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Synthesis of Δ^7-prostaglandin A_1 methyl ester

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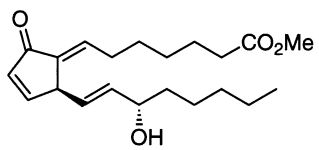
Abstract—Aldol reaction at the α′ position of 4-alkenyl cyclopentenone was investigated briefly in order to develop a synthesis of the target molecule. The efficient reaction conditions we found (LDA at −78°C in THF) were applied to the reaction between the cyclopentenone possessing the ω-chain and the α-chain aldehyde to afford the *anti* and *syn* aldols in 73 and 15% yields, respectively. Mesylation of the *anti* aldol followed by elimination of the mesyloxy group and desilylation of the TBS-oxy group at C(15) furnished the title molecule, which was also produced from the *syn* aldol in good yield.

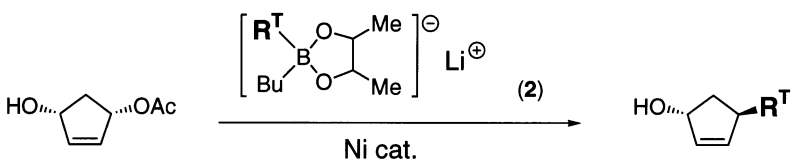
Recently, we reported the reaction of sp^2-carbon-based nucleophiles (aryl and alkenyl groups) and cyclopentenediol monoacetate **1** to produce substituted cyclopentenols **3** (Eq. (1)).[1] The major advantages of this reaction are that: (1) the reaction proceeds efficiently with only 1.2–1.8 equiv. of lithium borates **2** because the borates are not quenched by the hydroxyl group in the substrate **1**; and (2) both enantiomers of **1** can be prepared easily (the (1*S*,3*R*)-isomer is shown in Eq. (1)). In addition, most of the reaction products **3** were unregistered previously in CAS. Thus, it is quite certain that **3** is of potential use as a new starting compound for asymmetric synthesis of cyclopentanoids.[2] This possibility has been demonstrated by efficient and stereoselective synthesis of the primary prostaglandin (PG) intermediates[1b] and aristeromycin.[3]

Herein, we present another example: that is, a synthesis of Δ^7-prostaglandin A_1 methyl ester (**4**), which is an artificial PG introduced by the Noyori group[4] and which possesses antitumor activity.[5]

According to Noyori, the alkylidene cyclopentenone chromophore is the key structure responsible for the



Δ^7-Prostaglandin A_1 Methyl Ester (**4**)



1 **3**

R^T: aryl, alkenyl

(1)

Keywords: aldol reactions; cyclopentenones; nickel and compounds; prostanoids.

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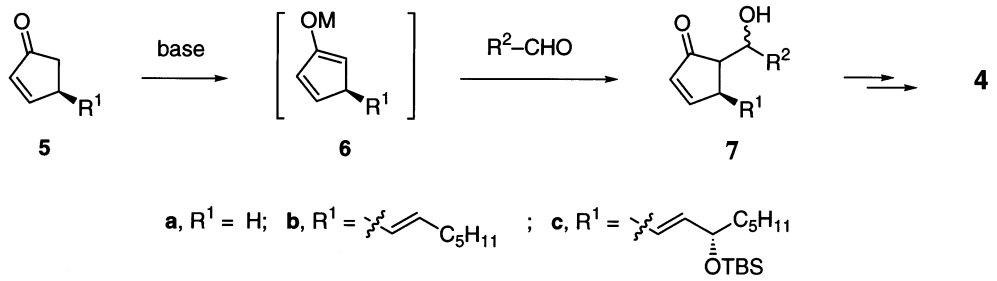
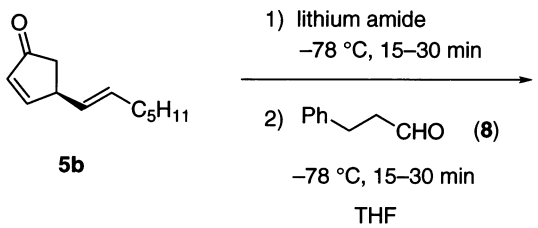


Scheme 1. A strategy for the synthesis of Δ^7-PGA$_1$ methyl ester (**4**).

biological activity,[6,7] and is constructed by the 1,4-addition of organocopper reagents onto 4-silyloxy-2-cyclopenten-1-one followed by aldol reaction with the α-chain aldehyde and subsequent dehydration.[4]

We envisioned that installation of the α′ and β′ side chains onto cyclopentenones would be attained regioselectively by aldol reaction of **5c** possessing the PG ω-chain (R^1=(*E*)-CH=CHCH(OTBS)C_5H_{11}) with an aldehyde corresponding to the α-side chain, and that subsequent dehydration of the resulting aldol **7c** would produce the target molecule (Scheme 1). The key anion **6c**, which should be generated from **5c**, is one of the α′ enolates derived from the α,β-unsaturated carbonyl compounds. Although the α′ enolates derived from cyclohexenones have been utilized extensively in organic synthesis,[8] enolates generated from cyclopentenones have been studied only with 2-cyclopenten-1-one (**5a**) (R^1=H)[9] and the rather specific cyclopentenones (structures not shown).[10] In addition to these limited examples, the conditions used for the preparation of the enolate from **5a** are different. Namely, D. W. Brown used LDA,[9a] while M. Shibasaki found that Zr(O-*i*-Pr)$_4$ is a better base than LDA though the yield of the product (aldol) was moderate in his case.[9b] We were concerned that those results would cause a little confusion when applied to the full-scale synthesis of compound **5c**. Consequently, aldol reaction of substituted enone **5b**, prepared in 71% yield by PCC oxidation of the corresponding alcohol **3b** (R^T=(*E*)-CH=CHC_5H_{11}), was preliminarily investigated with aldehyde **8** in order to obtain relevant information for the synthesis of **4** (Eq. (2)).

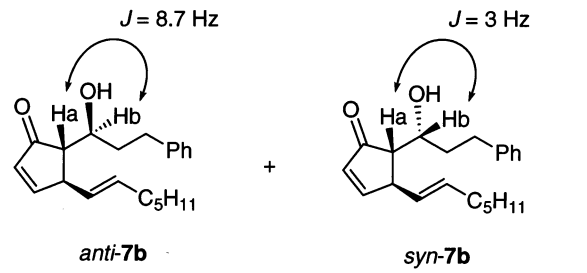


Lithium amide	Yield (%)	*anti*:*syn*
LDA	85	2:1
LiN(*c*-Hex)(*i*-Pr)	88	4.8:1
Li(TMS)$_2$	86	3.5:1

We examined LDA, LiN(*c*-C_6H_{11})(*i*-Pr), and LiN(TMS)$_2$ as bases for the aldol reaction. Enone **5b** was treated with base at −78°C for 20–30 min in THF and then aldehyde **8** was added to the solution at the same temperature. The reaction was completed within 30 min (checked by TLC) to furnish a mixture of the aldols *anti*-**7b** and *syn*-**7b** in reasonable yields. It should be noted that longer reaction times (>60 min) and/or higher temperatures (>−50°C) for the anion generation decreased the yield of the aldol, thus indicating the somehow unstable nature of the α′ enolate. The *anti* and *syn* stereochemistry for the major and minor aldols was determined on the basis of the coupling constants between Ha and Hb of *anti*-**7b** (J_{Ha-Hb}=8.7 Hz) and *syn*-**7b** (J_{Ha-Hb}=3 Hz) in the ^{1}H NMR (300 MHz) spectra,[11] and the selective production of the *anti* isomer **7b** was consistent with the chair-like cyclic transition state involving the lithium enolate and the aldehyde. Aldol reaction of **5b** with other aldehydes (*i*-PrCHO, PhCHO, PhCH=CHCHO) was examined with LDA to furnish the corresponding aldols, in which the *anti* isomers were the major stereoisomers (Eq. (3)).

(3)

R	Yield (%)	*anti*:*syn*
i-Pr	66	>20:1
Ph	75	1.6:1
(*E*)-CH=CHPh	65	1.7:1

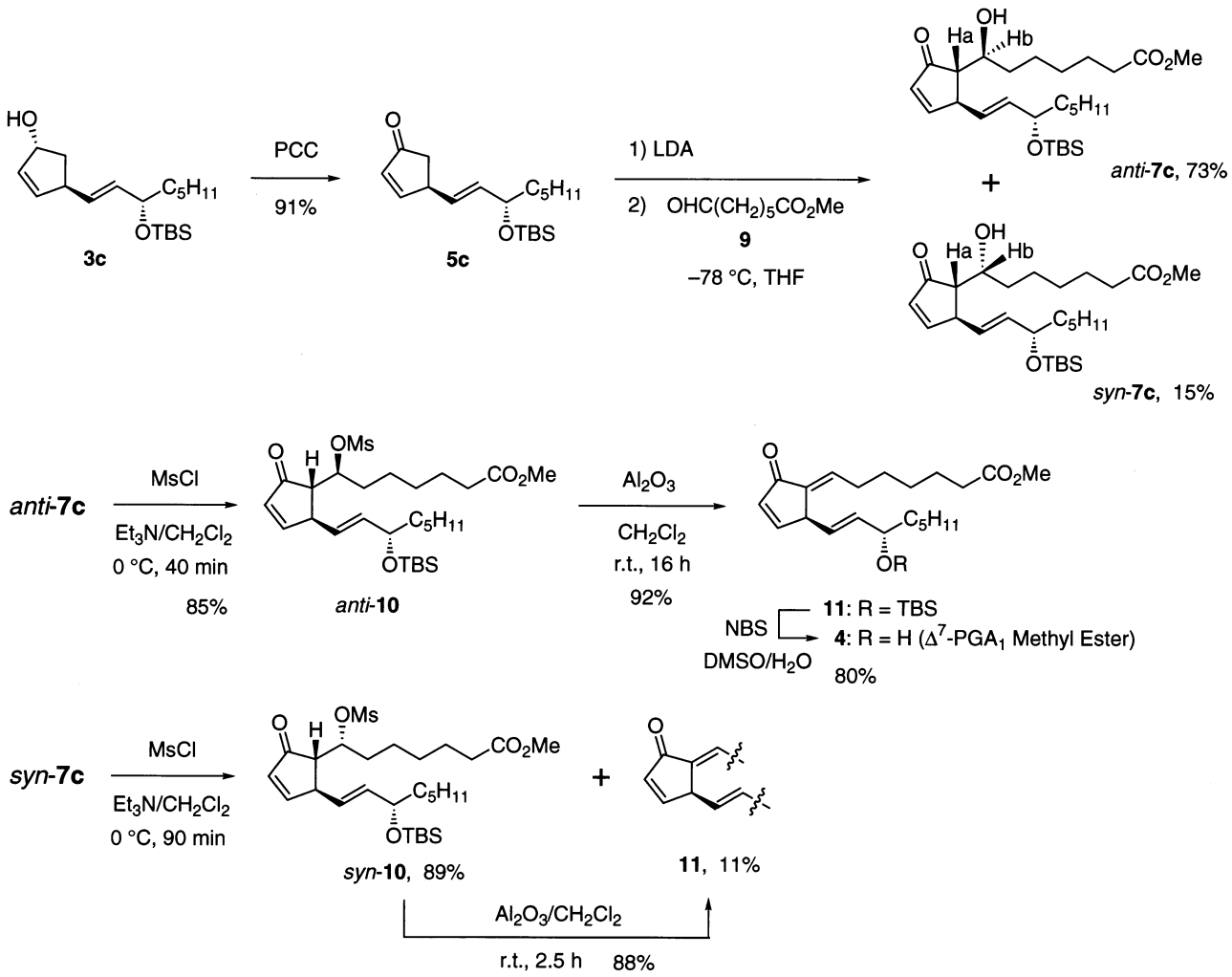


(2)

With the above results in mind, synthesis of the prostaglandin **4** was investigated and the results are summarized in Scheme 2. Enantiomerically enriched alcohol **3c** was prepared according to the reaction shown in Eq. (1) with (1*S*,3*R*)-**1**[12] (>99% ee) and the corresponding lithium borate (>99% ds at C(15), structure not shown) as reported earlier.[1b] Oxidation of **3c**

with PCC afforded enone **5c** in 91% yield. Aldol reaction of **5c** with aldehyde **9** was carried out under the conditions optimized for the model aldol reaction (Eq. (2)) to produce a mixture of the *anti* and *syn* aldols **7c** in 73 and 15% yields, respectively, after chromatography ($J_{Ha-Hb}=9$ Hz for *anti*-**7c**, 3 Hz for *syn*-**7c**).[13] Subsequently, dehydration of **7c** was examined through the mesylate. Mesylate *anti*-**10**, prepared from the major aldol (*anti*-**7c**) with MsCl and Et_3N in 85% yield, was treated with Et_3N in CH_2Cl_2 at room temperature. However, no elimination of the mesyloxy group was induced under these conditions. The use of other amines, such as DBU, *i*-Pr_2NEt and DMAP, was also insufficient. Fortunately, this conversion was accomplished with Al_2O_3[14] (Alumina N-Super I from ICN) in CH_2Cl_2 at room temperature for 16 h to furnish olefin **11** in good yield. The (*Z*) isomer of **11** was not detected by ^1H NMR spectroscopy or by TLC of the crude reaction product. The minor aldol (*syn*-**7c**), on the other hand, was converted into **11** within a shorter period of time. Thus, mesylation of *syn*-**7c** with MsCl and Et_3N at room temperature for 90 min produced a mixture of mesylate *syn*-**10** and olefin **11** in 89 and 11% yields, respectively, and elimination of the mesyloxy group in *syn*-**10** was completed within 2.5 h with Al_2O_3.

Different reactivity observed in the elimination of *anti*- and *syn*-mesylates **10** to afford (*E*)-olefin **11** is understood with the *syn* elimination (E1cB) and *anti* elimination (E2 or E1cB) mechanisms, respectively, though the *anti* elimination is a process generally more favorable. In the case of *anti*-**10**, *anti* elimination requires this mesylate to take the sterically-congested conformation **A** in which the C(1)–C(6) chain is projected in the direction of the carbonyl oxygen, thus increasing the activation energy for production of the (*Z*)-olefin (path A). The failure of the elimination with the amines we have examined is consistent with the difficulty of this process. Consequently, the course was replaced by the less common *syn* elimination to furnish **11** slowly, but efficiently through **B** which is probably assisted by coordination of the Al atom in Al_2O_3 to the oxygen of the Ms group (path B). On the other hand, conformer **C** of *syn*-**10**, being ready for the *anti* elimination, is sterically less congested (path C), and Al_2O_3 triggered off the elimination to furnish (*E*)-olefin **11** (Fig. 1).



Scheme 2. Synthesis of Δ^7-prostaglandin A_1 methyl ester (**4**).

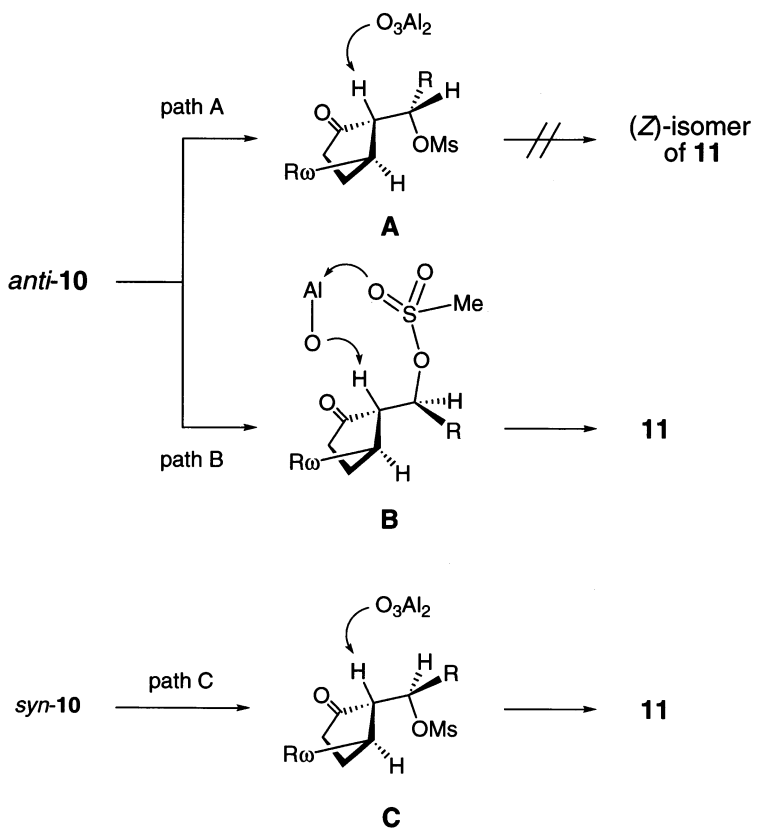


Figure 1. Transition-state conformers **A** and **B** for *anti*-**10**, and **C** for *syn*-**10**. R: $(CH_2)_5CO_2Me$, Rω: CH=CHCH(OTBS)C_5H_{11}.

Finally, deprotection[15] of the TBS group with NBS[16] in aqueous DMSO furnished the target compound **4** in 80% yield: $[\alpha]_D^{26}=+165$ (*c* 0.13, $CHCl_3$). The ^1H NMR spectrum of the synthetic PG **4** was identical with that of the enantiomer reported by the Noyori group.[5b]

Acknowledgements

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13. To a solution of LDA, prepared from *i*-Pr_2NH (0.054 mL, 0.38 mmol) and *n*-BuLi (0.14 mL, 2.26 M in hexane, 0.32 mmol) in THF (7.4 mL), was added enone **5c** (95.0 mg, 0.295 mmol) dissolved in THF (2 mL) at −78°C. The solution was stirred for 10 min at −78°C and then aldehyde **9** (56 mg, 0.37 mmol) was injected. After 20 min at −78°C, the solution was poured into an ice-cold mixture of Et_2O and saturated NH_4Cl with vigorous stirring. Isolation as usual and purification by chromatography furnished *anti*-**7c** (103 mg, 73%) and *syn*-**7c** (21 mg, 15%). *anti*-**7c**: ^{1}H NMR δ 0.007 (s, 3 H), 0.036 (s, 3 H), 0.88 (br s, 12 H), 1.2–1.7 (m, 16 H), 2.10 (dd, $J=9$, 3 Hz, 1 H), 2.30 (t, $J=8$ Hz, 2 H), 3.19–3.27 (m, 1 H), 3.66 (s, 3 H), 3.68–3.76 (m, 1 H), 4.04–4.13 (m, 2 H, C(15)-H and OH), 5.49 (dd, $J=16$, 8 Hz, 1 H), 5.60 (dd, $J=16$, 6 Hz, 1 H), 6.18 (dd, $J=6$, 2 Hz, 1 H), 7.52 (dd, $J=6$, 2 Hz, 1 H); ^{13}C NMR δ 212.9, 174.4, 167.1, 136.8, 133.2, 128.2, 72.8, 72.1, 56.4, 51.5, 47.7, 38.2, 35.5, 34.0, 31.8, 29.1, 25.9, 24.87, 24.83, 22.6, 18.2, 14.0, −4.3, −4.8. *syn*-**7c**: ^{1}H NMR δ 0.005 (s, 3 H), 0.033 (s, 3 H), 0.88 (br s, 12 H), 1.1–1.7 (m, 16 H), 1.84–1.90 (m, 1 H), 2.17 (t, $J=3$ Hz, 1 H), 2.30 (t, $J=8$ Hz, 2 H), 3.66 (s, 3 H), 3.58–3.70 (m, 1 H), 4.07 (q, $J=6$ Hz, 1 H), 4.12–4.24 (m, 1 H), 5.50 (dd, $J=15$, 8 Hz, 1 H), 5.60 (dd, $J=15$, 6 Hz, 1 H), 6.18 (dd, $J=6$, 2 Hz, 1 H), 7.55 (dd, $J=6$, 3 Hz, 1 H); ^{13}C NMR δ 211.0, 174.4, 167.6, 136.4, 133.7, 129.1, 73.0, 70.4, 57.6, 51.5, 44.9, 38.2, 34.8, 34.0, 31.8, 28.9, 25.87, 25.81, 24.88, 24.82, 22.6, 18.2, 14.0, −4.3, −4.8.
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