

THE SYNTHESSES OF (R)-(+)- $\beta$ -VANILLYL- $\gamma$ -BUTYROLACTONE  
AND OF CHIRAL LIGNANS THEREFROM

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Abstract - (R)-(+)- $\beta$ -vanillyl- $\gamma$ -butyrolactone was obtained in 4 steps including a resolution, from vanillin and dimethyl succinate, and was used for the total syntheses of 5 naturally occurring and optically active lignans such as (+)-isolariciresinol 20.

We recently described efficient syntheses of the (R)-(+)- and (S)-(-)-lactones 1 and 2, which are key-intermediates for biologically active chiral lignan derivatives.<sup>1</sup> We now describe here the synthesis of the hitherto unknown (R)-(+)- $\beta$ -vanillyl- $\gamma$ -butyrolactone 3 which we used for the syntheses of naturally occurring, and optically active lignans.

A Stobbe condensation between vanillin and dimethyl succinate could be carried out without preliminary protection of the phenolic hydroxyl, when using methanolic lithium methoxide (2.6 equ.) as a base. The resulting ethylenic half-ester 4, mp 142-144°C (MeOH), was thus obtained in 90% yield. When the same reaction was carried out by means of sodium methoxide, the yield of the half-ester 4 was 20% only. Catalytic hydrogenation (H<sub>2</sub>, Pd-C, AcOH) of the latter gave the racemic half-ester 5, mp 91-93°C (85% yield) which was next treated with 1 equ. (R)-(+)- $\alpha$ -methylbenzylamine in AcOEt. The least soluble salt was purified by recrystallization giving fine needles, mp 126-134°C,  $[\alpha]_D^{20} +28^\circ$  (c 1, CHCl<sub>3</sub>) (74% yield). Treatment of this salt with aqueous HCl nearly quantitatively afforded the pure half-ester (R)-(+)-5, mp 97.5-100.5°C (Et<sub>2</sub>O) and  $[\alpha]_D +29^\circ$  (c 1.2, MeOH). Recrystallization of the more soluble salt gave big macles, mp 104-108°C,  $[\alpha]_D -12^\circ$  (c 1.2, CHCl<sub>3</sub>) and in 68% yield. Acidic treatment of the latter gave the half-ester (S)-(-)-5, mp 98-101°C and  $[\alpha]_D -29^\circ$  (c 1.1, MeOH).

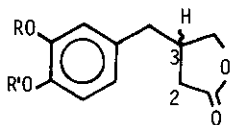
Reduction of the potassium salt of the half-ester (R)-(+)-5 was carried out in EtOH for 4 days at room temperature (RT) using a tenfold excess of Ca(BH<sub>4</sub>)<sub>2</sub> as the reducing agent,<sup>2</sup> thus affording the desired  $\beta$ -vanillyl- $\gamma$ -butyrolactone (R)-(+)-3 in 83% yield, mp 119.5-121.5°C (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O) and  $[\alpha]_D +10^\circ$  (c 1, CHCl<sub>3</sub>). The half-ester (S)-(-)-5 similarly yielded the lactone (S)-(-)-3, mp 119-121°C and  $[\alpha]_D -10^\circ$  (CHCl<sub>3</sub>).

Syringaldehyde was *O*-benzylated using benzyl chloride (EtOH/KI/K<sub>2</sub>CO<sub>3</sub>, 6 h reflux, 90% yield) and subsequent NaBH<sub>4</sub> reduction of the aldehydic carbonyl quantitatively afforded the alcohol 7, mp 47-49°C (Et<sub>2</sub>O/petroleum ether) which was described as an oil.<sup>3</sup> Treatment of the latter with PBr<sub>3</sub> in ether quantitatively yielded the hitherto unknown and unstable bromide 8, mp 40-42°C. Since our preliminary attempts failed to alkylate the lactone (R)-(+)-3 at C-2 using the bromide 8 and 2.2 equ. of LDA as a base, we therefore decided to protect the phenolic hydroxyl of (R)-(+)-3 by means of benzyl chloride (2 equ.) in a similar way as above (Me<sub>2</sub>CO, 16 h). The resulting compound (R)-(+)-6 was thus obtained in 90% yield, mp 80-81.5°C and [α]<sub>D</sub> +4° (CHCl<sub>3</sub>).

The lithium anion of the lactone (R)-(+)-6 was generated using LDA in THF and was treated with the bromide 8 for 3 h at -80°C, thus giving the amorphous compound 9, [α]<sub>D</sub> -20° (c 1, CHCl<sub>3</sub>), in 78% yield after chromatography. The benzyl groups of 9 were cleaved by catalytic hydrogenolysis (H<sub>2</sub>, 3 bars, Pd-C, AcOEt, 15 h) and (-)-thujaplicatin methyl ether 10 was thus obtained in 78% yield, having mp 168-168.5°C (Me<sub>2</sub>CO/H<sub>2</sub>O) and [α]<sub>D</sub> -44° (c 1.1, Me<sub>2</sub>CO), after recrystallization from Me<sub>2</sub>CO/H<sub>2</sub>O. The literature<sup>4</sup> indicates mp 167-167.5°C and [α]<sub>D</sub> -48.7° (c 4, Me<sub>2</sub>CO).

Formation of the lithium anion of the lactone (R)-(+)-6, using lithium hexamethyldisilylamide (LHDS) in THF at -80°C, followed by slow addition of the known bromide 11<sup>5</sup> gave *O*-dibenzylmatairesinol 12 as a viscous colourless oil in 87% yield after chromatography, having [α]<sub>D</sub> -22° (c 1, CHCl<sub>3</sub>). When this alkylation reaction was carried out using LDA instead of LHDS, the resulting compound 12 thus obtained was contaminated with an impurity of same R<sub>f</sub>, presumably a dialkylated product. The fact that the use of LHDS may lead to a purer alkylation product was recently disclosed in the literature.<sup>6</sup> Catalytic hydrogenation (H<sub>2</sub>, Pd-C, AcOEt) of the benzyl groups of 12 gave natural (-)-matairesinol 13 in 80% yield after chromatography, mp 70-72°C (EtOH/H<sub>2</sub>O) and [α]<sub>D</sub> -43° (c 0.84, Me<sub>2</sub>CO). The literature<sup>7</sup> indicates mp 117-119°C (CHCl<sub>3</sub>) and [α]<sub>D</sub> -42.8° (Me<sub>2</sub>CO). LiAlH<sub>4</sub> reduction in THF at RT of the lactone ring of compound 12 gave the diol 14, mp 113-114.5°C, [α]<sub>D</sub> -24° (c 0.9, CHCl<sub>3</sub>) in 66% yield. Catalytic hydrogenolysis (H<sub>2</sub>, Pd-C, AcOEt) of the benzyl groups of 14 afforded natural (-)-secoisolariciresinol 15 in 76% yield, mp 112-113.5°C, [α]<sub>D</sub> -32° (c 0.8, Me<sub>2</sub>CO). The literature<sup>8</sup> indicates mp 112-114°C, [α]<sub>D</sub> -32° (Me<sub>2</sub>CO). The diol 15 was dehydrated and cyclized by means of HClO<sub>4</sub> in refluxing acetone for 20 min, thus leading to natural (-)-anhydrosecoisolariciresinol 16, mp 120.5-121.5°C, [α]<sub>D</sub> -62° (c 0.5, EtOH) in 74% yield after chromatography. The literature indicates mp 118-118.5°C and [α]<sub>D</sub> -58° (EtOH).

The lactone (R)-(+)-6 was next hydroxyalkylated with *O*-benzylvanillin using LHDS in benzene at 0°C for 5 min, giving the amorphous mixture of epimeric carbinols 17 in 87% yield after chromatography. The intramolecular cyclization of alcohols 17 by means of trifluoroacetic acid in the usual way, or by means of H<sub>2</sub>SO<sub>4</sub>, afforded mixtures containing partially debenzylated products. However the mixture of alcohols 17 was intramolecularly cyclized in a neat fashion using 60% aqueous perchloric



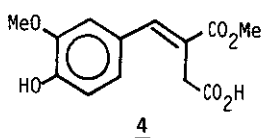
(R)-(+): H-3 $\alpha$ ; (S)-(-): H-3 $\beta$

1 R, R' = CH<sub>2</sub>

2 R = R' = Me

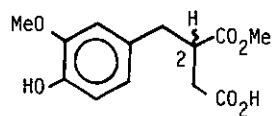
3 R = Me; R' = H

6 R = Me; R' = Bz



4

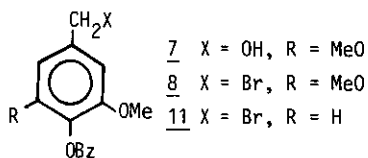
Bz = -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>



(R,S)-5

(R)-(+)-5: H-2 $\alpha$

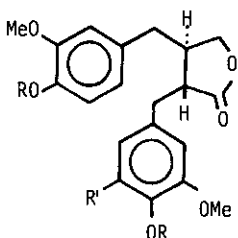
(S)-(-)-5: H-2 $\beta$



7 X = OH, R = MeO

8 X = Br, R = MeO

11 X = Br, R = H

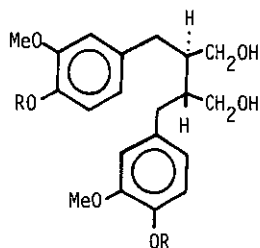


9 R = Bz; R' = MeO

10 R = H; R' = MeO

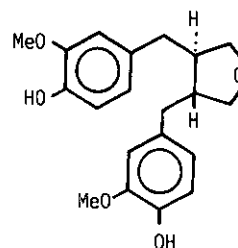
12 R = Bz; R' = H

13 R = R' = H



14 R = Bz

15 R = H

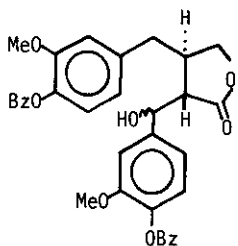


16

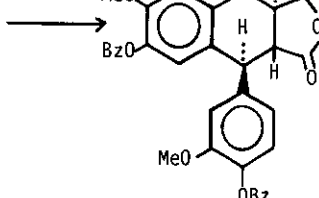
4  $\longrightarrow$  (R,S)-5  $\longrightarrow$  (R)-(+)-5  $\longrightarrow$  (R)-(+)-3  $\longrightarrow$  (R)-(+)-6

(R)-(+)-6 + 8  $\longrightarrow$  9  $\longrightarrow$  10

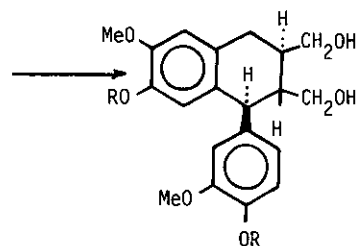
(R)-(+)-6 + 11  $\longrightarrow$  12  $\longrightarrow$  13    12  $\longrightarrow$  14  $\longrightarrow$  15



17



18



19 R = Bz    20 R = H

acid in AcOH/CH<sub>2</sub>Cl<sub>2</sub> for 4 h 30 min at RT, thus affording 0-dibenzylretrodendrin 18, mp 178-180°C (CH<sub>2</sub>Cl<sub>2</sub>/MeOH), [α]<sub>D</sub> -63° (c 1.15, CHCl<sub>3</sub>) and in 78% yield after chromatography. LiAlH<sub>4</sub> reduction of the lactone ring of 18 in THF at RT for 1 h gave 0-dibenzylisolariciresinol 19, mp 122-123.5°C (AcOEt/Et<sub>2</sub>O), [α]<sub>D</sub> +1° (c 1, CHCl<sub>3</sub>), and in 80% yield after chromatography. <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ(ppm) : 7.7-7.2 (10H, m), 6.9 (1H, d), 6.7 (3H, m), 6.3 (1H, s), 5.16 (2H, s), 4.86 (2H, s), 3.83 (3H, s), 3.71 (3H, s), 3.66 (1H, m), 3.5 (2H, d), 3.36 (2H, d), 2.96-2.6 (4H, m), 2.15-1.56 (2H, m). Finally, catalytic hydrogenolysis (H<sub>2</sub> 3 atm., Pd-C, AcOEt, RT, 18 h) of the benzyl groups of 19 furnished natural (+)-isolariciresinol 20, mp 149-151°C (CHCl<sub>3</sub>), [α]<sub>D</sub> +68° (c 0.84, Me<sub>2</sub>CO) and in 81% yield after chromatography. The literature indicates<sup>9</sup> mp 155-157°C (CHCl<sub>3</sub>/MeOH) and [α]<sub>D</sub> +68° (c 1, Me<sub>2</sub>CO).

All the compounds described in this paper were characterized by IR and <sup>1</sup>H-NMR spectroscopy. The twelve new compounds (R)-3, (S)-3, 4, (R,S)-5, (R)-5, (S)-5, (R)-6, 9, 12, 14, 18 and 19 also gave good microanalytical results.

### Conclusion

The present work confirms the fact that resolution of α-benzylhemisuccinic esters can provide an efficient and easy access to natural lignans and their enantiomers. By this method, in the present work as well as in previous ones,<sup>1</sup> we were able to obtain in a preparative fashion eighteen optically active lignoids, including ten natural lignans.

### REFERENCES

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Received, 15th December, 1986