Tetrahedron Letters No. 47, pp 4687 - 4690.

0040-4039/78/1115-4687$02.00/0

STUDIES DIRECTED TOWARDS THE ASYMMETRIC TOTAL SYNTHESIS OF ANTILEUKEMIC LIGNAN LACTONES

——SYNTHESIS OF (-)-PODORHIZON——

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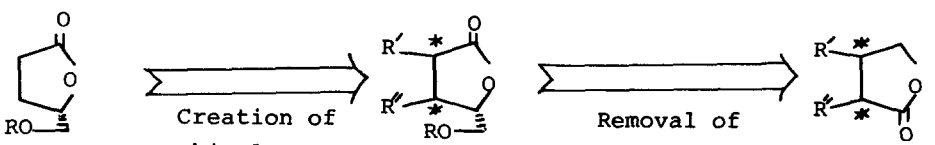
Some biologically potent natural lignans having bis-benzylbutyrolactone skeleton, steganacin (1)[1], podophyllotoxin (2)[2], (-)-trans-2-(3,4,5-trimethoxy benzyl)-3-(3,4-methylenedioxybenzyl)butyrolactone (3)[3], are known to be optically active. Interestingly steganacin has the absolute configuration opposite to those of the other natural lignans. As a consequence of our intention to engage in the total synthesis of steganacin and related lignans in optically active forms we have initiated studies on the development of a new methodology for the construction of optically active 2,3-disubstituted-γ-lactones. The general approach under consideration for the synthesis of these compounds in optically active forms involves the asymmetric induction shown in Scheme 1 wherein the optically active γ-lactone easily available from optically active glutamic acid might be expected to be a useful synthon not only as a chiral source, but also as a part of the skeleton of the target molecules. The purpose of this preliminary communication is to demonstrate that this approach to the synthesis of optically active 2,3-disubstituted-γ-lactones related to the compounds cited above will proceed in a satisfactory fashion to afford the desired compounds.

Scheme 1



The benzyl ether (4)[4] of (+)-γ-hydroxymethyl-γ-lactone prepared from L-glutamic acid was treated with LDA (two equivalents), $ClPO(OEt)_2$, and piperonal successively[5] to give, after column chromatography (SiO_2, $CHCl_3$), the unsaturated lactone (5)[6,7] as colorless needles of mp 90°, $[\alpha]_D^{20}$ +167°(c=1.15, $CHCl_3$) in 50% yield. Catalytic hydrogenation of 5 over 5% Pd on carbon in EtOH-EtOAc (1:1) at room temperature afforded, after column chromatography (SiO_2, EtOAc-$CHCl_3$=1:4), the corresponding saturated lactone (6) as an oil of $[\alpha]_D^{20}$ + 72.7°(c=1.06, EtOH) in 74% yield. The determination of the degree of asymmetric induction in this step (5 to 6) and removal of the original chiral group were accomplished by the conversion of 6 into (-)-podorhizon (12)[8] as follows.

Lithium aluminum hydride reduction of 6 afforded the triol (7) as an oil of $[\alpha]_D^{20}$ -10.1°(c=0.93, EtOH) in 67% yield, which was oxidatively cleaved by the action of sodium metaperiodate in aqueous t-BuOH at room temperature to give, after preparative tlc (SiO_2, Et_2O), the hemiacetal (8) as an oil of $[\alpha]_D^{20}$ -21.1° (c=1.05, $CHCl_3$), NMR δ 5.54 (anomeric proton) in 77% yield. Collins oxidation of 8 afforded, after preparative tlc (SiO_2, CH_2Cl_2), the lactone (9)[9] as an oil of $[\alpha]_D^{20}$ -3.2°(c=1.14, $CHCl_3$), IR 1770 cm^{-1} in 77% yield.

Finally the anion of 9 (two equivalents of LDA in THF, -78°) was treated with the mixed anhydride (10)[10] prepared from the acid (11) to give, after preparative tlc (SiO_2, $CHCl_3$), (-)-podorhizon (12)[8] as a foam of $[\alpha]_D^{21}$ -40.0°(c= 0.80, $CHCl_3$) in 74% yield. The optical rotation value of this synthetic 12 shows that the optical purity of this 12 is 50% and therefore the yield of the asymmetric induction in the step 5 to 6 is 50%, and further the addition of hydrogen took place preferentially from the less hindered bottom side of 5[11]. Single recrystallization of this 12 from MeOH afforded optically pure (-)-podorhizon (12)[8] (mp 125-127°, $[\alpha]_D^{21}$ -75.6°(c=0.57, $CHCl_3$)) in 40% recovery yield. Since (+)-podorhizon has been converted into (-)-podorhizol[8], this synthesis of 12 means the formal asymmetric total synthesis of (+)-podorhizol[12].

The first successful asymmetric total synthesis of (-)-podorhizon from chiral γ-lactone easily available from L-glutamic acid holds promise for the asymmetric syntheses of various optically active lignan lactones from optically active glutamic acid. Further studies along this line, especially the approach

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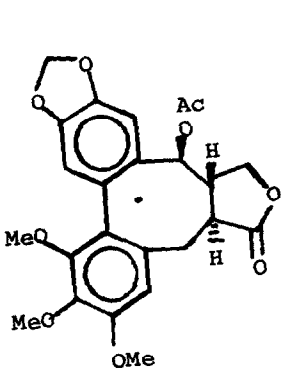

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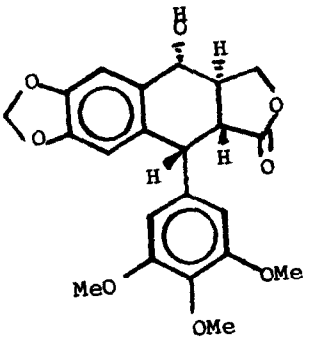

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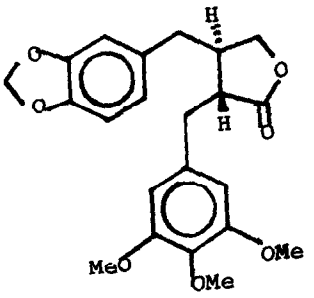

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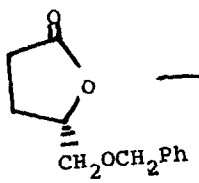

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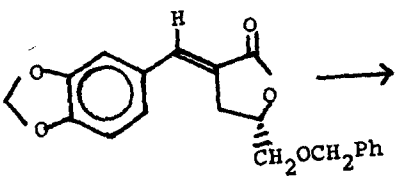

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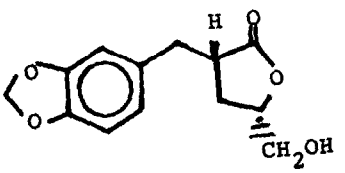

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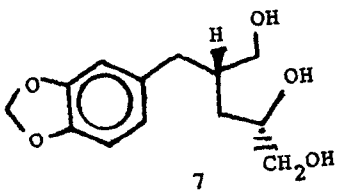

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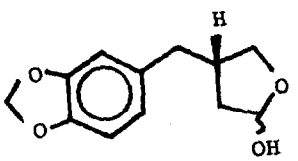

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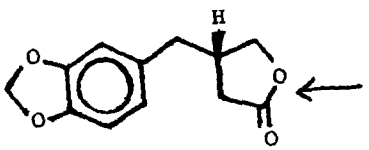

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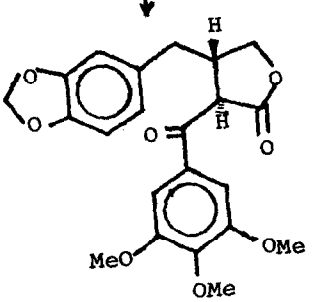

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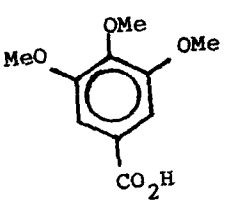

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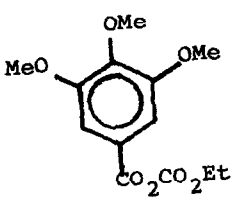

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towards the antileukemic lignan lactones[13], are now in progress in our laboratory.

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(5) cf. a) D. Comins, A. F. Jacobine, J. L. Marshall, and M. M. Turnbull, Synthesis, 309 (1978); b) A. I. Meyers, K. Tomioka, and M. P. Fleming, J. Org. Chem., in press

(6) The stereochemistry of 5 was presumed by the comparison of NMR data of 5 with those of the related compounds reported by M. Kuhn et al. See ref. 8.

(7) Satisfactory spectral and analytical data were obtained for all new compounds.

(8) (+)-Podorhizon (mp 129-130°, $[\alpha]_D^{21}$ +79.5°(c=0.588, $CHCl_3$)) has been obtained from naturally occurring podorhizol-β-D-glucoside. M. Kuhn and A. von Wartburg, Helv. Chim. Acta., 50, 1546 (1967)

(9) The spectral data of 9 were agreed well with those of reported compound (ref. 8). Tlc behavior of 9 was also identical with the racemic 9 prepared by the desulfurization of the reported dithiane derivative of 9 (ref. 12).

(10) Quantitative yield (NEt_3, $ClCO_2Et$ in THF), Mp 94°

(11) cf. S. A. M. T. Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, Chem. Comm., 873 (1974)

(12) The conversion of (±)-podorhizol into (±)-deoxyepipodophyllotoxin has been reported. F. E. Ziegler and J. A. Schwarts, J. Org. Chem., 43, 985 (1978)

(13) The conversion of (±)-3 into (±)-isostegane has been reported. R. E. Damon, R. H. Schlessinger, and J. F. Blount, J. Org. Chem., 41, 3772 (1976)

(Received in Japan 19 August 1978)