (enol form) ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.52 (tt, J = 7.5, 1.5 Hz, 1H), 7.47–7.43 (m, 2H), 6.18 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 183.3, 134.9, 132.3, 128.6, 127.0, 96.7, 25.9.

Conclusions

We have demonstrated a novel tandem reaction initiated by a 1,4-addition of the zinc reagent prepared from an umpolung method. Using the umpolung of π-allylpalladium species by bis(iodozincio)methane (**1**), we could prepare the zinc dienolate to perform this tandem reaction efficiently. The cyclic product **4** was obtained with quite high diastereoselectivity, and therefore this reaction would be one of the useful methods to construct multiple adjacent stereocenters in a single process. This reaction required the use of a reagent having a certain level of reactivity with superb balance, since there are many functional groups in both the substrates **2** and the products **4**. On this point, the *gem*-dizinc **1** was an excellent reagent and we could show another useful transformation that utilized the characteristic feature of **1**.

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