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THE USE OF D-RIBONOLACTONE IN ORGANIC SYNTHESIS. I. TOTAL SYNTHESIS OF (-)-LITSENOLIDES C_1 AND C_2.

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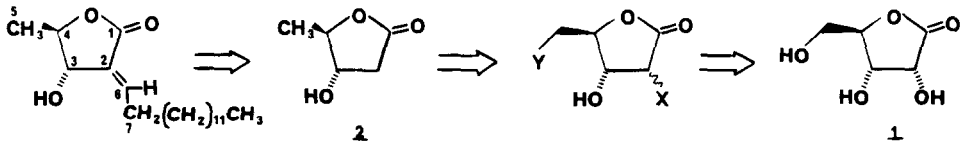
ABSTRACT D-Ribonolactone, an inexpensive, commercially available sugar, has been transformed stereoselectively into naturally occurring lactones, the litsenolides C_1 and C_2.

During the course of chemical studies on Litsea Japonica (Thunb) Juss., a plant from the Lauraceae family, Ishii and coworkers[1] isolated six lactones identified as litsenolides A_1, A_2, B_1, B_2, and C_1 and C_2. These compounds are three pairs of β-hydroxy-γ-methyl-α,β'-unsaturated γ-lactones having a hydrocarbon chain at the α,β'-position which is terminated by an allyl group (A series), a propargyl group (B series), or a methyl group (C series). The two components of each pair differ only in the cis or trans geometry at the α,β' double bond. The absolute geometry has been determined as S at the β-hydroxyl group (C-3) and R at the γ-methyl group (C-4). Similar lactones have been isolated from other plants belonging to the Lauraceae family.[2] Compounds containing exocyclic double bonds have been of interest because of their potential tumor inhibition activity.[3] Therefore, the synthesis of structurally related γ-lactones isolated from plants of the Lauraceae family has been the aim of several research groups. A short, stereoselective synthesis of (±) litsenolide C_1 from α-bromo-γ-valerolactone was reported by Wollenberg.[4] Katzenellenbogen and co-workers[5] devised a general method for the synthesis of α-alkylidene-β-hydroxy-γ-methylenebutyrolactones including epilitsenolides. A five-step stereoselective synthesis of (±)-litsenolides C_1 and C_2 from ethyl phenylthioacetate and 1-bromotetradecane was also described.[5] A stereospecific route to litsenolides A_2, B_2, and C_2 was devised by Kende and Toder.[6] Although several stereoselective approaches to the litsenolides have been reported, introduction of chirality at the β- and γ-positions has not been accomplished.

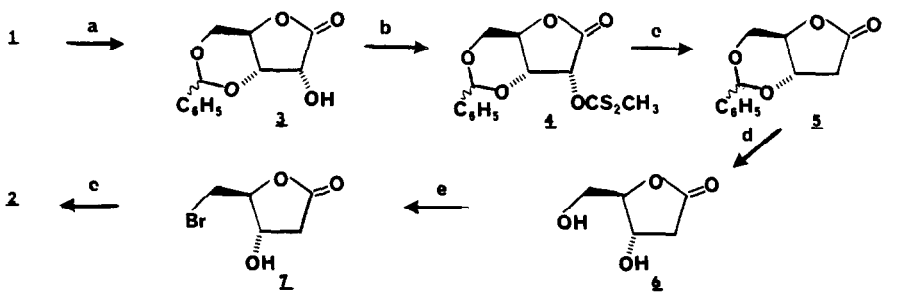
As a continuation of our investigations on the utilization of sugars as chiral intermediates in the synthesis of natural products,[7] we chose D-ribonolactone as a precursor for the α-alkylidene-β-hydroxybutyrolactone moiety of the Lauraceae lactones. D-Ribonolactone is a promising starting material because of its low cost, availability and versatility. We now wish to report the total synthesis of (-)-litsenolides C_1 and C_2 using the chirality of D-ribonolactone (1). A retrosynthetic analysis is shown in Scheme 1.

Scheme 1



The first target was the key intermediate 2,5-dideoxy-D-erythro-pentono-γ-lactone (2). The first approach to this compound is seen on Scheme 2. Treatment of 1 with benzalde-

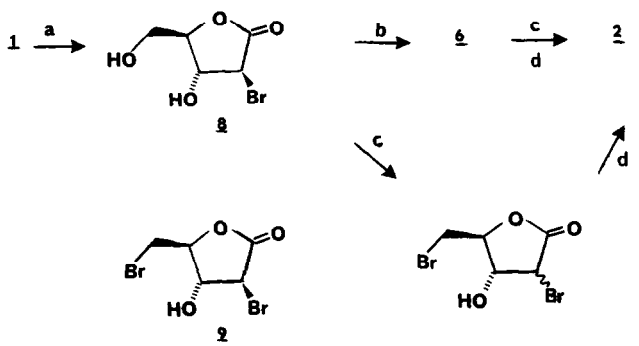
Scheme 2



[a] C_6H_5CHO, HCl; [b] NaH, CS_2, MeI, DMF; [c] n-Bu_3SnH, Tol, Δ; [d] TFA, $CHCl_3$, H_2O; [e] CBr_4, $P(C_6H_5)_3$, MeCN

hyde and concentrated hydrochloric acid for 7 h afforded the known benzylidene derivative 3 in 92.7% yield, mp 230-231.5°C, $[\alpha]_D^{23}$ = -177.0° (c 2.37, DMF); lit[8] 233-235.5°C, $[\alpha]_D^{23}$ = -174.1°. The reaction of 3 with carbon disulfide in the presence of sodium hydride in dry DMF was followed by alkylation with methyl iodide to give the corresponding xanthate (4)[9] in 75.5% yield, mp 145-146°C, $[\alpha]_D^{23}$ = -314.3° (C 2.01, $CHCl_3$). Reduction of 4 with tri-n-butyltin hydride afforded 5 in 92.5% yield,[9] mp 139-139.5°C, $[\alpha]_D^{23}$ = -172.3° (c 1.71, $CHCl_3$). Deprotection of 5 with 50% aqueous trifluoroacetic acid in chloroform at 70°C for 10 h gave 6[10] which after selective bromination of the primary alcohol with carbon tetrabromide and triphenyl phosphine in acetonitrile afforded 7[10] in 30% yield, $[\alpha]_D^{22}$ = +13.8° (c 1.70, acetone). Debromination of 7 with tri-n-butyltin hydride[11] gave 2,[9] in 91.7%, bp 108-110°C (0.025 mm Hg, Kugelrohr), $[\alpha]_D^{23}$ = +10.9°(c 2.42, $CHCl_3$). Alternate routes to 2 are shown in Scheme 3.

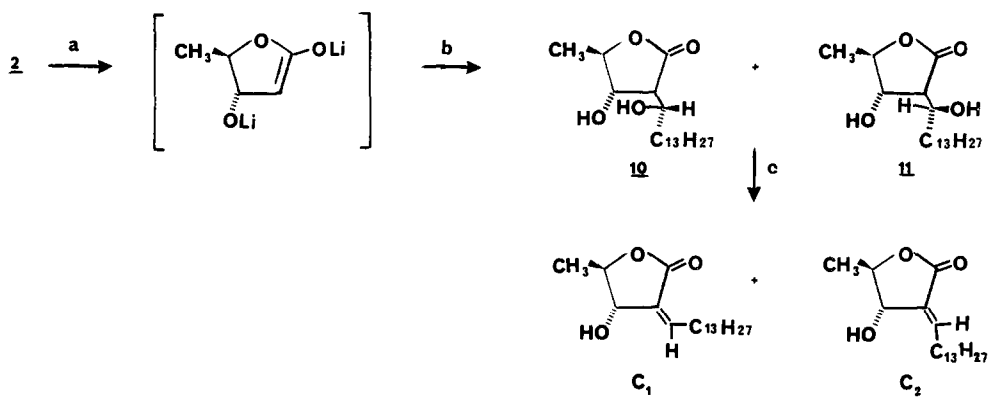
Scheme 3



[a] (1) 35% HBr, HOAc; (2) MeOH; [b] Pd/C, H_2, Et_3N, EtOAc; [c] CBr_4, $P(C_6H_5)_3$, MeCN; [d] n-Bu_3SnH

Treatment of 1 with a ∿ 35% solution of hydrogen bromide in acetic acid for 4 h at room temperature was followed by deacetylation with methanol. After work up of the reaction mixture, 2,5-dibromo-2,5-dideoxy-D-arabinono-γ-lactone (9) was obtained from solution, 4.3% yield.[10] Continuous extraction of the solution with ether overnight afforded 2-bromo-2-deoxy-arabinono-γ-lactone (8), 65.1% yield, mp 79-81°C, $[\alpha]_D^{22}$ = +70.3° (c 3.85, ethyl acetate); lit[10] mp 79-81°C, $[\alpha]_D^{21}$ = + 72° (c 4.1, ethyl acetate). The absolute configuration of 8 was confirmed by X-ray crystallography.[12] Hydrogenolysis of 8 yielded 2-deoxy-D-erythro-pentono-γ-lactone (6), followed by the selective bromination described before gave 7[10] in 71.8% yield. Tri-n-butyltin hydride reduction of 7 or 9 gave the identical key intermediate 2. The conversion of 2 into litsenolides C_1 and C_2 is shown in Scheme 4.

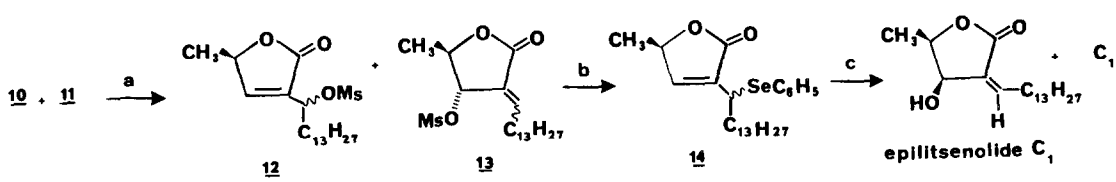
Scheme 4



[a] 2 eq. LDA, THF, -78°C; [b] (1) 1 eq. $ZnCl_2$, THF; (2) $CH_3(CH_2)_{12}CHO$, THF; [c] 200°C

Generation of the dilithium enolate of 2, at -78°C, with lithium diisopropylamide in THF, followed by subsequent addition of zinc chloride in THF and myristyl aldehyde at -50°C afforded a diastereomeric mixture of α,β'-dihydroxyl derivatives 10 and 11 (59.8% yield, $[\alpha]_D^{23}$= +12.66° (c 1.23, $CHCl_3$).[9] Compounds 10 and 11 were converted to the corresponding litsenolides C_1 and C_2 in 15% yield, by heating at 200°C. The physical properties of the synthetic litsenolide were identical in every respect with those of the natural products.[1] Litsenolide C_1 was prepared in better yield using Wollenberg's procedure.[4] The diastereomeric mixture of 10 and 11 in CH_2Cl_2 was treated with triethylamine and 2 eq. of methanesulfonyl chloride at 0°C. Chromatography on silica gel (ether:petroleum ether, 2:1) afforded compounds 12,[9] $[\alpha]_D^{22}$= -7.3° (c 5.7, $CHCl_3$) and 13 in a 10:1 ratio (100% yield). This mixture was converted to 14[9] (78% yield) with 1.5 eq. of sodium phenylselenide.[4] Oxidation of 14 with 30% hydrogen peroxide in CH_3CN gave litsenolide C_1 and epilitsenolide C_1 in a 7:1 ratio (85% yield). These reactions are shown in Scheme 5.

Scheme 5



[a] MsCl, Et_3N, CH_2Cl_2, 0°C, 15 min.; [b] $NaSeC_6H_5$, EtOH, -20°C, 1 h; [c] 30% H_2O_2, CH_3CN, -20°C

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REFERENCES AND NOTES

1. K. Takeda, K. Sakurawi, and H. Ishii, Tetrahedron, 1972, 21, 3757.
2. J.C. Martinez, V.M. Yoshida, and O.R. Gottlieb, Phytochemistry, 1981, 20, 459.
3. E. Fugita and Y. Nagao, Bioorganic Chemistry, 1977, 6, 287.
4. R.H. Wollenberg, Tetrahedron Lett., 1980, 3139.
5. S.W. Rollinson, R.A. Amos, and J.A. Katzenellenbogen, J.Amer.Chem.Soc., 1981, 103, 4114.
6. A.S. Kende and B.H. Toder, J.Org.Chem., 1982, 47, 163.
7. P.C. Wang and M.M. Joullié, J.Org.Chem., 1980, 45, 5359.
8. H. Zinner, H. Voigt, and J. Voigt, Carbohyd.Res., 1968, 7, 39.
9. All new compounds gave satisfactory elemental analyses and spectral data. Selected spectral data: ^{1}H NMR ($CDCl_3$, 250 MHz) δ; 4, 2.64 (s,3H), 4.42 (dd, 1H, $J_{5,5'}$ = 13.6, $J_{4,5}$ = 1.5), 4.62 (d,1H), 4.73 (dd,1H,$J_{3,4}$ = 8.1), 4.97 (dd,1H, $J_{2,3}$ = 2.9), 5.81 (s,1H), 6.45 (d,1H), 7.35-7.55 (m,5H); 5, 2.63 (dd,1H,$J_{2,2'}$ = 15.8, $J_{2,3}$=3.7), 3.05 (dd,1H,$J_{2,3}$ = 2.6), 4.23 (dd,1H, $J_{4,5}$ = 1.8, $J_{5,5'}$ = 12.9), 4.58 (q,1H), 4.59 (dd,1H,$J_{3,4}$ = 1.1), 4.79 (ddd,1H), 5.76 (s,1H), 7.3-7.6 (m,5H); 7, 2.46 (dd, 1H, $J_{2,2'}$ = 18.0, $J_{2,5}$ = 7.0), 2.99 (dd,1H, $J_{2,3}$ = 3.4), 3.70 (dd,1H, $J_{5,5'}$ = 11.3, $J_{4,5}$ = 5.4), 3.77 (dd,1H, $J_{4,5'}$ = 4.8), 4.47 (m,1H, $J_{3,4}$ = 3.1), 4.58 (m,1H), 4.93 (d,1H, $J_{3,3\text{-OH}}$ = 3.9, D_2O exchangeable); 2, 1.37 (d,3H, $J_{4,5}$ = 6.6), 2.53 (dd,1H, $J_{2,2'}$ = 18.0, $J_{2,3}$ = 3.6), 2.85 (dd,1H, $J_{2',3}$ = 6.5), 3.37 (d,1H, $J_{3,3\text{-OH}}$ = 4.4, D_2O exchangeable), 4.24 (m,1H), 4.52 (dq,1H, $J_{2,4}$ = 2.8); 10, 0.88 (t,3H,J=6.9), 1.30 (bs,22H), 1.43 (d,3H, $J_{4,5}$ = 6.0), 1.68 (m,2H), 2.69 (dd,1H, $J_{2,6}$ = 3.4, $J_{2,3}$ = 8.5), 3.4, 3.5 (bs,2H), 4.14 (m,1H), 4.18 (m, 1H), 4.26 (dq,1H, $J_{4,5}$ = 6.1, $J_{3,4}$ = 7.3); 11, (major isomer) 0.88 (t,3H, $J_{19,20}$ = 6.5), 1.31 (bs,22H), 1.43 (d,3H, $J_{3,5}$ = 6.2), 1.85 (m,2H), 2.65 (dd,1H, $J_{2,6}$ = 3.8, $J_{2,3}$ = 9.3), 3.86 (m,2H), 3.97 (dd,1H), 4.25 (dq,1H, $J_{3,4}$ = 7.7), 4.40 (bs,1H); 12, 0.86(t,3H,J$\sim$6.0), 1.1-1.6(m,22H), 1.96(m,2H), 3.06(s,3H), 5.12 (dq,1H), 5.36(m,1H), 7.42 (d,1H). 13, 0.86(t,3H), 1.2-1.6(m,22H), 1.18(d,minor), 1.19(d, major) (3H), 2.21(dt,2H), 3.06(s,3H), 4.83(q,major),5.02(q,minor)(1H), 5.46(bs,1H), 7.20(dt,1H).
10. K. Bock, I. Lundt, and C. Pedersen, Carbohydrate Res., 1981, 90, 17.
11. Hydrogenolysis of 5-bromo-2,5-dideoxy-D-erythro-pentono-Y-lactone (7) in ethyl acetate and triethylamine over palladium on carbon gave a mixture of the expected lactone (2) and 3-hydroxypentanoic acid in a 1:2 ratio, in addition to triethylamine hydrobromide.
12. The X-ray crystallographic analysis was performed by Dr. P.J. Carroll and the details will be published somewhere else.

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