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# A CONVENIENT SYNTHESIS OF β-ALKYNYLPROPIONIC ACIDS FROM β-PROPIOLACTONES. SYNTHESIS OF 4,4,5,5-TETRADEHYDRO-9(O)-METHANO-$\Delta^{6(9\alpha)}$-$PGI_1$.

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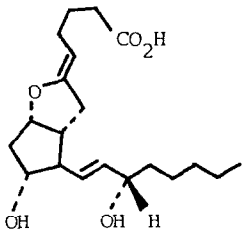
*Summary:* *A new prostacyclin analog, 4,4,5,5-tetradehydro-9(O)-methano-$\Delta^{6(9\alpha)}$-$PGI_1$, has been synthesized by utilizing the regiocontrolled cleavage of the β-propiolactone with the dialkylaluminum acetylide.*

Since prostacyclin ($PGI_2$) 1 was found to be the most potent inhibitor of platelet aggregation and a potent vasodilator with fairly short-life, considerable efforts have been expended to prepare chemically more stable and biologically more selective analogs.[1] Recently Ikegami and co-workers[2] reported the synthesis of 9(O)-methano-$\Delta^{6(9\alpha)}$-$PGI_1$ 2, which is more potent than well-known carbacyclin in inhibiting platelet aggregation. This result prompted us with the aim of developing more attractive compounds to prepare the new carbon analog 3, which contains the triple bond at $C_4$-$C_5$ (PG numbering). We wish to report herein the first synthesis of 3, which utilizes the regiocontrolled ring cleavage of β-propiolactones with dialkylaluminum acetylides for the construction of the upper side chain of 3.

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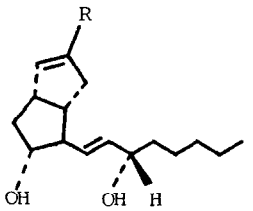
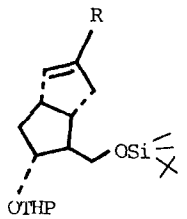



2 R:-$(CH_2)_4CO_2H$

3 R:-$C{\equiv}C(CH_2)_2CO_2H$




4 R:-CHO

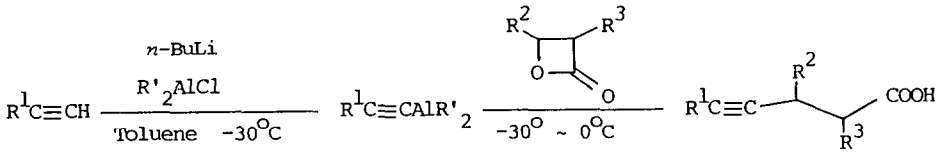
5 R:-CH(OH)-CH(SO2Ph)-$(CH_2)_2CO_2CH_3$

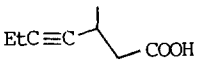
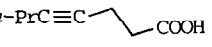
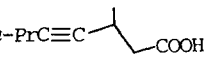
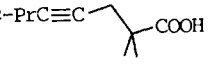
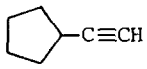
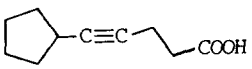
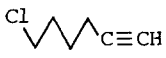
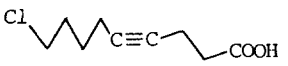
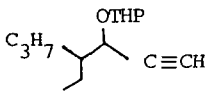
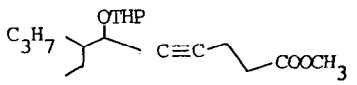
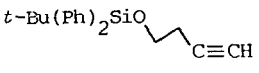
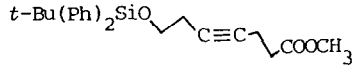
6 R:-$C{\equiv}C(CH_2)_2CO_2CH_3$

7 R:-$C{\equiv}CH$

8 R:-$CH{=}CCl_2$

Table. Reaction of Aluminum Acetylides with β-Propiolactones



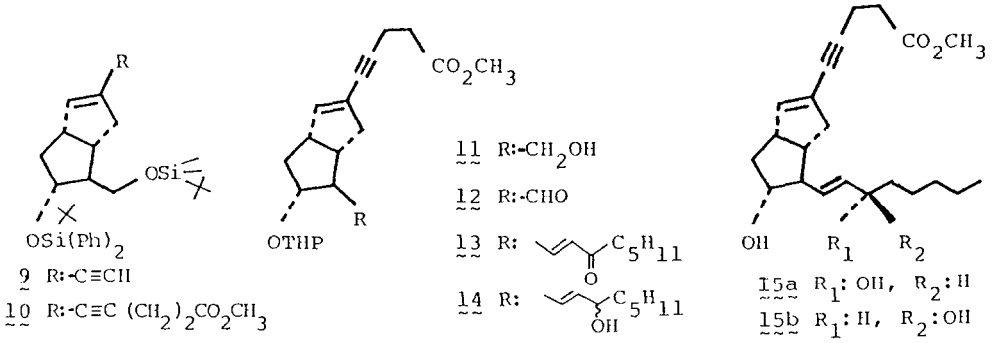

| No. | $R^1C\equiv CH$ | Lactone | Product | Yield(%)[a] |
|---|---|---|---|---|
| 1 | PhC≡CH |  |  | 74 |
| 2 | EtC≡CH |  |  | 44 |
| 3 | n-PrC≡CH |  |  | 84 |
| 4 | n-PrC≡CH |  |  | 48 |
| 5 | n-PrC≡CH |  |  | 68 |
| 6 |  |  |  | 95 |
| 7 |  |  |  | 92 |
| 8 |  |  |  | 77[b) c)] |
| 9 |  |  |  | 38[b) c)] |

a) All yields are for isolated pure compounds. No other product was ditected. b) The molar ratio of $R^1C\equiv CH$/ n-BuLi/ $Me_2AlCl$/ β-propiolactone is 1.0 : 4.0 : 4.0 : 6.0. c) Isolated as a methyl ester by treating with diazomethane.

The aldehyde 4,[3] which is now readily available from the well-known Corey lactone, appeared to be the most suitable synthetic intermediate for 3 as a result of retrosynthetic analysis. In order to obtain 6 by the introduction of an upper side chain, the desulfonylation[4] of the sulfone 5,[5] which was readily obtained from 4, was first attempted under a variety of conditions. However, the desired product 6 was not obtained in any case. Therefore, we turned our attention to three carbon homologation of the enyne 7; that is, introduction of $CH_2CH_2COOH$ to the enyne 7.

Although the conjugate addition of alkynylaluminum reagents to α,β-unsaturated ketones[6] is a well-known useful method, such addition to α,β-unsaturated esters has not been reported. The regioselective ring cleavage of β-propiolactones has been extensively established by the use of organometallic compounds such as dialkyl and dialkenylcuprates[7], Grignard reagents[8] and organocadmium compounds[9] to afford β-substituted propionic acids. However, such cleavage with alkynylmetals to afford β-alkynylpropionic acids has not been reported. Accordingly we have examined the cleavage of β-propiolactones with alkynylmetals and found that dimethylaluminum acetylides, which are easily prepared from lithium acetylides and dimethylaluminum chloride, react with β-propiolactones at -35°C to afford β-alkynylpropionic acids in 38-95% yields. The individual cases are summarized in the Table. In the case of β-methyl-β-propiolactone (Table, entries 2,4), the corresponding products were obtained in moderate yields. A general experimental procedure follows. A solution of 1-pentyne (340 mg, 5.0 mmol) in anhydrous toluene (10 ml) under argon was metallated with *n*-BuLi (1.54 M in *n*-hexane, 5.5 mmol) at -35°C for 30 min. The resulting solution was treated with dimethylaluminum chloride (1.2 M, 5.5 mmol) at the same temperature. Stirring at -35°C was continued for 30 min followed by addition of β-propiolactone (432 mg, 6.0 mmol). The reaction mixture was stirred at -35°C for 2.5 hr, quenched with methanol, poured into water and extracted with ether. Purification by column chromatography gave 4-octynoic acid (585 mg, 84%).

The synthetically useful method described above was applied to the synthesis of 6. Treatment of 1.1 equiv of $(EtO)_2P(O)CCl_2Li$[10] at -100°~-20°C afforded the *gem*-dichloroalkene 8 in 89% yield. The enyne 7 was obtained by reaction of 8 with 2.0 equiv of *n*-BuLi[10] in 75% yield and converted to the ester 6 by using 6.0 equiv of *n*-BuLi, 6.0 equiv of dimethylaluminum chloride and 9.0 equiv of β-propiolactone at -40°~-30°C followed by treatment with diazomethane in 42% yield. Instead of 7, 9 was also converted to 10 under the same conditions in 58% yield. Treatment of 6 with $Bu_4N^+F^-$ in THF gave the key intermediate 11[11] in quantitative yield.



The alcohol 11 was then transformed to 4,4,5,5-tetradehydro-9(O)-methano-$\Delta^{6(9\alpha)}$-$PGI_1$ 3 in usual manner. Oxidation of 11 with $SO_3$-pyridine complex and triethylamine in DMSO gave the aldehyde 12, which was directly treated with dimethyl (2-oxoheptyl)phosphonate-sodium hydride in THF to provide the enone 13 in 72% overall yield. Reduction of 13 with sodium borohydride in methanol at -20°C afforded the $C_{15}$-epimeric alcohols 14 (PG numbering), which, after deprotection of the THP group, gave the more polar diol 15a in 39% overall yield together with the less polar diol 15b (27%). Finally, hydrolysis of 15a with sodium hydroxide in aqueous ethanol followed by acidic extraction provided 4,4,5,5-tetradehydro-9(O)-methano-$\Delta^{6(9\alpha)}$-$PGI_1$ 3[12] as a white powder in 64% yield.

Preliminary biological results obtained with 3 indicated very weak inhibitory activity in human platelet aggregation induced by ADP.

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## References and Notes

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5) PMR($CDCl_3$)δ(ppm): 7.3~8.1(m, 5H), 5.70(broad s, 1H), 4.5~4.8(m, 2H), 3.67(s, 3H), 0.90(s, 9H), 0,05 (s, 6H). IR $\nu_{max}$(neat): 3500, 1735, 1305, 1140, 1085 $cm^{-1}$.

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11) PMR($CDCl_3$)δ(ppm): 5.87(broad s, 1H), 4.5~4.7(m, 1H), 3.70(s, 3H), 2.60(broad s, 4H). IR $\nu_{max}$(neat): 3400, 1730, 1075, 1030 $cm^{-1}$. Mass(CI) m/z: 348, 264, 215, 155, 85.

12) mp.128-129°C. PMR($CDCl_3$)δ(ppm):5.84(s, 1H), 5.4~5.5(m, 2H), 4.47(dd, J= 3Hz, 2Hz, 1H). IR $\nu_{max}$(KBr): 3400, 1698, 1085. Mass(CI) m/z: 328, 284.

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