

New α -methylidenecyclopentenone block from Corey lactone diol

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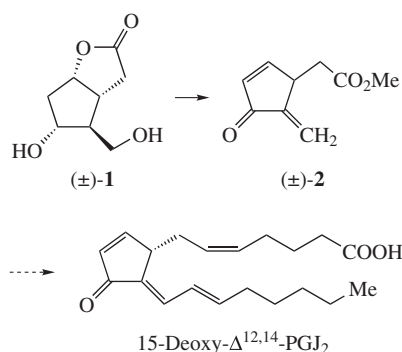
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Methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate was prepared from racemic Corey lactone diol in three steps in 82% overall yield.

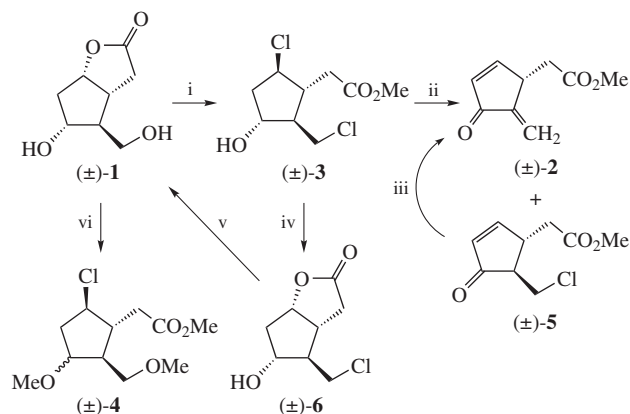
Corey lactone diol **1**¹ is a versatile intermediate for the synthesis of E-, F-prostaglandins (PG),² carbacycline³ carbanucleosides (Entecavir)⁴ and others. We have earlier reported on the successful resolution of racemic **1**.⁵ In this paper, we describe a simple and practical synthetic protocol for converting (\pm)-**1** into a new block **2** (Scheme 1), which may find application in access to a wide range of highly unsaturated antiviral and antitumor cyclopentenone prostaglandins,⁶ in particular Δ^{12} -PGJ₂,⁷ 15-deoxy- $\Delta^{12,14}$ -PGJ₂,⁸ marine prostanoids,⁹ as well as in the synthesis of didemnonones¹⁰ and several α -alkylidene cyclopentenone antibiotics and analogues.¹¹



Scheme 1

The principal reaction determining novelty and efficiency of conversion **1** \rightarrow **2** is an easy cleavage of lactone cycle **1** with methanolic HCl with the formation of methyl ester of dichlorocyclopentanol carboxylate **3** (Scheme 2). Solution of HCl was prepared by slow mixing MeOH and SOCl₂ at 0 °C (2:1, by volume). The reaction proceeds at room temperature within 6–7 h. To isolate the product partial neutralization of a reaction mixture up to pH ~6 is necessary. After the removal of the solvent the yield of dichloro ester **3**[†] is 92%. If the neutralization

[†] Methyl (5-chloro-2-chloromethyl-3-hydroxycyclopentyl)acetate **3**. A solution of **1** (1.6 g) in methanol (5 ml) at 0 °C was dropwise added to a solution of thionyl chloride (10 ml) in methanol (15 ml). The mixture was stirred at room temperature for 7 h, neutralized with saturated solution of NaHCO₃ to pH 6.5–7.0 and concentrated *in vacuo*. The residue was extracted with ethyl acetate and dried (Na₂SO₄). Concentration and purification by column chromatography (ethyl acetate–light petroleum, 1:1) afforded 2.1 g (92%) of methyl ester **3** as brown liquid, *R*_f = 0.4 (SiO₂, 50% EtOAc in hexane). ¹H NMR (500 MHz, CDCl₃) δ : 1.89–1.96 (br. s, 1H), 2.01–2.09 (m, 1H), 2.15 (ddd, 1H, *J* 6.4, 8.5 and 14.6 Hz), 2.23–2.34 (m, 2H), 2.58 (dd, 1H, *J* 7.0 and 16.2 Hz), 2.69 (dd, 1H, *J* 5.2 and 16.2 Hz), 3.59 (dd, 1H, *J* 7.0 and 11.0 Hz), 3.71 (s, 3H), 3.76 (dd, 1H, *J* 5.2 and 11.0 Hz), 4.22 (q, 1H, *J* 8.2 Hz), 4.28–4.35 (m, 1H). ¹³C NMR (125 MHz,



Scheme 2 Reagents and conditions: i, SOCl₂–MeOH (1:2), room temperature, 7 h, then NaHCO₃; ii, Jones oxidation, 1.5 h; iii, NEt₃, C₆H₆, room temperature, 8 h; iv, KOH, MeOH–H₂O, room temperature, 2 h, then H₃O⁺; v, KOH, MeOH–H₂O, reflux, 8 h, then H₃O⁺; vi, SOCl₂–MeOH (1:5), reflux, 2 h.

is avoided, during evaporation of MeOH acidity would rise and trimethoxy derivative **4**[‡] is rapidly formed. The same compound was obtained by refluxing **1** in less concentrated methanolic HCl (see Scheme 2).

The proof of β -orientation of chlorine atom in compound **3** was its transformations under basic conditions. At room temperature, hydrolysis of the ester group in **3** occurred resulting in S_N2-substitution of secondary chlorine atom with formation of lactone **6**.⁸ At reflux of any compound **3** or **6** in KOH–H₂O–MeOH solution the starting Corey lactone diol **1**[¶] was obtained.

As one can see from Scheme 2, conversion **1** \rightarrow **3** represents an excellent chemorational functionalization giving the opportunity

CDCl₃) δ : 35.8, 43.9, 45.9, 48.0, 51.9, 54.2, 60.3, 73.8, 172.4. IR (neat, ν /cm⁻¹): 3441, 2953, 1732, 1456, 1438, 1296, 1197, 1166, 1080, 727. MS, *m/z*: 239 [M–H, ³⁵Cl]⁺, 223, 169. Found (%): C, 44.55; H, 5.61; Cl, 29.25. Calc. for C₉H₁₄Cl₂O₃ (%): C, 44.83; H, 5.85; Cl, 29.41.

[‡] Methyl [5-chloro-3-methoxy-2-(methoxymethyl)cyclopentyl]acetate **4**. A solution of **1** (1.2 g) in methanol (10 ml) was added at 0 °C dropwise to a solution of thionyl chloride (5 ml) in methanol (15 ml). The mixture was stirred at reflux for 2 h and concentrated *in vacuo*. Purification by column chromatography (ethyl acetate–light petroleum, 1:3) afforded 1.5 g (85%) of compound **4**. Brown liquid, *R*_f = 0.4 (SiO₂, 25% EtOAc in hexane). ¹H NMR (500 MHz, CDCl₃) δ : 2.19–2.44 (m, 4H), 2.53 (dd, 1H, *J* 7.2 and 16.0 Hz), 2.68 (dd, 1H, *J* 4.8 and 16.1 Hz), 3.60 (dd, 1H, *J* 5.0 and 11.6 Hz), 3.62 (s, 3H), 3.64 (s, 3H), 3.69 (s, 3H), 3.80–3.85 (m, 1H), 4.15–4.19 (m, 1H), 4.89–4.94 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ : 35.35, 35.39, 42.33, 42.44, 44.25, 44.28, 46.68, 46.75, 48.33, 48.38, 48.66, 51.91, 51.95, 51.98, 59.39, 59.45, 74.21, 74.53, 171.85. IR (neat, ν /cm⁻¹): 2953, 1732, 1438, 1203, 958, 707. MS, *m/z*: 250 [M, ³⁵Cl]⁺. Found (%): C, 52.41; H, 7.47; Cl, 13.96. Calc. for C₁₁H₁₉ClO₄ (%): C, 52.70; H, 7.64; Cl, 14.14.

to apply tandem procedures ‘oxidation–elimination’ as a way to product **2**. Indeed, oxidation of compound **3** with Jones reagent proceeded rapidly and led to mixture **2** + **5** inseparable by column chromatography. Therefore, this mixture, without separation, was treated with triethylamine in benzene for 8 h affording smoothly the target cyclopentenone **2**.^{††}

[§] *4-Chloromethyl-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one 6*. A solution of **3** (0.2 g) in methanol (10 ml) was added to a 40% aqueous solution of KOH (2 ml) and stirred at room temperature for 2 h, acidified with 10% HCl to pH 2–3 and concentrated *in vacuo*. The residue was extracted with ethyl acetate and dried (Na₂SO₄). Concentration and purification by column chromatography (ethyl acetate–light petroleum, 1:3) afforded 0.15 g (94%) of compound **6**. Light yellow liquid, *R*_f = 0.6 (SiO₂, 25% hexane in EtOAc). ¹H NMR (300 MHz, CDCl₃) δ: 1.89–1.96 (br. s, 1H), 2.09 (dd, 1H, *J* 7.3 and 18.9 Hz), 2.20–2.26 (m, 1H), 2.48 (dt, 1H, *J* 6.4 and 15.0 Hz), 2.60 (d, 1H, *J* 17.4 Hz), 2.80–2.92 (m, 2H), 3.64 (d, 2H, *J* 5.5 Hz), 4.24 (q, 1H, *J* 6.1 Hz), 4.97 (td, 1H, *J* 2.5 and 6.7 Hz). ¹³C NMR (75 MHz, CDCl₃) δ: 35.33, 40.55, 40.58, 44.85, 55.25, 74.54, 83.23, 177.01. IR (neat, ν/cm⁻¹): 3423, 2922, 1762, 1444, 1359, 1296, 1180, 1166, 1089, 1037, 736. MS (ACPI), *m/z*: 191 [M+H, ³⁵Cl]⁺, 173, 157, 147. Found (%): C, 50.12; H, 5.80; Cl, 18.44. Calc. for C₈H₁₁ClO₃ (%): C, 50.41; H, 5.82; Cl, 18.60.

[¶] *Transformation of 3 into 1*. 40% aqueous solution of KOH (2 ml) was added to a solution of **3** (0.2 g) in methanol (10 ml) and the mixture was stirred for 8 h at reflux, then acidified with 10% HCl to pH 2–3 and concentrated *in vacuo*. The residue was extracted with CH₂Cl₂ and dried over Na₂SO₄. The extract was concentrated and purified by column chromatography (MeOH–CHCl₃, 1:3) to afford 0.13 g (90%) of Corey lactone diol **1**, identical with the authentic sample.

^{††} *Methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate 2*. To a solution of methyl ester **3** (0.5 g) in acetone (10 ml), Jones reagent [CrO₃ (0.35 g) + H₂SO₄ (0.125 ml) + H₂O (2.5 ml)] was added and the mixture was stirred for 4 h at room temperature, then quenched with PrOH (0.2 ml) and the resulting mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. A dried (Na₂SO₄) extract containing the mixture **2** + **5** in 4:1 ratio (according to ¹H NMR spectra) was dissolved in a solution of triethylamine (0.5 ml) in benzene (10 ml) and stirred at room temperature for 8 h. The resulting mixture was concentrated and the residue was purified by column chromatography on SiO₂. Elution with ethyl acetate–light petroleum (1:5) gave product **2** (0.3 g, 89%). Colourless liquid, *R*_f = 0.4 (SiO₂, 15% EtOAc in hexane). ¹H NMR (500 MHz, CDCl₃) δ: 2.50 (dd, 1H, *J* 8.5 and 16.4 Hz), 2.67 (dd, 1H, *J* 6.4 and 16.2 Hz), 3.73 (s, 3H), 3.75–3.85 (m, 1H), 5.48 (s, 1H), 6.15 (s, 1H), 6.41 (dd, 1H, *J* 1.2 and 5.9 Hz), 7.71 (ddd, 1H, *J* 1.1, 2.4 and 6.1 Hz). ¹³C NMR (125 MHz, CDCl₃) δ: 37.6, 40.6, 52.0, 117.7, 135.5, 144.4, 161.0, 171.7, 195.7. IR (neat, ν/cm⁻¹): 2953, 1734, 1707, 1437, 1242, 1197, 1170, 844. MS, *m/z*: 166 [M]⁺, 138, 135, 107, 106, 59. Found (%): C, 64.93; H, 5.81. Calc. for C₉H₁₀O₃ (%): C, 65.05; H, 6.07.

Methyl (5-chloromethyl-4-oxocyclopent-2-en-1-yl)acetate 5 (in a mixture with **2**): *R*_f = 0.4 (SiO₂, 15% EtOAc in hexane). ¹H NMR (500 MHz, CDCl₃) δ: 2.40–2.44 (m, 2H), 2.58–2.65 (m, 1H), 3.31–3.41 (m, 1H), 3.65–3.71 (m, 1H), 3.72 (s, 3H), 3.84–3.79 (m, 1H), 6.41 (dd, 1H, *J* 2.0 and 5.9 Hz), 7.71 (dd, 1H, *J* 2.4 and 5.7 Hz). ¹³C NMR (125 MHz, CDCl₃) δ: 41.5, 43.3, 52.3, 117.7, 134.1, 144.4, 166.1, 171.7, 195.7.

Thus, we have developed a simple and practical procedure to convert a commercially available lactone diol **1** into synthetically attractive compound **2** in overall yield 82%.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.11.005.

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