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TOTAL SYNTHESIS OF (+)-PRELOG-DJERASSI LACTONIC ACID

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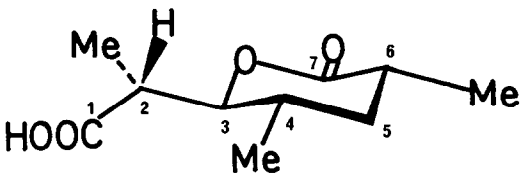
Summary: Optically active Prelog-Djerassi Lactonic Acid 1 was synthesized from D-glucal; the crucial point being the elaboration of the carboxylic group as shown in eq. 1 and 2 which involve the sequential process [i] asymmetric addition of methyl anion onto the hetero-olefin 2, [ii] trapping the carbanion intermediate 3 [E=Li to SePh] and [iii] oxidative hydrolysis of 3 via sila-pummerer rearrangement into 4.

Much synthetic effort to synthesize Prelog-Djerassi Lactonic Acid 1 has been made for substantial application of the new methodologies which should control the elaboration of the asymmetric carbon atoms.[1] We herein would like to describe a new synthesis of 1 which involves heteroconjugate addition[2] of MeLi onto an optically active pyranosyl hetero-olefin[3] preparable from a D-hexopyranose. The stereochemistry of the 2-position of 1 would be controlled by the acyclic asymmetric



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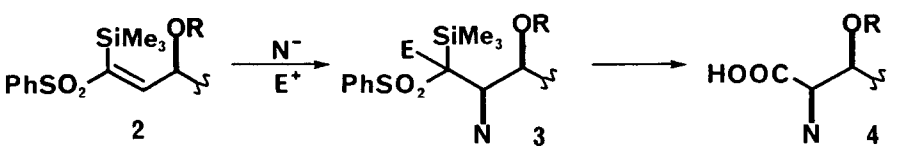
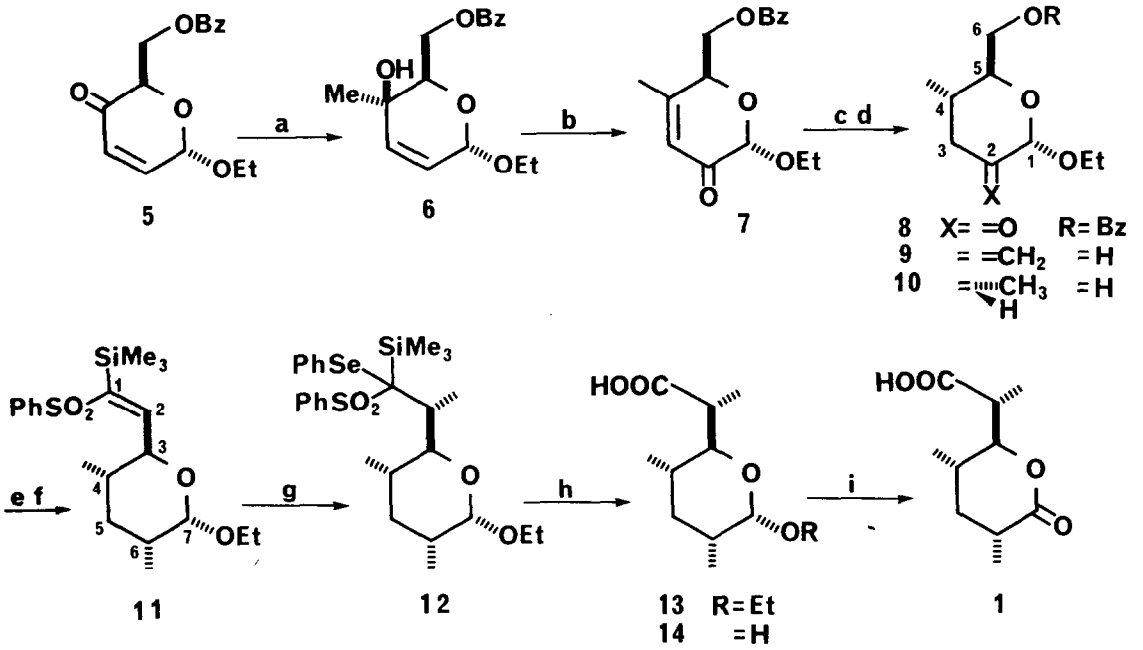
induction which we have previously reported,[2,3] since the threo-asymmetric induction should be readily accessible via the heteroconjugate addition. The particularly crucial step in this strategy is the development to form the carboxylic group along eq. 1.



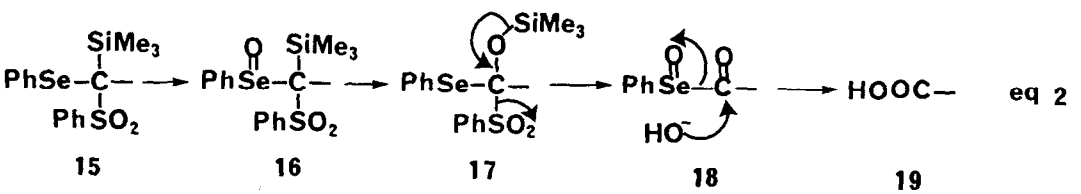
2 3 4 eq 1

Ethyl 6-O-benzoyl-2,3-dideoxy-α-D-glycerohex-2-enopyranosid-4-ulose 5 was employed as the chiral starting material which was synthesized in five steps from D-glucal by the method reported by Fraser-Reid et al.[4a] Addition of methyllithium to 5 in a mixture of i-Pr_2O and Et_2O (4:1) at -72° C gave 6 which was further oxidized with Jones reagent and then separated by SiO_2 to afford the enone 7: $[\alpha]_D$= -5.94°(c=0.99); pmr δ 1.23(3H, t, J= 7 Hz)ppm, 2.04(3H, s), 4.71(1H, brs), 4.83 (1H, s), 5.98(1H, s); ν1720, 1690 cm^{-1}: in 35 % overall yield.[5] Reduction of the olefin 7 with H_2/Pd-C yielded quantitatively the pure ketone 8: $[\alpha]_D$= +59.3°(c=1.08); ν 1720 cm^{-1}: the stereochemistry[4b] of which was analyzed by 400 MHz pmr: 2.55(H-3ax, dd, J= 15, 12), 2.44(H-3eq, ddd, J= 15, 4.5, 1). Treatment of 8 with triphenylphosphonium methylide in DMSO at 50°C for two overnights and distillation of the product (140°C/20 mmHg) afforded the exomethylene alcohol 9: $[\alpha]_D$= +133.6°(c= 1.24); pmr 0.9(3H, d, J= 7), 1.23(3H, t, J= 7), 4.43(1H, s), 4.61(2H, brs): in more than 90 % overall yield from 7. Exo-olefin was reduced with H_2/Pd-C in EtOAc afforded quantitatively the desired product 10 and its epimer [X = ] in 77 / 23 ratio [δ4.60(d, J= 3) /δ4.50(s)], respectively. The alcohol 10 was converted into the hetero-olefin 11 as was reported[3]; thus, Swern oxidation[6] was followed by condensation with bis(trimethylsilyl)-thiophenylmethyllithium[7] and then with mCPBA in 60 % overall yield affording 11 : $[\alpha]_D$= -22.5°(c=1.04); mp 82°C; pmr 0.27(9H, s), 0.56(Me-4, d, J= 6), 0.87(Me-6, d, J= 7), 1.18(3H, t, J= 7), 1.6-1.8(4H), 3.15-3.86(2H), 4.55(1H, d, J= 3), 4.97(1H, t, J= 10), 6.31(1H, d, J= 10), 7.48(3H), 7.86(2H). Addition of methyllithium to 11 in THF at -78°C over a period of 5 min[3b] and then PhSeCl yielded the adduct 12 in quantitative yield. Since this selenide was labile upon standing, it was successively treated with 30% H_2O_2 in aq. THF at room temperature for 0.5 hr to give the carboxylic acid 13 : $[\alpha]_D$= +127.1°(c=1.05); mp 105° C, ν 1710 cm^{-1}; pmr 0.86(6H), 1.15(3H, d, J= 7), 1.17(3H, t, J= 7), 1.3-3.4(4H), 2.77(1H, dq, J= 3, 7), 3.2-3.9(2H), 4.00(1H, dd, J= 10, 3), 4.62(1H, d, J= 3), 8.9(1H, brs): in 68 % yield. Hydrolysis of 13 with 0.4 N HCl in aq. 1,4-dioxane and subsequent oxidation of the hemiacetal 14 with bromine in aqueous DMF in the presence of NaOAc gave in 98 % yield the crystalline Prelog-Djerassi Lactonic Acid 1 : $[\alpha]_D$= +38.6(c=1.92); mp 123.5°C; pmr in 400 MHz 1.02(3H, d, J= 6.5), 1.21(3H, d, J= 7.5), 1.29(3H, d, J= 7), 1.43(1H, q, J= 12.5), 1.85-2.0(2H, m), 2.52(1H, ddq, J= 12.5, 7, 7), 2.76(1H, dq, J= 7.5, 2.5), 4.57(1H, dd, J= 10.5, 2.5), 10.04((1H, brs); cmr in 25 M Hz, 8.3, 16.8, 17.2, 30.8, 36.2, 37.2, 41.0, 86.3, 174.5, 177.7 ppm: identical with those data reported in the literature.[8]

In the total synthesis of 1 described above, the formation of the carboxylic group was achieved from a carbon like 12 bearing Me_3Si-, $PhSO_2$- and PhSe- on it by treatment with H_2O_2 at room temp.



a) MeLi/i-Pr_2O b) CrO_3 c) H_2/Pd-C d) $Ph_3P{=}CH_2$ e) $(COCl)_2$/DMSO/Et_3N
f) $PhS(Me_3Si)_2CLi$: mCPBA g) MeLi : PhSeCl h) H_2O_2/H_3O^+ i) Br_2/AcONa



eq 2

This conversion may involve the following multiple process as indicated in eq. 2; thus, i) oxidation of the selenide 15 into its oxide 16, ii) rearrangement to 17 via sila-pummerer process.[9] iii) sequential hydrolytic elimination of the benzensulfonyl group (see 17) and benzeneselenoxy group (18) with concomitant oxidation, into 19. The detail of above mechanism and further supporting experiments will be described elsewhere.

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8. See the references # 1g and 1h for the comparison data. No signals in cmr at 12.8 nor 12.3ppm corresponding to 2-epi or 2,6-diepi- 1 were found even when the reaction from 11 to 1 were achieved successively without any purification on the way.
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