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A NEW SYNTHETIC ROUTE OF COREY LACTONE HAVING ω-SIDE CHAIN

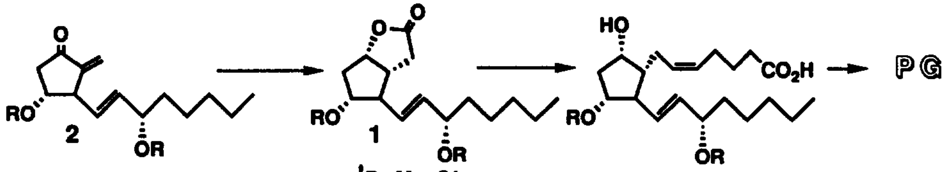
Katsuaki Miyaji, Yoshio Ohara, Yuka Miyauchi, Toshihiko Tsuruda
and Kazutaka Arai*.

Central Research Institute, Nissan Chemical Ind.Ltd.,
Tsuboi, Funabashi, Chiba 274, Japan

Abstact: Corey lactone having ω-side chain **1a** is an important intermediate for syntheses of prostaglandins. Now we have succeeded in developing a new synthetic route of **1a** from methylenecyclopentanone having ω-side chain **2a**. The new synthetic route has two crucial steps as follows. 1) Hydroxymethyl unit introduction by using organozinc reagent. 2) Oxidation of diol to lactone by using N-oxoammonium salt in combination with sodium bromite.

Corey lactone is one of the most important key intermediates in prostaglandin syntheses because of the wide applicability and availability[1]. Especially Corey lactone having ω-side chain **1a** is very versatile because we can build prostaglandin skeleton with four chiral centers by only two steps from **1a**[1]. In this report we introduce a new synthetic route to **1a** from cyclopentanone having ω-side chain **2a**, which we had developed[2] (Scheme 1). Umemoto had reported a synthetic route to **1b** (R=ethoxyethyl) from **2b** (R=Ethoxyethyl) in 1978[3]. When we applied this route to t-butyldimethylsilyl protected cyclopentanone **2a**, yield of the last step of this route, Neff reaction, was lower (c.a. 50%) than reported on ethoxyethyl protected cyclopentanone. This phenomenon is thought to be due to unstability of silyl group under Neff reaction condition ($TiCl_4$, $AcONH_4$ / $AcOH$-H_2O). Though we tried some modification of reaction conditions for optimization of yield, we could not improve it . Finally we have succeeded in developing a new synthetic route.

Scheme 1



a=ᵗBuMe₂Si
b=Ethoxyethyl

A new synthetic route is shown in Scheme 2. The first crucial step of this route is introduction of a hydroxymethyl unit using functionalized zinc-copper reagent. The preparation of the organozinc compound **3** and its 1,4-addition reaction to **2a** via organocopper compound was carried out according to the Knochel's method[4]. Thus the enone **2a** was reacted with copper reagent of **3** in the presence of Me_3SiCl to provide the silyl enol ether **4**, which on work up with aqueous HCl provided the ketone **5** having the hydroxymethyl unit in 83% yield. In this step, we could not isolate the β-isomer of **5**, which was formed in only trace amount.

The results of the selective reduction of carbonyl group on 5-membered ring are summarized in Table 1. Yamamoto-Ono reduction[5] of **5** gave the desired α-alcohol **6** in 81% and its isomer **7** in 6% yield. Though Selectride® reduction[6] gave no β-isomer **7**, a new byproduct was formed. Especially in the K-Selectride® reduction, the byproduct was produced in 17 % yield even when the reaction was quenched at -78 °C. The structure of this byproduct was assigned to be **8** by ^{1}H-NMR, ^{13}C-NMR and MS analyses. The byproduct **8** was assumed to be formed via the enone **9** based on the following observation. The isolation of the enone **9** in 10% yield in K-Selectride® reduction at -78°C. The correlation between the basicity of reagents and the yields of **8** (K-Selectride®>L-Selectride®>$NaBH_4$>>Y.O. Reduction). The yield of the desired α-alcohol **6** was maximum when using L-Selectride® was used at -78 °C.

Table 1. Selective reduction of 5.

Reagent	Equivalent	Condition	Yield of 6	Yield of 7	Yield of 8
Y.O. reduction	10 eq	-78 to 0 °C	81%	6%	-
L-Selectride®	1.7 eq	-78 °C	89%	-	4%
	1.7 eq	-78 to 0 °C	80%	-	9%
K-Selectride®	1.7 eq	-78 °C	52%	-	17%
	1.7 eq	-78 to 0 °C	57%	-	21%
$NaBH_4$	4.0 eq	0 °C	52%	35%	12%

(All yields are the isolated yields by column chromatography.)

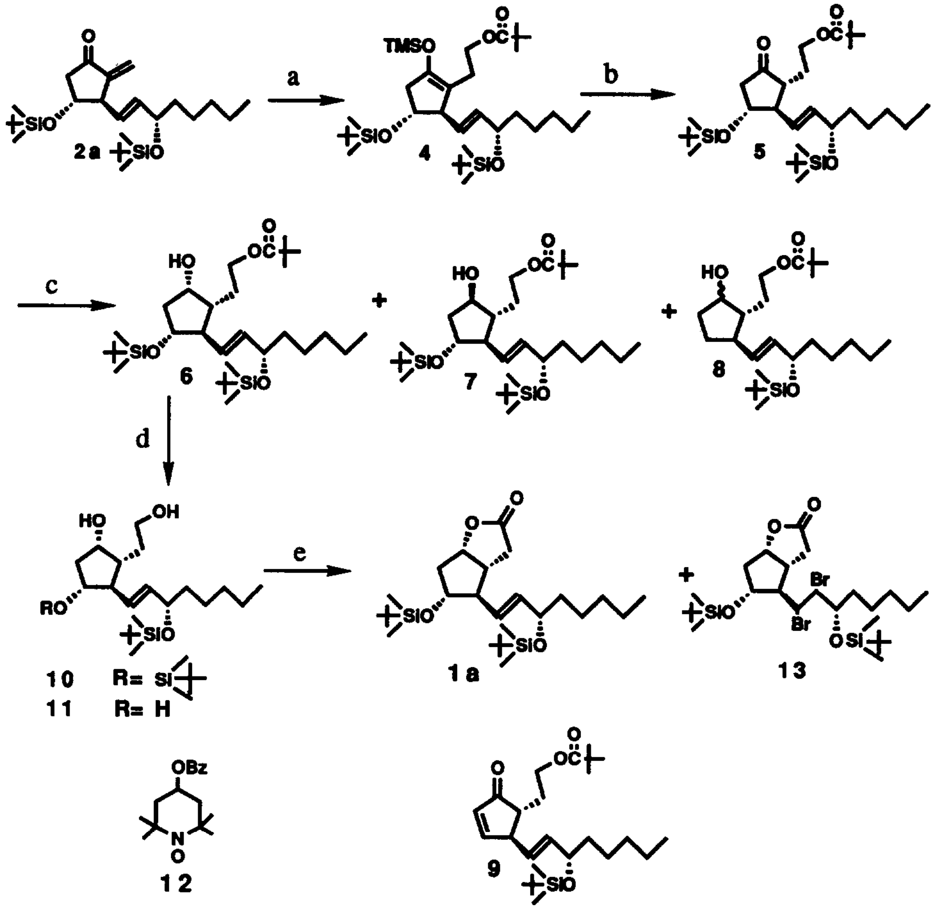
Removal of pivaloyl group of **6** with $LiAlH_4$ produced desired diol **10** only in 39% yield and undesired triol **11** in 34 % yield. After some examination, we found that DIBAH could remove the pivaloyl group without formation of **11** and gave the desired diol **10** in 86% yield.

The next crucial step of this route is derivation of **10** to the desired lactone **1a**. To this aim, we tried the new method reported by Torii, that could oxidize only primary hydroxy group in the presence of secondary hydroxy group and form lactone[7]. To our knowledge, this is the first application of Torii's method to diol having double bond in its molecule. The oxidation of the diol **10** with N-oxoammonium salt, activated from 4-benzoyloxy 2,2,6,6-tetramethylpiperidine-1-oxyl **12**, in combination with sodium bromite gave the desired lactone in high yield. But when we added sodium bromite into the reaction system at once, undesired lactone **13** was formed in 8% yield in addition to **1a** in 71% yield. So we tried some examination to avoid the formation of **13**, and found that gradual addition of sodium bromite gave only the desired lactone **1a** in 88 % yield.

Analytical and spectral data of this sample are all in complete agreement with those of an authentic sample synthesized by Umemoto's method.[8]

Thus we have succeeded in developing a new synthetic route of Corey lactone having ω-side chain.

Scheme 2



a) $IZnCH_2Opiv$ 3 (2eq), CuCN-2LiCl (2.3eq), TMSCl (1eq) in THF.
b) 1N HCl in MeOH-THF. 2 steps Y=83%.
c) Hydride reduction. The yield is shown in Table1.
d) DIBAH (3eq) in Toluene. Y=86%.
e) $NaBrO_2$ (4eq)-12 (cat) in CH_2Cl_2-$NaHCO_3$. Y=88%.

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8. ^{1}H-NMR ($CDCl_3$, 500 MHz) : δ -0.01, 0.02, 0.03, 0.04 (4s, 3Hx4), 0.86 (s, 9H), 0.87 (s, 9H), 1.10-1.20 (10H, m), 1.97 (2H, broud d), 2.23 (dt, 15.4 Hz, 6Hz), 2.40-2.55 (m, 2H), 2.60-2.70 (m, 1H), 2.74 (dd, 11Hz, 18 Hz, 1H), 3.96 (dd, 10.7Hz, 5.2 Hz), 4.03 (dd, 12.1Hz, 6.1 Hz, 1H), 4.93 (td, 7.1Hz, 2.3Hz, 1H), 5.36 (dd, 15.4Hz, 7.6Hz), 5.48 (dd, 15.4 Hz, 5.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 500MHz) : δ -4.82, -4.68, -4.63, -4.20, 14.11, 18.32, 22.69, 25.11, 25.80, 25.95, 31.85, 35.12, 38.46, 40.73, 42.38, 56.80, 72.97, 78.19, 83.51, 128.5, 135.9, 177.1. IR : 2920, 2840 and 1750 cm^{-1}. MS : M$^+$=496, M-Me=481, M-^{t}Bu=439.

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