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AN EASY PREPARATION OF (-) AND (+)-β-PIPERONYL-γ-BUTYROLACTONES, KEY-INTERMEDIATES FOR THE SYNTHESIS OF OPTICALLY ACTIVE LIGNANS

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Summary : Methyl α-piperonylhemisuccinate was resolved into both its (R)-(+) and (S)-(-)-antipodes by (-) and (+)-ephedrine, respectively. Calcium borohydride reduction of the (R)-(+) and (S)-(-)-hemiesters afforded the crystalline, optically pure, (R)-(+) and (S)-(-)-β-piperonyl-γ-butyrolactones, respectively, and in high yields. The latter were converted into (-) and (+)-isodeoxypodophyllotoxin, respectively.

β-Benzyl-γ-butyrolactones, such as the piperonyllactone 1, are key-intermediates for various biologically active lignans.[1-4] KOGA described in 1979 a "self-immolative" synthesis of the lactone (R)-(+)-1 in five steps from the optically active intermediate 2, itself deriving from natural L-glutamic acid.[1] ACHIWA obtained the "non-natural" antipode (S)-(-)-1 in 23-78% optical yields, by assymmetric hydrogenation of the ethylenic half-ester 3.[5] In 1984, POSNER described a gram scale synthesis of the optically active (+)-butenolide 4 in seven steps from propargyl alcohol and (-)-menthyl p-toluenesulfinate.[6] Two further steps led to the "non-natural" lactone (S)-(-)-1 (isolated by preparative tlc).[6]

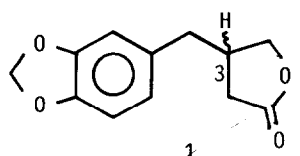
As far as we are concerned, we found that both antipodes of lactone 1 can be obtained rapidly and in a preparative manner according to the following method.

Thus, the known and readily available racemic half-ester 5 (10 g) was treated with (-)-ephedrine (6.21 g) in 95% EtOH (40 cm^3). The crystallized salt (ca. 10g) was recrystallized 4 times from the same solvent, to reach constant m.p. 132-134°C and specific rotation $[\alpha]_D^{20}$ +2.4° (c = 1.044, $CHCl_3$). The pure salt (4.4 g, 54% yield) was treated with dilute HCl, quantitatively yielding the optically pure half-ester (R)-(+)-5, m.p. 102-104°C, $[\alpha]_D^{20}$ +30.4° (c = 2, MeOH). In a similar fashion, the racemic half-ester 5 was resolved with (+)-ephedrine, affording optically pure (S)-(-)-5, m.p. 102-104°C, $[\alpha]_D^{20}$ -30.5° (c = 1.35, MeOH) in 48% yield.

A sample of optically active hemiester (S)-(-)-5, $[\alpha]_D^{20}$ -30°, was racemized by refluxing with 2 equivalents of sodium methoxide in dry methanol for several hours.

The half-ester (R)-(+)-5 was reduced with calcium borohydride as described in the racemic series,[7] to afford the lactone (R)-(+)-1, m.p. 31-33.5°C, $[\alpha]_D^{20}$ +4.87° (c = 0.87, $CHCl_3$) in 82% yield after molecular distillation. This compound was described as an oil, having $[\alpha]_D^{20}$ +4.8° ($CHCl_3$).[9] Similarly (S)-(-)-5 afforded the lactone (S)-(-)-1, m.p. 31.5-34°C, $[\alpha]_D$ -4.78° (c = 1.14, $CHCl_3$) in 80% yield after purification as above.

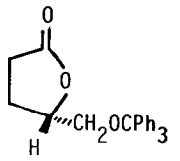
The lactone (R)-(+)-1 was next hydroxyalkylated with 3,4,5-trimethoxybenzaldehyde using hexamethyldisilylazide as a base, followed by intramolecular cyclization with trifluoroacetic acid,[2] giving (-)-isodeoxypodophyllotoxin 6 as the sole product, m.p. 249.5-250°C,



1

(R)-(+)-1 H-3α

(S)-(-)-1 H-3β



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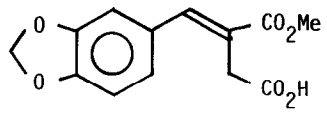

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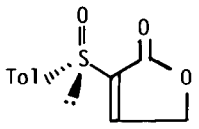

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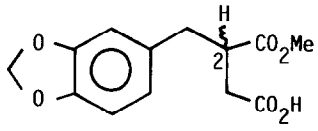
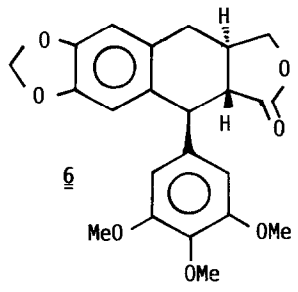


5

(R)-(+)-5 H-2α

(S)-(-)-5 H-2β



6

$[\alpha]_D^{20}$ -80.3° (c = 0.597, $CHCl_3$) in ca. 80% yields. Lit. m.p. 250-253°C, $[\alpha]_D^{21}$ -80.8° ($CHCl_3$),[1] and $[\alpha]_D^{21}$ -84.6° ($CHCl_3$).[9] A similar treatment of the lactone (S)-(-)-1 afforded (+)-isodeoxypodophyllotoxin (the antipode of 6) as the sole product, m.p. 249.5-251°C, $[\alpha]_D^{20}$ -80.5° ($CHCl_3$) in the same yield as the levorotary enantiomer.

Conclusion

We have synthesized the (R)-(+)-β-piperonyl-γ- butyrolactone 1 in four steps from piperonal, including resolution of the intermediate methyl (±)-α-piperonylhemisuccinate 5 by means of (-)-ephedrine. Since a partially resolved and/or undesirable enantiomer of 5 can be racemized and recycled in view of further resolution, we believe this represents one of the simplest and most economical routes leading to (S)-(-)-1 and (R)-(+)-1 which are key-intermediates for various lignans.

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