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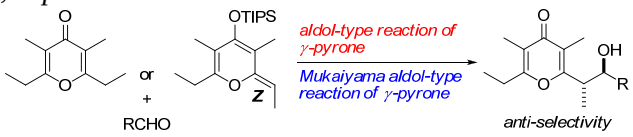

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Toward the synthesis of γ-pyrone-containing natural products: Diastereoselective aldol-type reaction of a γ-pyrone

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ABSTRACT

The diastereoselective aldol-type reaction of a γ-pyrone via a sodium anion has been developed. This reaction is useful for synthesizing γ-pyrone-containing natural products. Also, we applied the Mukaiyama aldol-type reaction of silyl enol ether of γ-pyrone by using $TiCl_4$. This Mukaiyama aldol-type reaction of γ-pyrone indicated higher *anti*-aldol selectivity than the aldol-type reaction of a γ-pyrone with NaHMDS.

Keywords:
diastereoselective aldol-type reaction of a γ-pyrone
Mukaiyama aldol-type reaction of a γ-pyrone
anti-aldol selectivity

1. Introduction

A number of γ-pyrone-containing compounds have been isolated from marine animals (Figure 1).[1] Among them, onchitriols I (**1**) and II (**2**) exhibit significant cytotoxicity against some cancer cell lines,[2] and onchidione (**3**) is a chemical defense compound of mollusks.[3] Auripyrones A (**7**) and B (**8**), polypropionates isolated from the sea hare *Dolabella auricularia* (Aplysiidae) by Yamada and co-workers,[4] exhibit cytotoxicity against HeLa S_3 cells with IC_{50} values of 0.26 and 0.48 μg/mL, respectively. Because these γ-pyrone-containing compounds possess asymmetric centers at neighboring positions of the γ-pyrone part, the development of methods to synthesize γ-pyrone-containing compounds with stereogenic centers is an important topic in natural product synthesis. We have preliminarily reported a diastereoselective aldol-type reaction of a γ-pyrone with NaHMDS.[5] We describe herein details of the diastereoselective aldol-type reaction and the Mukaiyama aldol-type reaction of a γ-pyrone, 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**), as a substrate; both of these reactions are applicable to the synthesis of naturally occurring γ-pyrone-containing compounds.

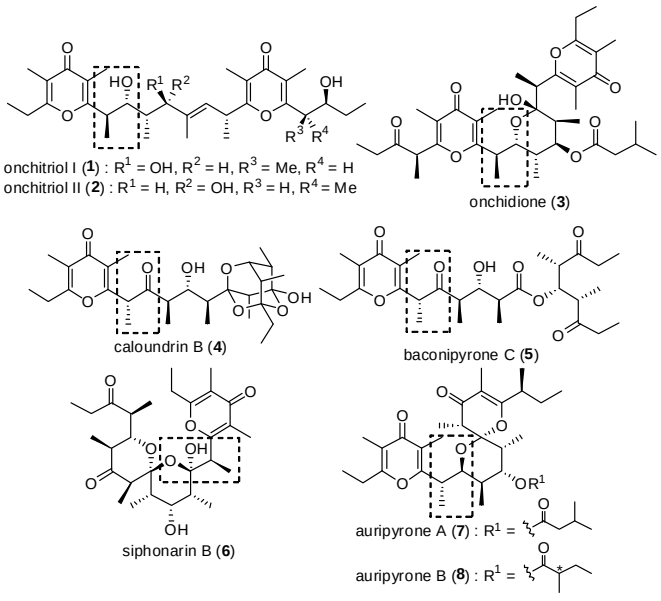
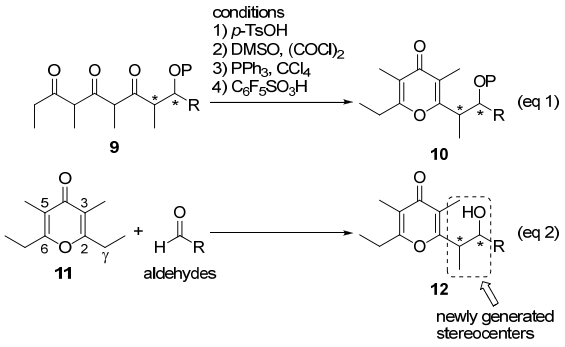


Fig. 1. γ-Pyrone-containing marine natural products.

2. Results and Discussion

Generally, γ-pyrone skeletons are synthesized by the dehydrative cyclization of 1,3,5-triketones.[6] When the γ-pyrone compounds involved asymmetric centers at neighboring positions of a γ-pyrone part, these asymmetric centers are expected to be installed in the cyclization precursors in advance (Scheme 1, eq

1).[7] Although this method is well established, the requirement of multiple steps in a linear synthetic sequence remains as a significant problem. For instance, when triketone **9** contains unstable functional groups under the dehydrative cyclization conditions, it is difficult to cyclize at the endgame of total synthesis. Thus, we planned to develop an efficient method for synthesizing a γ-pyrone-containing skeleton with stereogenic centers by using a diastereoselective aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**)[6h] and aldehydes (Scheme 1, eq 2). This approach has the benefits of straightforward access even to complex molecules and of the construction of two stereogenic centers at once.[5] Although examples of alkylation at the γ-position of γ-pyrones have been reported,[8] to the best of our knowledge, aldol-type reactions of γ-pyrones have been demonstrated only for the 2,6-dimethyl-4-pyrone and the 2-methoxy-3,5,6-trimethyl-4-pyrone.[9] However, these reactions did not control the newly generated stereocenters.

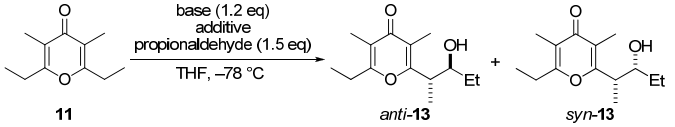


Scheme 1. Approaches to polypropionate-derived γ-pyrones.

2.1. Aldol-type reaction of γ-pyrone via an anion

Table 1 summarizes the investigation of the diastereoselective aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and propionaldehyde.[5] The reaction between γ-pyrone **11** and propionaldehyde using LDA as a base gave the aldol adduct **13**, but this result was not reproducible (entry 1). The configuration of two newly generated stereocenters of aldol adducts **13** has been determined by *J*-based configuration analysis (Figure 2).[10] The addition of LiCl[9a] or HMPA was not effective in this case (entries 2 and 3). An attempt at the aldol-type reaction with lithium tetramethylpiperidide (LTMP) gave aldol adducts **13**, but the yield was low (9%) (entry 4). In entry 5, we tried the aldol reaction using LHMDS[9b] to give the desired aldol adducts **13** in 69% yield. Therefore, we next screened other metal bis(trimethylsilyl)amides to serve as a base. The reaction with KHMDS gave the desired adducts **13** in 15% yield (entry 6). On the other hand, NaHMDS afforded aldol adducts **13** (76% yield) with *anti*-aldol selectivity (*anti*/*syn* = 2.8 : 1) (entry 7). The addition of 15-crown-5 was not effective (entry 8). From these results, the aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and propionaldehyde was most efficiently achieved by using NaHMDS (entry 7).

Table 1 Aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and propionaldehyde



entry	base	additive (equiv)	yield of **13** (%)[a]	*anti*-**13** : *syn*-**13**[b]	recovery of **11** (%)
1	LDA	–	45	3.1 : 1	11
2	LDA	LiCl (8.0)	53	3.7 : 1	14
3	LDA	HMPA (8.6)	16	0.6 : 1	62
4	LTMP	–	9	1.5 : 1	trace
5	LHMDS	–	69	2.9 : 1	17
6	KHMDS	–	15	2.8 : 1	62
7	NaHMDS	–	76	2.8 : 1	12
8	NaHMDS	15-crown-5 (1.2)	9	1.3 : 1	69

[a] Combined yield of isolated *anti*- and *syn*-**13**.

[b] The ratio was calculated from respective yields of *anti*- and *syn*-**13**.

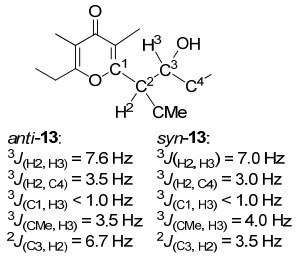
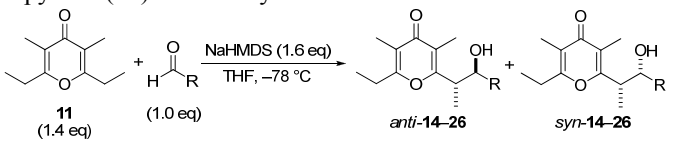


Fig 2. Coupling constants of aldol adducts *anti*-**13** and *syn*-**13** for *J*-based configuration analysis.

Next, we investigated the generality of the aldehyde in the aldol-type reaction of 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) (Table 2).[5] The aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and aliphatic aldehydes without steric hindrance afforded aldol adducts **14**–**16** in moderate to good yields (entries 1–3). Pivalaldehyde showed lower reactivity and gave adducts **17** in 36% yield, maybe because of the steric bulkiness of pivalaldehyde (entry 4). The diastereoselectivity of this aldol-type reaction with aliphatic aldehydes indicated *anti*-aldol selectivity (*anti*/*syn* = 2 : 1 to 3 : 1 range).[11] The reaction with α,β-unsaturated aliphatic aldehydes, crotonaldehyde and methacrolein, gave only 1,4-adducts (entries 5 and 6). We next employed aromatic aldehydes as substrates. The aldol-type reaction with benzaldehyde and aromatic aldehydes with para- or meta-substituents smoothly proceeded to give aldol adducts in good yield (entries 7–10 and 12). When the reaction was carried out with *p*-nitrobenzaldehyde, the decomposition of materials was observed on TLC and adduct **22** was obtained in only 30% yield (entry 11). This aldol-type reaction with aromatic aldehydes also showed *anti*-aldol selectivity (*anti*/*syn* = 1.9 : 1 to 2.7 : 1 range) (entries 7–12). The reaction with ortho-substituted aromatic aldehydes afforded aldol adducts **24**–**26** in excellent yield (92–99%). However, sterically hindered substituents at the ortho-position tended to give aldol adducts with *syn* selectivity (entries 13–15).

Table 2 Aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and aldehydes



entry	R	yield (%)[a]	*anti* : *syn*[b]
1	*n*-Pr	76 (**14**)	2.9 : 1
2	*i*-Pr	57 (**15**)	2.8 : 1
3	Cy	64 (**16**)	2.1 : 1
4	*t*-Bu	36 (**17**)	2.6 : 1[c]
5	*trans*-CH_3CH=CH–	–	–
6	CH_2=$C(CH_3)$–	–	–
7	Ph	95 (**18**)	2.4 : 1
8	*p*-MeC_6H_4	92 (**19**)	2.1 : 1
9	*p*-$MeOC_6H_4$	94 (**20**)	2.5 : 1
10	*p*-BrC_6H_4	86 (**21**)	1.9 : 1
11	*p*-$NO_2C_6H_4$	30 (**22**)	1.9 : 1
12	*m*-MeC_6H_4	85 (**23**)	2.7 : 1
13	*o*-MeC_6H_4	92 (**24**)	1.2 : 1
14	*o*-BrC_6H_4	99 (**25**)	0.5 : 1
15	Mes	93 (**26**)	0.5 : 1

[a] Combined yield of isolated *anti* and *syn* adduct.

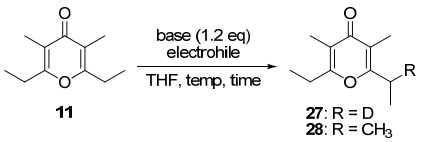
[b] The ratio was calculated from respective yields of *anti* and *syn* adduct.

[c] The ratio was calculated by ^{1}H NMR.

2.2. Transition state model of aldol-type reaction of γ-pyrone

It is conceivable that the counter cation would affect deprotonation from the γ-position of **11** and/or the activation of aldehydes. We next investigated the role of the counter cations in this aldol-type reaction. We attempted the reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) and other electrophiles, D_2O and CH_3I (Table 3).[5] The reaction with D_2O and the enolate of **11** prepared with LDA afforded deuterated compound **27** in 34% yield (entry 1). However, each enolate of **11** prepared with metal bis(trimethylsilyl)amide gave **27** in nearly quantitative yields (entries 2–4). From entries 1–4, LDA was found to be unsuitable and metal bis(trimethylsilyl)amides were found to deprotonate quantitatively. The reaction with CH_3I and enolate of **11** prepared with LDA gave mono-methylated compound **28**, but the yield was low (entry 5). An attempt at alkylation with LHMDS gave mono-methylated compound **28** in 26% yield (entry 6). From entries 2 and 6, lithium enolate of **11** was unstable and thus decomposed in a couple of hours. In contrast, the reaction with KHMDS or NaHMDS afforded mono-methylated compound **28** in good yields (entries 7 and 8). In these reactions, enol methyl ethers could not be obtained (entries 5–8). Comparing the results shown in Tables 1 and 3, it is interesting that the reactivity of metal enolates of **11** prepared with bis(trimethylsilyl)amides changed significantly depending on the nature of the metal counter cations and electrophiles. Through these studies, it was determined that sodium enolates of γ-pyrone was optimal for the described aldol-type reactions.

Table 3 Reaction with **11** and D_2O or CH_3I

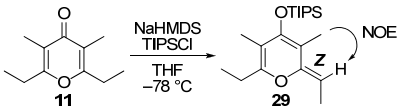


entry	base	electrophile (equiv)	temperature	time/h	yield (%) [deuteration yield (%)][a]
1	LDA	D_2O (excess)	–78 °C to RT	0.5	34[b] [59]
2	LHMDS	D_2O (excess)	–78 °C to RT	0.5	quant.[b] [>95]
3	KHMDS	D_2O (excess)	–78 °C to RT	0.5	quant.[b] [>95]
4	NaHMDS	D_2O (excess)	–78 °C to RT	0.5	quant.[b] [>95]
5	LDA	CH_3I (1.5)	–78 °C	3	10
6	LHMDS	CH_3I (1.5)	–78 °C	3	26
7	KHMDS	CH_3I (1.5)	–78 °C	3	75
8	NaHMDS	CH_3I (1.5)	–78 °C	3	79

[a] The percentage of deuterated compound **27** was determined by ^{1}H NMR.

[b] Combined yield of isolated **11** and **27**.

We considered the transition state of this aldol-type reaction as follows. In a previous work, we tried to trap the enolate of γ-pyrone **11** as the corresponding silyl ether (TMS, TBS, or TES) to get information about the stereochemistry of the enolate. However, this attempt resulted in failure, presumably due to the instability of the silyl ethers.[5] In the present study, we attempted to synthesize the triisopropylsilyl enol ether of γ-pyrone **11** to afford corresponding (*Z*)-silyl enol ether **29** (Scheme 2). The geometry of triisopropylsilyl enol ether **29** was determined by a NOE experiment, as shown in Scheme 2. From these results, we propose the transition state model of this aldol-type reaction. Thus, treatment of γ-pyrone **11** with NaHMDS afforded *Z* enolate of γ-pyrone **11**, which was coordinated with aldehydes through the counter cation. Although the Zimmerman–Traxler model is generally accepted,[12] the cyclic transition state of this aldol-type reaction is unlikely based on the construction of a highly strained eight-membered state (Figure 3, **30a** and **30b**). We therefore suggested that the transition state would exist as an oligomeric or open form (Figure 3, **31a** and **31b**). The diastereoselectivity of this aldol-type reaction is illustrated in Figure 3. Thus, the transition state model **31a** is favored, owing to the steric hindrance between the R group in the aldehyde and methyl group at the β-position in γ-pyrone. Therefore, this aldol-type reaction showed *anti*-aldol selectivity.



Scheme 2. Formation of triisopropylsilyl enol ether of γ-pyrone

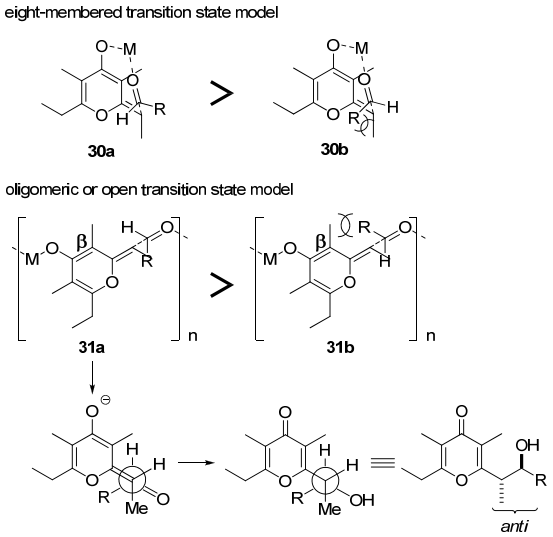


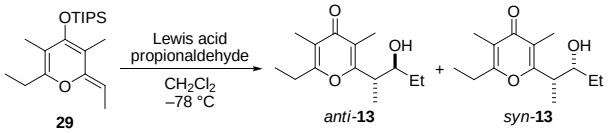
Fig 3. Plausible transition state model.

2.3. Mukaiyama aldol-type reaction of triisopropylsilyl enol ether of γ-pyrone

Because this aldol-type reaction with aldehyde **32** by using NaHMDS showed moderate yield and diastereoselectivity, we next investigated the diastereoselective Mukaiyama aldol-type reaction[13] of silyl enol ether **29**. The results of the Mukaiyama aldol-type reaction between silyl enol ether **29** and propionaldehyde with several Lewis acids are summarized in Table 4. The Mukaiyama aldol-type reactions between triisopropylsilyl enol ether **29** and propionaldehyde using nonmetallic Lewis acids, such as $BF_3{\cdot}OEt_2$ or TMSOTf, were attempted (entries 1 and 2). However, the yields and diastereoselectivity were low. The reaction with $Sn(OTf)_2$ gave aldol adducts in only 3% yield (entry 3). In entry 4, an attempt at the aldol reaction with $SnCl_4$ improved the yield and diastereoselectivity (70% yield, *anti*/*syn* = 4.5 : 1). From these results, metal (IV) reagents as Lewis acids were expected to be effective for this aldol reaction. Therefore, we next screened metal (IV) reagents of group 4 as Lewis acids (entries 5－8). As a result, the Mukaiyama aldol-type reaction of silyl enol ether **29**

was most efficiently effected by using $TiCl_4$ as a Lewis acid (entry 6). Compared with our previous anionic conditions (Table 1),[5] this Mukaiyama aldol-type reaction condition improved the diastereoselectivity of aldol adduct **13**.

Table 4 Optimization of Lewis acids for Mukaiyama aldol-type reaction



entry	Lewis acid	yield of **13** (%)[a]	*anti*-**13** : *syn*-**13**[b]	recovery of **11** (%)
1	$BF_3{\cdot}OEt_2$	25	1.1 : 1	54
2	TMSOTf	33[c]	1.0 : 1	54
3	$Sn(OTf)_2$	3	1.9 : 1	94
4	$SnCl_4$	70	4.5 : 1	30
5	$TiCl_2(O\text{-}i\text{-}Pr)_2$	18	1.6 : 1	64
6	$TiCl_4$	70	6.4 : 1	28
7	$ZrCl_4$	37	4.2 : 1	37
8	$HfCl_4$	40	4.4 : 1	32

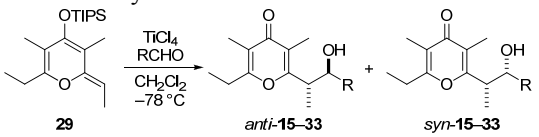
[a] Combined yield of isolated *anti*- and *syn*-**13**.

[b] The ratio was calculated by ^{1}H NMR.

[c] Corresponding silylated derivatives were obtained (6% yield, *anti* : *syn* = 1.7 : 1).

We next investigated the generality of the Mukaiyama aldol-type reaction between silyl enol ether **29** and aldehydes (Table 5). In entry 1, the Mukaiyama aldol-type reaction between triisopropylsilyl enol ether **29** and isobutyraldehyde gave results similar to those of the aldol-type reaction of a γ-pyrone with NaHMDS (Table 2, entry 2). The Mukaiyama aldol-type reaction with aromatic aldehydes showed higher *anti*-aldol selectivity (entries 2–5) than that in the aldol-type reaction of a γ-pyrone with NaHMDS (Table 2, entries 7, 11, 14, and 15). Although the aldol-type reaction of 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) with sterically hindered aromatic aldehydes tended to give *syn* aldol adducts, the Mukaiyama aldol-type reaction with sterically hindered aromatic aldehydes, such as *o*-bromobenzaldehyde and mesityl aldehyde, exhibited *anti*-aldol selectivity (entries 4 and 5). Interestingly, the Mukaiyama aldol-type reaction with α,β-unsaturated aliphatic aldehydes, crotonaldehyde and methacrolein, gave 1,2-adducts with high *anti*-aldol selectivity (entries 6 and 7). Thus, the Mukaiyama aldol-type reaction exhibited higher *anti*-aldol selectivity than that of the aldol-type reaction of a γ-pyrone with NaHMDS.

Table 5 Mukaiyama aldol-type reaction between silyl enol ether **29** and aldehydes



entry	R	yield (%)[a]	*anti* : *syn*[b]
1	*i*-Pr	53 (**15**)	3.0 : 1
2	Ph	57 (**18**)	4.2 : 1
3	$p\text{-}NO_2C_6H_4$	38 (**22**)	2.8 : 1
4	$o\text{-}BrC_6H_4$	54 (**25**)	1.1 : 1
5	Mes	44 (**26**)	1.5 : 1
6	*trans*-$CH_3CH{=}CH–$	35 (**32**)	>10 : 1
7	$CH_2{=}C(CH_3)–$	35 (**33**)	4.2 : 1

[a] Combined yield of isolated *anti* and *syn* adduct.

[b] The ratio was calculated by ^{1}H NMR.

3. Conclusion

In conclusion, we have developed the diastereoselective aldol-type reaction of a γ-pyrone by using NaHMDS. This reaction is a useful method for obtaining γ-pyrone-containing natural products. Also, we trapped the enolate of γ-pyrone **11** as the corresponding silyl ether **29** and determined the stereostructure of the enolate. As a result, we have proposed the transition state model of this aldol-type reaction. Furthermore, we have developed the Mukaiyama aldol-type reaction of silyl enol ether of γ-pyrone by using $TiCl_4$. This aldol-type reaction with a silylated-γ-pyrone gave higher *anti*-selectivity than that of the sodium enolate of the γ-pyrone. This strategy is now being applied to the synthesis of γ-pyrone-containing natural products are in progress.[14]

4. Experimental Section

4.1. General

All reagents and dry solvents were used as obtained from commercial supplies unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled by standard procedure. Column chromatography was performed using silica gel (75–200 μm or 45–75 μm). All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Optical rotations were measured on digital polarimeter at room temperature, using the sodium D line. Infrared (IR) spectra were recorded on a FT IR system and only selected peaks are reported. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were run at various field strengths as indicated. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) or $CDCl_3$ (δ_H 7.26 and δ_c 77.1). Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The coupling constants (for *J*-based configuration analysis) are reported in Hz (see Supporting Information). High resolution mass spectra (HRMS) were recorded by electrospray ionization (ESI)/time-of-flight experiments (TOF). Melting points are uncorrected.

4.2. Typical procedure of aldol-type reaction of γ-pyrone.

After treatment of 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) (49 mg, 0.27 mmol) with NaHMDS (1.0 M solution in THF, 0.29 mL, 0.29 mmol) in THF (1.0 mL) for 2 h at –78 °C, aldehyde (0.18 mmol) was added to the mixture, and the mixture was stirred for 3 h at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc. Combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (hexane–EtOAc) afforded *anti* and *syn* aldol adducts.

4.3. Typical procedure of Mukaiyama aldol-type reaction of γ-pyrone.

To a stirred solution of triisopropylsilyl chloride (0.57 mL, 2.00 mmol) in hexane (2.0 mL) was added triethylamine (0.370 mL, 2.00 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 (**11**) (36 mg, 0.200 mmol) in THF (1.0 mL) was added NaHMDS (1.0 M solution in THF, 0.220 mL, 0.220 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, 0.220 mL, 0.220 mmol) was added. The mixture was stirred at –78 °C for 10 min, concentrated under inert atmosphere at 0 °C to give triisopropylsilyl enol ether **28** as a yellow solid, which was used for the next reaction without further purification.

To a stirred solution of triisopropylsilyl enol ether **28** in CH_2Cl_2 (0.8 mL) were added aldehyde (0.305 mmol) and $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.220 mL, 0.220 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, hexane–EtOAc) to give *anti* and *syn* aldol adducts.

4.4. Characterization data for 13–26, 32, 33

*4.4.1. anti-**13** (R = Et).*

colorless oil (for anionic conditions: 25 mg, 56% yield; for Mukaiyama aldol-type reaction conditions: 29 mg, 61% yield): R_f = 0.20 (1:1 hexane/EtOAc); IR (neat) 3392, 1653, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.72 (br m, 1H), 3.04 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.98 (s, 3H), 1.95 (s, 3H), 1.72–1.60 (m, 1H), 1.51–1.32 (m, 1H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.8, 164.4, 164.2, 119.5, 117.9, 75.2, 41.3, 27.3, 24.7, 14.4, 11.2, 10.1, 9.7 (2C); HRMS (ESI) *m/z* 261.1471, calcd for $C_{14}H_{22}O_3Na$ $[M+Na]^+$ 261.1467.

*4.4.2. syn-**13** (R = Et).*

colorless oil (for anionic conditions: 8.8 mg, 20% yield; for Mukaiyama aldol-type reaction conditions: 4.5 mg, 9% yield): R_f = 0.28 (1:1 hexane/EtOAc); IR (neat) 3400, 1650, 1592 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.73 (br m, 1H), 2.98 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.97 (s, 3H), 1.94 (s, 3H), 1.55–1.35 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.8, 164.7, 164.2, 118.6, 117.9, 75.4, 41.4, 27.8, 24.7, 14.1, 11.3, 10.1, 9.7, 9.5; HRMS (ESI) *m/z* 261.1462, calcd for $C_{14}H_{22}O_3Na$ $[M+Na]^+$ 261.1467.

*4.4.3. anti-**14** (R = n-Pr).*

colorless crystals (for anionic conditions: 25 mg, 56% yield): R_f = 0.22 (1:1 hexane/EtOAc); mp 76–77 °C; IR (neat) 3398, 1653, 1591 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.78 (br m, 1H), 3.02 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.93 (s, 3H), 1.58–1.53 (m, 2H), 1.46–1.36 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 6.3 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.2, 164.0, 119.4, 117.8, 73.5, 41.7, 36.7, 24.8, 18.8, 14.4, 14.1, 11.4, 9.8, 9.6; HRMS (ESI) *m/z* 275.1666, calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623.

*4.4.4. syn-**14** (R = n-Pr).*

colorless oil (for anionic conditions: 8.8 mg, 20% yield): R_f = 0.31 (1:1 hexane/EtOAc); IR (neat) 3340, 1653, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.80 (br m, 1H), 2.96 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.97 (s, 3H), 1.94 (s, 3H), 1.52–1.25 (m, 4H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.2, 164.0, 118.6, 117.9, 73.8, 41.8, 37.3, 24.8, 19.1, 14.2, 14.0, 11.4, 9.8, 9.6; HRMS (ESI) *m/z* 275.1648, calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623.

*4.4.5. anti-**15** (R = i-Pr).*

white solid (for anionic conditions: 19 mg, 42% yield; for Mukaiyama aldol-type reaction conditions: 20 mg, 40% yield): R_f = 0.20 (1:1 hexane/EtOAc); mp 106–108 °C; IR (neat) 3400, 1655, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.60 (br m, 1H), 3.10 (dq, *J* = 8.1, 6.8 Hz, 1H), 2.61 (q, *J* = 7.7 Hz, 2H), 1.97 (s, 3H), 1.93 (s, 3H), 1.84 (m, 1H), 1.21 (t, *J* = 7.7 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 164.6, 163.9, 119.3, 117.8, 77.8, 39.1, 29.9, 24.8, 20.3, 15.0, 14.6, 11.5, 9.8, 9.6; HRMS (ESI) *m/z* 275.1607, calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623.

*4.4.6. syn-**15** (R = i-Pr).*

white solid (for anionic conditions: 8.9 mg, 15% yield; for Mukaiyama aldol-type reaction conditions: 6.7 mg, 13% yield): R_f = 0.33 (1:1 hexane/EtOAc); mp 98–101 °C; IR (neat) 3402, 1653, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.66 (br m, 1H),

2.96 (dq, *J* = 6.8, 6.8 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.98 (s, 3H), 1.94 (s, 3H), 1.57 (dqq, *J* = 3.8, 6.6, 6.9 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.1, 164.7, 164.0, 118.2, 78.2, 39.1, 30.9, 24.8, 20.3, 15.7, 14.6, 11.4, 9.7, 9.6; HRMS (ESI) *m/z* 275.1609, calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623.

*4.4.7. anti-**16** (R = Cy).*

colorless crystals (for anionic conditions: 22 mg, 43% yield): R_f = 0.32 (1:1 hexane/EtOAc); mp 133–136 °C; IR (neat) 3400, 1653, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.57 (br m, 1H), 3.15 (dq, *J* = 8.1, 7.0 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.93 (s, 3H), 1.88–1.40 (m, 11H), 1.21 (t, *J* = 7.6 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 164.7, 163.9, 119.3, 117.8, 77.7, 40.2, 38.4, 30.6, 26.6, 26.5, 26.2, 25.6, 24.9, 15.0, 11.4, 9.8, 9.6; HRMS (ESI) *m/z* 315.1935, calcd for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1936.

*4.4.8. syn-**16** (R = Cy).*

colorless crystals (for anionic conditions: 11 mg, 21% yield): R_f = 0.41 (1:1 hexane/EtOAc); mp 120–122 °C; IR (neat) 3400, 1653, 1593 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.62 (br m, 1H), 3.12 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.97 (s, 3H), 1.95 (s, 3H), 1.78–1.08 (m, 11H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.7, 164.1, 163.4, 142.1, 128.6, 128.2, 126.7, 119.9, 118.0, 76.8, 43.1, 24.8, 14.5, 11.3, 9.6, 9.5; HRMS (ESI) *m/z* 315.1931, calcd for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1936.

*4.4.9. diastereomixture of **17**.*

colorless oil (for anionic conditions: 18 mg, 36% yield): R_f = 0.35 (1:1 hexane/EtOAc); IR ($CHCl_3$) 3431 (br), 1652, 1594 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.59 (br m, 1H, *anti*), 3.40 (br m, 1H, *syn*), 3.20 (dq, *J* = 6.8, 6.8 Hz, 1H, *syn*), 3.12 (dq, *J* = 6.8, 6.8 Hz, 1H, *anti*), 2.61 (q, *J* = 7.7 Hz, 2H, *anti, syn*), 1.99 (s, 3H, *syn*), 1.98 (s, 3H, *anti*), 1.94 (s, 3H, *anti, syn*), 1.37 (d, *J* = 6.8 Hz, 3H, *syn*), 1.29 (d, *J* = 6.8 Hz, 3H, *anti*), 1.24 (t, *J* = Hz, 3H, *syn*), 1.22 (t, *J* = 7.7 Hz, 3H, *anti*), 0.89 (s, 9H, *anti*), 0.87 (s, 9H, *syn*), A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.9 (*anti*), 179.6 (*syn*), 166.5 (*anti*), 166.0 (*syn*), 164.0, 118.4 (*syn*), 118.3 (*syn*), 118.0 (*anti*), 116.9 (*anti*), 83.3 (*syn*), 79.9 (*anti*), 37.3 (*syn*), 36.0, 35.9 (*syn*), 26.3 (3C), 24.8 (*syn*), 24.7 (*anti*), 18.3 (*syn*), 15.6 (*anti*), 11.4, 9.8 (*syn*; 2C), 9.5 (*anti*; 2C); HRMS (ESI) *m/z* 289.1809, calcd for $C_{16}H_{26}O_3Na$ $[M+Na]^+$ 289.1780.

*4.4.10. anti-**18** (R = Ph).*

colorless crystals (for anionic conditions: 34 mg, 67% yield; for Mukaiyama aldol-type reaction conditions: 26 mg, 46% yield): R_f = 0.26 (1:1 hexane/EtOAc); mp 112–115 °C; IR (neat) 3369, 1653, 1589, 762, 702 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H), 4.79 (br d, *J* = 8.6 Hz, 1H), 3.30 (dq, *J* = 8.6 Hz, 7.3 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.91 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.7, 164.1, 163.4, 142.1, 128.6, 128.2, 126.7, 119.9, 118.0, 76.8, 43.1, 24.8, 14.5, 11.3, 9.6, 9.5; HRMS (ESI) *m/z* 309.1474, calcd for $C_{18}H_{22}O_3Na$ $[M+Na]^+$ 309.1467.

*4.4.11. syn-**18** (R = Ph).*

colorless crystals (for anionic conditions: 14 mg, 28% yield; for Mukaiyama aldol-type reaction conditions: 6.2 mg, 11% yield): R_f = 0.34 (1:1 hexane/EtOAc); mp 92–94 °C; IR (neat) 3369, 1651, 1589, 760, 702 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.23–7.18 (m, 5H), 4.82 (br d, *J* = 8.1 Hz, 1H), 3.30 (dq, *J* = 8.1, 6.8 Hz, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.87 (s, 3H), 1.68 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.0, 163.4, 142.2, 128.3, 128.1, 125.8, 119.0, 117.8, 77.0, 43.4, 24.7, 14.6, 11.3, 9.5, 9.3; HRMS (ESI) *m/z* 309.1469, calcd for $C_{18}H_{22}O_3Na$ $[M+Na]^+$ 309.1467.

*4.4.12. anti-**19** (R = p-MeC$_6$H$_4$).*

colorless crystals (for anionic conditions: 33 mg, 62% yield): R_f = 0.25 (1:1 hexane/EtOAc); mp 104–106 °C; IR (neat) 3369, 1651, 1589, 816 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.76 (br d, *J* = 8.6 Hz, 1H), 3.29 (dq, *J* = 8.6, 7.0 Hz, 1H), 2.62 (q, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.21 (t, *J* = 7.7 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.0, 163.6, 139.0, 137.8, 129.0, 126.5, 119.6, 117.8, 76.5, 43.1, 24.8, 21.2, 14.7, 11.4, 9.7, 9.6; HRMS (ESI) *m/z* 323.1627, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.13. syn-**19** (R = p-MeC$_6$H$_4$).*

colorless crystals (for anionic conditions: 16 mg, 30% yield): R_f = 0.35 (1:1 hexane/EtOAc); mp 112–114 °C; IR (neat) 3379, 1651, 1589, 816 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 4.77 (br d, *J* = 8.4 Hz, 1H), 3.28 (dq, *J* = 8.4, 6.8 Hz, 1H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.27 (s, 3H), 1.86 (s, 3H), 1.68 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.8, 163.4, 139.2, 137.7, 128.9, 125.6, 118.8, 117.7, 76.7, 43.5, 24.8, 21.2, 14.8, 11.5, 9.6, 9.4; HRMS (ESI) *m/z* 323.1624, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.14. anti-**20** (R = p-MeOC$_6$H$_4$).*

colorless crystals (for anionic conditions: 39 mg, 67% yield): R_f = 0.18 (1:1 hexane/EtOAc); mp 121–124 °C; IR (neat) 3369, 1653, 1587, 829 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.76 (br d, *J* = 8.6 Hz, 1H), 3.29 (dq, *J* = 8.6, 7.0 Hz, 1H), 2.62 (q, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.21 (t, *J* = 7.7 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.0, 163.6, 139.0, 137.8, 129.0, 126.5, 119.6, 117.8, 76.5, 43.1, 24.8, 21.2, 14.7, 11.4, 9.7, 9.6; HRMS (ESI) *m/z* 339.1583, calcd for $C_{19}H_{24}O_4Na$ $[M+Na]^+$ 339.1572.

*4.4.15. syn-**20** (R = p-MeOC$_6$H$_4$).*

colorless oil (for anionic conditions: 16 mg, 27% yield): R_f = 0.30 (1:1 hexane/EtOAc); IR (neat) 3375, 1653, 1587, 831 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 4.76 (br d, *J* = 8.6 Hz, 1H), 3.74 (s, 3H), 3.27 (dq, *J* = 8.4, 6.8 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.86 (s, 3H), 1.70 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.8, 163.5, 159.1, 134.3, 126.9, 118.8, 117.7, 113.6, 76.4, 55.2, 43.5, 24.8, 14.9, 11.5, 9.6, 9.5; HRMS (ESI) *m/z* 339.1570, calcd for $C_{19}H_{24}O_4Na$ $[M+Na]^+$ 339.1572.

*4.4.16. anti-**21** (R = p-BrC$_6$H$_4$).*

colorless crystals (for anionic conditions: 37 mg, 57% yield): R_f = 0.26 (1:1 hexane/EtOAc); mp 114–116 °C; IR (neat) 3352, 1653, 1587, 820 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.77 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.26 (dq, *J* = 8.4, 7.0 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.94 (s, 3H), 1.89 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.00 (d, *J* = 7.0 Hz,

3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.2, 163.3, 141.2, 131.4, 128.4, 121.7, 119.7, 117.8, 75.9, 43.1, 24.8, 14.3, 11.3, 9.7, 9.6; HRMS (ESI) *m/z* 387.0572, calcd for $C_{18}H_{21}O_3BrNa$ $[M+Na]^+$ 387.0572.

*4.4.17. syn-**21** (R = p-BrC$_6$H$_4$).*

colorless crystals (for anionic conditions: 19 mg, 29% yield): R_f = 0.35 (1:1 hexane/EtOAc); mp 150–153 °C; IR (neat) 3367, 1653, 1589, 821 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.78 (br d, *J* = 8.1 Hz, 1H), 3.26 (dq, *J* = 8.1, 6.8 Hz, 1H), 2.59 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.54 (dq, *J* = 15.2, 7.6 Hz, 1H), 1.86 (s, 3H), 1.68 (s, 3H), 1.38 (d, *J* =6.8 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.4, 163.9, 163.0, 141.3, 131.3, 127.5, 121.7, 119.0, 117.8, 76.0, 43.4, 24.8, 14.5, 11.4, 9.6, 9.5; HRMS (ESI) *m/z* 387.0561, calcd for $C_{18}H_{21}O_3BrNa$ $[M+Na]^+$ 387.0572.

*4.4.18. anti-**22** (R = p-NO$_2$C$_6$H$_4$).*

yellow solid (for anionic conditions: 12 mg, 20% yield; for Mukaiyama aldol-type reaction conditions: 19 mg, 28% yield): R_f = 0.16 (1:1 hexane/EtOAc); mp 167–169 °C; IR ($CHCl_3$) 3429 (br), 1655, 1598, 1525, 1349 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 8.9 Hz, 2H), 4.94 (br d, *J* = 8.1 Hz, 1H), 3.31 (dq, *J* = 8.1, 7.0 Hz, 1H), 2.63 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.57 (dq, *J* = 15.2, 7.6 Hz, 1H), 1.95 (s, 3H), 1.92 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.3, 162.7, 149.5, 147.5, 127.6, 123.5, 120.0, 118.0, 75.7, 43.2, 24.9, 14.3, 11.4, 9.8, 9.6; HRMS (ESI) *m/z* 354.1322, calcd for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$ 354.1317.

*4.4.19. syn-**22** (R = p-NO$_2$C$_6$H$_4$).*

yellow solid (for anionic conditions: 6.1 mg, 10% yield; for Mukaiyama aldol-type reaction conditions: 6.6 mg, 10% yield): R_f = 0.21 (1:1 hexane/EtOAc); mp 189–191 °C; IR ($CHCl_3$) 3371 (br), 1653, 1594, 1524, 1348 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 2H), 4.95 (br d, *J* = 7.6 Hz, 1H), 3.29 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.61 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.55 (dq, *J* = 15.2, 7.6 Hz, 1H), 1.85 (s, 3H), 1.67 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.3, 164.1, 162.6, 149.6, 147.3, 126.7, 123.4, 119.2, 118.1, 75.6, 43.4, 24.8, 14.1, 11.5, 9.6, 9.5; HRMS (ESI) *m/z* 354.1306, calcd for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$ 354.1317.

*4.4.20. anti-**23** (R = m-MeC$_6$H$_4$).*

white solid (for anionic conditions: 34 mg, 62% yield): R_f = 0.18 (1:1 hexane/EtOAc); mp 99–100 °C; IR (neat) 3369, 1652, 1589, 787 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27–7.10 (m, 4H), 4.76 (br d, *J* = 8.8 Hz, 1H), 3.30 (dq, *J* = 8.8, 7.0 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.0, 163.6, 142.0, 138.1, 128.8, 128.3, 127.2, 123.8, 119.7, 117.8, 76.8, 43.1, 24.8, 21.5, 14.7, 11.4, 9.7, 9.6; HRMS (ESI) *m/z* 323.1623, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.21. syn-**23** (R = m-MeC$_6$H$_4$).*

white solid (for anionic conditions: 13 mg, 23% yield): R_f = 0.25 (1:1 hexane/EtOAc); mp 97–99 °C; IR (neat) 3370, 1653, 1589, 781 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.12–6.96 (m, 4H), 4.78 (br d, *J* = 8.1 Hz, 1H), 3.30 (dq, *J* = 8.1, 6.9 Hz, 1H), 2.58 (q, *J* = 7.7 Hz, 2H), 2.26 (s, 3H), 1.87 (s, 3H), 1.70 (s, 3H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 7.7 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.8, 163.4, 142.0, 137.8, 128.8, 128.1, 126.4, 122.9, 118.9, 117.7, 76.9, 43.4, 34.8, 24.8, 21.4, 14.6, 11.5, 9.6, 9.5; HRMS (ESI) *m/z* 323.1645, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.22. anti-**24** (R = o-MeC$_6$H$_4$).*

colorless crystals (for anionic conditions: 27 mg, 50% yield): R_f = 0.28 (1:1 hexane/EtOAc); mp 129–131 °C; IR (neat) 3369, 1653, 1589, 760 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.41–7.13 (m, 4H), 5.16 (br d, *J* = 8.4 Hz, 1H), 3.37 (dq, *J* = 8.4, 7.0 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 1.93 (s, 3H), 1.93 (s, 3H), 1.25 (t, *J* = 7.7 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.9, 163.4, 140.2, 135.2, 130.4, 127.7, 126.4, 126.0, 119.8, 117.8, 72.5, 42.9, 24.8, 19.5, 14.5, 11.3, 9.7, 9.6; HRMS (ESI) *m/z* 323.1630, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.23. syn-**24** (R = o-MeC$_6$H$_4$).*

white solid (for anionic conditions: 23 mg, 42% yield): R_f = 0.36 (1:1 hexane/EtOAc); mp 99–101 °C; IR (neat) 3371, 1651, 1589, 758 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.41–7.01 (m, 4H), 5.08 (br d, *J* = 8.1 Hz, 1H), 3.35 (dq, *J* = 8.1, 6.8 Hz, 1H), 2.61 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.55 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.17 (s, 3H), 1.87 (s, 3H), 1.63 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.8, 163.4, 140.2, 134.5, 130.4, 127.6, 126.1, 126.0, 118.9, 117.8, 72.4, 42.5, 24.8, 18.9, 14.5, 11.4, 9.6, 9.4; HRMS (ESI) *m/z* 323.1628, calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623.

*4.4.24. anti-**25** (R = o-BrC$_6$H$_4$).*

colorless crystals (for anionic conditions: 22 mg, 33% yield; for Mukaiyama aldol-type reaction conditions: 22 mg, 28% yield): R_f = 0.16 (1:1 hexane/EtOAc); mp 140–142 °C; IR (neat) 3350, 1651, 1587, 756 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.32 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.16 (dt, *J* = 1.8, 7.6 Hz, 1H), 5.37 (br dd, *J* = 7.1, 3.8 Hz, 1H), 3.45 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.95 (s, 3H), 1.77 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 164.1, 162.6, 141.1, 132.6, 129.3, 128.0, 127.8, 122.7, 117.8, 74.9, 42.2, 24.9, 14.6, 11.3, 9.6, 9.5; HRMS (ESI) *m/z* 387.0581, calcd for $C_{18}H_{21}O_3BrNa$ $[M+Na]^+$ 387.0572

*4.4.25. syn-**25** (R = o-BrC$_6$H$_4$).*

white solid (for anionic conditions: 44 mg, 66% yield; for Mukaiyama aldol-type reaction conditions: 20 mg, 26% yield): R_f = 0.21 (1:1 hexane/EtOAc); mp 138–141 °C; IR (neat) 3352, 1649, 1587, 756 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.27 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.07 (dt, *J* = 1.6, 7.7 Hz, 1H), 5.24 (br dd, *J* = 7.1, 3.8 Hz, 1H), 3.41 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.60 (q, *J* = 7.7 Hz, 2H), 1.86 (s, 3H), 1.71 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.7 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.7, 164.2, 163.3, 141.1, 132.5, 129.1, 128.4, 127.4, 122.1, 118.9, 117.7, 74.4, 41.7, 24.9, 13.5, 11.3, 9.6, 9.5; HRMS (ESI) *m/z* 387.0563, calcd for $C_{18}H_{21}O_3BrNa$ $[M+Na]^+$ 387.0572.

*4.4.26. anti-**26** (R = Mes).*

colorless crystals (for anionic conditions: 18 mg, 30% yield; for Mukaiyama aldol-type reaction conditions: 17 mg, 26% yield): R_f = 0.39 (1:1 hexane/EtOAc); mp 148–149 °C; IR (neat) 3377, 1653, 1591, 850 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.39 (br d, *J* = 10.0 Hz, 1H), 3.74 (dq, *J* = 10.0, 7.0 Hz,

1H), 2.69 (q, *J* = 7.7 Hz, 2H), 2.49 (br s, 6H), 2.27 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.29 (t, *J* = 7.7 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.6, 164.1, 163.7, 137.1, 136.5, 134.0, 131.0, 119.6, 117.8, 72.6, 40.4, 24.9, 20.9, 20.8, 14.8, 11.2, 9.8, 9.6; HRMS (ESI) *m/z* 351.1936, calcd for $C_{21}H_{28}O_3Na$ $[M+Na]^+$ 351.1936.

*4.4.27. syn-**26** (R = Mes).*

colorless crystals (for anionic conditions: 37 mg, 63% yield; for Mukaiyama aldol-type reaction conditions: 12 mg, 18% yield): R_f = 0.49 (1:1 hexane/EtOAc); mp 172–175 °C; IR (neat) 3392, 1651, 1593, 850 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.70 (s, 2H), 5.18 (br d, *J* = 10.5 Hz, 1H), 3.68 (dq, *J* = 10.5, 6.8 Hz, 1H), 2.64 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.56 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.26 (br s, 6H), 2.17 (s, 3H), 1.89 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.5, 163.8, 163.0, 136.9, 136.0, 134.4, 130.0, 119.7, 117.8, 72.8, 40.5, 24.8, 20.7, 20.4, 15.1, 11.4, 9.6, 9.0; HRMS (ESI) *m/z* 351.1933, calcd for $C_{21}H_{28}O_3Na$ $[M+Na]^+$ 351.1936.

*4.4.28. anti-**32** (R = trans-$CH_3CH=CH-$).*

colorless oil (for Mukaiyama aldol-type reaction conditions: 18 mg, 35% yield): R_f = 0.22 (1:1 hexane/EtOAc); IR ($CHCl_3$) 3404 (br), 1712, 1654, 1593, 1428, 1379 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.50 (ddd, *J* = 15.2, 7.9, 1.6 Hz, 1H), 4.20 (dd, *J* = 8.2, 7.9 Hz, 1H), 3.04 (dq, *J* = 8.2, 7.1 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.98 (s, 3H), 1.93 (s, 3H), 1.73 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H), A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.8, 164.1, 163.8, 131.6, 129.7, 119.5, 117.9, 75.3, 41.6, 24.8, 17.8, 14.4, 11.3, 9.6, 9.5; HRMS (ESI) *m/z* 273.1446, calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467.

*4.4.29. syn-**32** (R = trans-$CH_3CH=CH-$).*

colorless oil (for Mukaiyama aldol-type reaction conditions: trace): R_f = 0.31 (1:1 hexane/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.63 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.41 (ddd, *J* = 15.4, 7.3, 1.6 Hz, 1H), 4.22 (dd, *J* = 7.4, 7.3 Hz, 1H), 3.06 (dq, *J* = 7.4, 7.0 Hz, 1H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.96 (s, 3H), 1.94 (s, 3H), 1.62 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), A signal due to one proton (OH) was not observed; HRMS (ESI) *m/z* 273.1456, calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467.

*4.4.30. anti-**33** (R = $CH_2=C(CH_3)-$).*

colorless oil (for Mukaiyama aldol-type reaction conditions: 14 mg, 28% yield): R_f = 0.26 (1:1 hexane/EtOAc); IR ($CHCl_3$) 3404 (br), 1720, 1653, 1593, 1460, 1428, 1378 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.05–5.00 (m, 1H), 5.00–4.95 (m, 1H), 4.24 (d, *J* = 9.2 Hz, 1H), 3.14 (dq, *J* = 9.2, 7.0 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.99 (s, 3H), 1.93 (s, 3H), 1.79–1.76 (m, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.8, 164.2, 163.8, 144.8, 119.8, 117.9, 114.8, 78.6, 38.9, 24.8, 16.3, 14.8, 11.3, 9.7, 9.5; HRMS (ESI) *m/z* 273.1457, calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467.

*4.4.31. syn-**33** (R = $CH_2=C(CH_3)-$).*

colorless oil (for Mukaiyama aldol-type reaction conditions: 3.4 mg, 7% yield): R_f = 0.36 (1:1 hexane/EtOAc); IR ($CHCl_3$) 3400 (br), 1722, 1653, 1593, 1455, 1428, 1379 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.90–4.85 (m, 1H), 4.81–4.77 (m, 1H), 4.29 (d, *J* = 8.2 Hz, 1H), 3.14 (dq, *J* = 8.2, 6.9 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.92 (s, 3H), 1.69–1.65 (m, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H), A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.9, 164.2, 164.0, 145.2, 118.5, 117.9, 113.2, 78.0, 39.7, 24.7, 17.4, 14.3, 11.3, 9.7, 9.5; HRMS (ESI) *m/z* 273.1455, calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467.

*4.4.32. Mono-methylated compound **28**.*

To a stirred solution of 2,6-diethyl-3,5-dimethyl-4-pyrone (**11**) (18.0 mg, 0.100 mmol) in THF (0.5 mL) was added NaHMDS (1.0 M solution in THF, 0.10 mL, 0.100 mmol) at –78 °C. After being stirred at –78 °C for 1 h, methyl iodide (9.00 μl, 0.140 mmol) was added. The mixture was stirred at –78 °C for 2.5 h, diluted with saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (6 g, hexane–EtOAc 3:1 → 1:1) to give methylated γ-pyrone **28** (15.3 mg, 79%) as a colorless oil: R_f = 0.60 (1:1 hexane–EtOAc); IR ($CHCl_3$) 1655, 1587, 1467, 1429, 1378 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.10 (qq, *J* = 6.9, 6.9 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.94 (s, 3H), 1.93 (s, 3H), 1.26–1.15 (m, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.8, 166.6, 163.9, 117.6, 116.7, 30.0, 24.8, 19.8 (2C), 11.3, 9.6, 9.3; HRMS (ESI) *m/z* 217.1186, calcd for $C_{12}H_{18}O_2Na$ $[M+Na]^+$ 217.1204.

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Supplementary data

Supplementary data related to this article can be found, in the online version, at doi:XX.XXXX/j.tet.XXXX.XX.XXX.

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