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Aldol-type reaction of a 4-pyrone: a straightforward approach to 4-pyrone-containing natural products

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ABSTRACT

A straightforward approach to 4-pyrone-containing natural products has been developed, which includes an aldol-type reaction between 2,6-diethyl-3,5-dimethyl-4-pyrone and aldehydes. The counter cation of the carbanion of the pyrone was found to play an important role in this reaction.

Polyketide compounds with 4-pyrone moieties have been isolated from marine natural sources. These compounds show valuable biological activities represented by cytotoxic activity (Fig. 1).[1] Their structures and bioactivities have attracted the interest of synthetic chemists, and total synthesis has been achieved for some of them.[2]

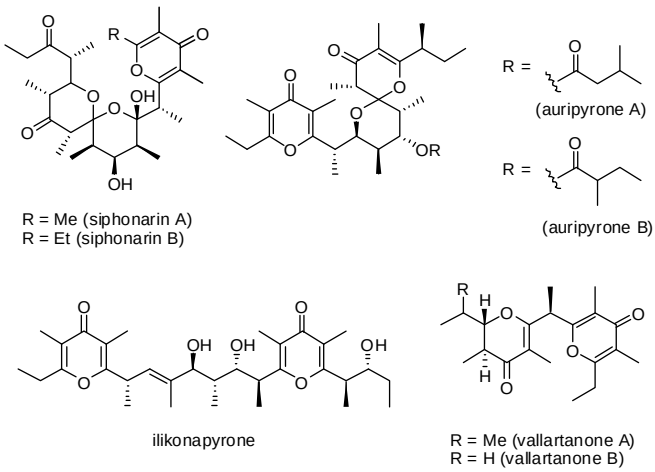
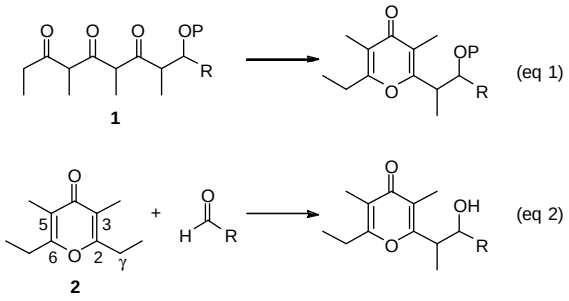


Figure 1. Natural products containing 4-pyrone.[1]

Generally, the synthesis of 4-pyrone-containing natural products is achieved via the dehydrative cyclization of long-chain triketones **1** as a precursor of the 4-pyrone moiety with a stoichiometric amount of reagents (Scheme 1, Eq. 1). Although this method has been well established[3] and a successful catalytic system has recently been reported,[4] the requirement of multisteps in linear synthetic sequence remains a significant problem.

Another approach is the installation of a side-chain into a 4-pyrone (Scheme 1, Eq. 2). This approach has the benefit of straightforward access even to complex molecules and the construction of two stereogenic centers at once. Although examples of alkylation at the γ-position of 4-pyrones have been reported,[5] to the best of our knowledge, aldol-type reactions have been demonstrated only for the simple 4-pyrone, 2,6-di-substituted-4-pyrone.[6] We now report an aldol-type reaction of the polypropionate-derived 4-pyrone, 2,6-diethyl-3,5-dimethyl-4-pyrone (**2**), as a substrate, which



Scheme 1. Approach to polypropionate-derived 4-pyrone.

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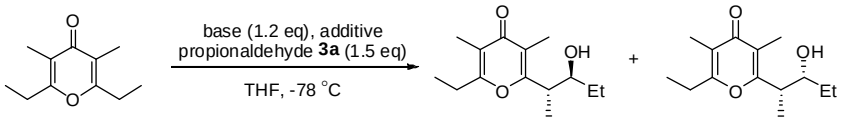
Table 1
Aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone **2** and propionaldehyde **3a**[a]



2 *anti*-**4a** *syn*-**4a**

Entry	Base	Additive (equiv)	Yield of **4a**[b] (%)	*anti*-**4a**:*syn*-**4a**[c]	Recovery of **2** (%)
1	LDA	—	45	3.1:1	11
2[d]	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	LiHMDS	—	69	2.9:1	17
6	LiHMDS	LiCl (8.0)	38	3.2:1	39
7	KHMDS	—	15	2.8:1	62
8	NaHMDS	—	76	2.8:1	12
9	NaHMDS	NaCl (8.0)	56	2.5:1	10
10	NaHMDS	15-Crown-5 (1.2)	9	1.3:1	69

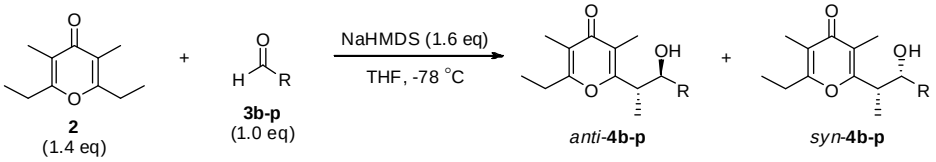
[a] Experimental conditions: After treatment of **2** (0.20 mmol) with base (0.24 mmol) in THF (1.0 ml) for 2 h at −78 °C, propionaldehyde (0.30 mmol) was added to the mixture, and the mixture was stirred for 3 h at the same temperature. The additive was added to the reaction mixture concurrently with corresponding base. Spectral data for **4a** are shown in Ref. 8.
[b] Combined yield of isolated *anti*- and *syn*-**4a**.
[c] The ratio was calculated from respective yields of *anti*- and *syn*-**4a**.
[d] The conditions described in Ref. 5 were applied.

will be applicable to the synthesis of naturally occurring 4-pyrone compounds, as shown in Figure 1.

We initially screened an assortment of bases and additives (Table 1). The configuration of diastereomers was determined by *J*-based configuration analysis.[7] Under the simple condition with lithium diisopropylamide (LDA), aldol adducts were obtained in moderate yield (entry 1), but this result was not reproducible. The addition of LiCl[6] or hexamethyl phosphoramide (HMPA) did not give improved results (entries 2 and 3). When the reaction was carried out with lithium tetramethylpiperidide (LTMP), **4a** was produced in only 9% yield (entry 4). When the reaction was carried out with lithium dialkylamide, pyrone **2** was decomposed and recovered in poor yield (trace-14%) except for the case of entry 3.

On the other hand, an appropriate amount of **2** was recovered in each reaction with metal bis(trimethylsilyl)amides. The reaction with lithium bis(trimethylsilyl)amide (LiHMDS) or potassium bis(trimethylsilyl)amide (KHMDS) gave the desired adduct in 69% or 15% yield, respectively (entries 5 and 7). The addition of LiCl did not give improved yield, but slightly advanced in diastereoselectivity (entry 6). The reaction with sodium bis(trimethylsilyl)amide (NaHMDS), which was revealed to be the most

Table 2
Aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone **2** and aldehydes **3**[a,b]

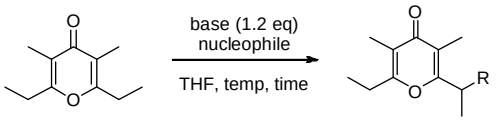


2 (1.4 eq) **3b-p** (1.0 eq) *anti*-**4b-p** *syn*-**4b-p**

Entry	R	Yield[c] (%)	*anti*-**4**:*syn*-**4**[d]
1	*n*-Pr (**3b**)	76 (**4b**)	2.9:1
2	*i*-Pr (**3c**)	57 (**4c**)	2.8:1
3	C_6H_{11} (**3d**)	64 (**4d**)	2.1:1
4	*t*-Bu (**3e**)	36 (**4e**)	2.6:1[e]
5	*trans*-$CH_3CH{=}CH$ (**3f**)	—[f]	—
6	$CH_2{=}CCH_3$ (**3g**)	—[f]	—
7	Ph (**3h**)	95 (**4h**)	2.4:1
8	*p*-$CH_3C_6H_4$ (**3i**)	92 (**4i**)	2.1:1
9	*p*-$CH_3OC_6H_4$ (**3j**)	94 (**4j**)	2.5:1
10	*p*-BrC_6H_4 (**3k**)	86 (**4k**)	1.9:1
11	*p*-$NO_2C_6H_4$ (**3l**)	30 (**4l**)	1.9:1
12	*m*-$CH_3C_6H_4$ (**3m**)	85 (**4m**)	2.7:1
13	*o*-$CH_3C_6H_4$ (**3n**)	92 (**4n**)	1.2:1
14	*o*-BrC_6H_4 (**3o**)	99 (**4o**)	0.5:1
15	Mesityl (**3p**)	93 (**4p**)	0.5:1

[a] All reactions were carried out with NaHMDS (0.29 mmol), **2** (0.27 mmol), and aldehyde (0.18 mmol).
[b] See experimental procedure in Ref. 9.
[c] Combined yield of isolated *anti*- and *syn*-**4**.
[d] The ratio was calculated from respective yields of *anti*- and *syn*-**4**.
[e] The ratio of *anti*- and *syn*-**4e** was calculated from ^{1}H NMR.
[f] 1,4-Adducts were obtained.

Table 3
Reaction with **2** and nucleophiles



2

Entry	Base	Nucleophile (equiv)	Temperature	Time (h)	Yield (%)
1	LDA	D_2O (excess)	−78 °C to rt	0.5	34[a] (59)[b]
2	LiHMDS	D_2O (excess)	−78 °C to rt	0.5	Quant.[a] (>95)[b]
3	KHMDS	D_2O (excess)	−78 °C to rt	0.5	Quant.[a] (>95)[b]
4	NaHMDS	D_2O (excess)	−78 °C to rt	0.5	Quant.[a] (>95)[b]
5	LDA	CH_3I (1.5)	−78 °C	3	10[c]
6	LiHMDS	CH_3I (1.5)	−78 °C	3	26[c]
7	KHMDS	CH_3I (1.5)	−78 °C	3	75[c]
8	NaHMDS	CH_3I (1.5)	−78 °C	3	79[c]

[a] Combined yield of isolated **2** and **5**.
[b] The percentage of deuterated compound **5** was determined by ^1H NMR.
[c] Isolated yield.

suitable base for this reaction, afforded **4a** in 76% yield with moderate diastereoselectivity (2.8:1) (entry 8), while the addition of NaCl had little effect (entry 9). The addition of 15-crown-5 disturbed the reaction and afforded **4a** in 9% yield (entry 10).

The generality of this reaction was then evaluated (Table 2). The configuration of the aliphatic adducts **4b–e** was determined by a comparison of spectral data with those of **4a**, and the configuration of aromatic adducts **4i–p** was determined by comparison with **4h**, whose structure was confirmed by X-ray crystallographic analysis. Saturated alkylaldehydes **3b–d** gave aldol adducts **4b–d** in moderate to good yields (57–76%) (entries 1–3). Pivalaldehyde **3e** showed somewhat lower reactivity and afforded **4e** in 36% yield (entry 4). The diastereomeric ratios of adducts were in the 2:1 to 3:1 range. In contrast, the reaction with unsaturated alkylaldehydes **3f** and **3g** predominantly afforded 1,4-adducts (entries 5 and 6). Among the aromatic aldehydes, both *para*- and *meta*-substituents did not affect the reaction (entries 7–10 and 12). When the reaction was carried out with *p*-nitrobenzene **3l**, decomposition of materials was observed on TLC, and adduct **4l** was obtained in only 30% yield (entry 11). The reaction with *ortho*-substituted aromatic aldehydes **3n–p** gave adducts **4n–p** in excellent yield (92–99%), whereas the diastereoselectivity varied widely depending on the *ortho*-substituents (entries 13–15). A sterically hindered substituent at the *ortho*-position tended to give adducts with *syn* selectivity.

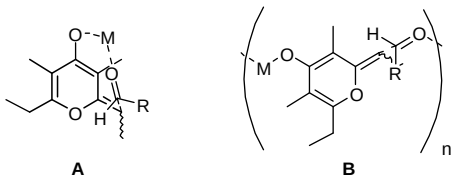
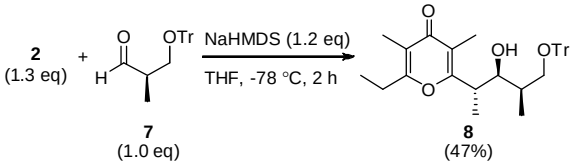


Figure 2. Plausible transition state model.



Scheme 2. Application to an optically active substrate **7**.

It is conceivable that the counter cation would affect deprotonation from **2** and/or activation of aldehydes. To probe the role of the counter cations in this aldol-type reaction, **2** was allowed to react with other nucleophiles (Table 3). D_2O and CH_3I, respectively, were employed as nucleophiles to obtain information about the degree of deprotonation and the nucleophilicity of the enolates. When the reaction was carried out with D_2O, the enolate generated from **2** and LDA was deuterated only in low yield (entry 1). However, each enolate prepared from **2** and metal bis(trimethylsilyl)amide gave **5** in nearly quantitative yields (entries 2–4). In the nucleophilic addition toward CH_3I, the reactions with KHMDS and NaHMDS gave mono-methylated compound **6** in good yields (entries 7 and 8), while the enolates generated with LDA and LiHMDS gave **6** in poor yields (entries 5 and 6). As expected from the results in Table 1, the reactions of the enolate generated with LDA gave the products in lower yields than those generated with bis(trimethylsilyl)amides due to the decomposition of the anion species. It is interesting that the reactivity of metal enolates of **6** prepared with bis(trimethylsilyl)amides was changed significantly depending on the nature of the metal counterion and electrophile (see also Table 1, entries 5–7).

The results shown in Table 3 indicate that counter cations will not participate in the deprotonation step, but in the activation of aldehydes. From these results, we suggest two plausible transition states (Fig. 2). Both involved the coordination of the aldehyde to the metal ion.[10]

Finally, we applied this aldol-type reaction to an optically active aldehyde **7**[11] for the preliminary study of natural product synthesis (Scheme 2). The adduct was obtained as a mixture of diastereomers in 68% yield. After purification via silica gel column chromatography, an adduct **8**,[12] the building block of auripyrones and ilikonapyrone shown in Figure 1, was obtained in 47% yield, and the other adducts were obtained as the inseparable mixture in 21% yield.

In conclusion, we have demonstrated an efficient aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone. The diastereomeric ratio of adducts was influenced by steric factors around the aldehyde, especially on *ortho*-substituted benzaldehydes. We expect that this reaction may be potentially applicable to the synthesis of 4-pyrone-containing natural products.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.017.

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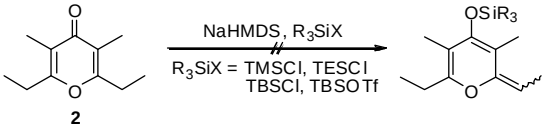
8. *Spectral data*: *anti*-**4a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.72 (br m, 1H), 3.04 (quint, J = 7.2 Hz, 1H), 2.62 (q, J = 7.6 Hz, 2H), 1.98 (s, 3H), 1.95 (s, 3H), 1.60–1.72 (m, 1H), 1.32–1.51 (m, 1H), 1.22 (t, J = 7.6 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) 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; IR (neat) 3392, 1653, 1593 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}O_3Na$ (M+Na)$^+$ 261.1467, found 261.1471. *syn*-**4a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.73 (br m, 1H), 2.98 (quint, J = 7.0 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 1.97 (s, 3H), 1.94 (s, 3H), 1.35–1.55 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H), 1.21 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (68 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; IR (neat) 3400, 1650, 1592 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}O_3Na$ (M+Na)$^+$ 261.1467, found 261.1462.
9. *Typical procedure for aldol-type reaction*: After treatment of **2** (0.27 mmol) with NaHMDS (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*-**4** and *syn*-**4**.
Selected spectral data: *anti*-**4h**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 4.79 (br d, J = 8.6 Hz, 1H), 3.30 (dq, J = 8.6 Hz, 7.0 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); ^{13}C NMR (68 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; IR (neat) 3369, 1653, 1589, 762, 702 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}O_3Na$ (M + Na)$^+$ 309.1467, found 309.1474.
syn-**4h**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.18–7.23 (m, 5H), 4.82 (br d, J = 8.1 Hz, 1H), 3.30 (dq, J = 8.1 Hz, 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); ^{13}C NMR (68 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; IR (neat) 3369, 1651, 1589, 760, 702 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}O_3Na$ (M+Na)$^+$ 309.1467, found 309.1469.
10. To provide further insight into the reaction, we tried to trap the enolate as the corresponding silyl ether. However, this attempt resulted in failure, presumably due to the instability of the silyl ethers



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12. The configuration of **8** was determined by ^{1}H NMR and NOESY correlations with the corresponding acetonide derivative