# THE SYNTHESES OF (R)-(+)-β-VANILLYL-γ-BUTYROLACTONE AND OF CHIRAL LIGNANS THEREFROM

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Abstract - (R)-(+)-β-vanillyl-γ-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.[1] We now describe here the synthesis of the hitherto unknown (R)-(+)-β-vanillyl-γ-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 ($H_2$, 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)-(+)-α-methylbenzylamine in AcOEt. The least soluble salt was purified by recrystallization giving fine needles, mp 126-134°C, $[\alpha]_D^{20}$ +28° (c 1, $CHCl_3$) (74% yield). Treatment of this salt with aqueous HCl nearly quantitatively afforded the pure half-ester (R)-(+)-5, mp 97.5-100.5°C ($Et_2O$) and $[\alpha]_D$ +29° (c 1.2, MeOH). Recrystallization of the more soluble salt gave big macles, mp 104-108°C, $[\alpha]_D$ -12° (c 1.2, $CHCl_3$) and in 68% yield. Acidic treatment of the latter gave the half-ester (S)-(-)-5, mp 98-101°C and $[\alpha]_D$ -29° (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 $Ca(BH_4)_2$ as the reducing agent,[2] thus affording the desired β-vanillyl-γ-butyrolactone (R)-(+)-3 in 83% yield, mp 119.5-121.5°C ($CH_2Cl_2/Et_2O$) and $[\alpha]_D$ +10° (c 1, $CHCl_3$). The half-ester (S)-(-)-5 similarly yielded the lactone (S)-(-)-3, mp 119-121°C and $[\alpha]_D$ -10° ($CHCl_3$).

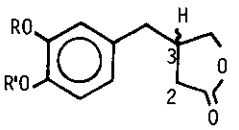
Syringaldhyde was O-benzylated using benzyl chloride ($EtOH/KI/K_2CO_3$, 6 h reflux, 90% yield) and subsequent $NaBH_4$ reduction of the aldehydic carbonyl quantitatively afforded the alcohol 7, mp 47-49°C ($Et_2O$/petroleum ether) which was described as an oil.[3] Treatment of the latter with $PBr_3$ 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 ($Me_2CO$, 16 h). The resulting compound (R)-(+)-6 was thus obtained in 90% yield, mp 80-81.5°C and $[\alpha]_D$ +4° ($CHCl_3$).

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, $[\alpha]_D$ -20° (c 1, $CHCl_3$), in 78% yield after chromatography. The benzyl groups of 9 were cleaved by catalytic hydrogenolysis ($H_2$, 3 bars, Pd-C, AcOEt, 15 h) and (-)-thujaplicatin methyl ether 10 was thus obtained in 78% yield, having mp 168-168.5°C ($Me_2CO/H_2O$) and $[\alpha]_D$ -44° (c 1.1, $Me_2CO$), after recrystallization from $Me_2CO/H_2O$. The literature[4] indicates mp 167-167.5°C and $[\alpha]_D$ -48.7° (c 4, $Me_2CO$).

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[5] gave O-dibenzylmatairesinol 12 as a viscous colourless oil in 87% yield after chromatography, having $[\alpha]_D$ -22° (c 1, $CHCl_3$). 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 Rf, presumably a dialkylated product. The fact that the use of LHDS may lead to a purer alkylation product was recently disclosed in the literature.[6] Catalytic hydrogenation ($H_2$, Pd-C, AcOEt) of the benzyl groups of 12 gave natural (-)-matairesinol 13 in 80% yield after chromatography, mp 70-72°C ($EtOH/H_2O$) and $[\alpha]_D$ -43° (c 0.84, $Me_2CO$). The literature[7] indicates mp 117-119°C ($CHCl_3$) and $[\alpha]_D$ -42.8° ($Me_2CO$).

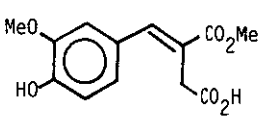
$LiAlH_4$ reduction in THF at RT of the lactone ring of compound 12 gave the diol 14, mp 113-114.5°C, $[\alpha]_D$ -24° (c 0.9, $CHCl_3$) in 66% yield. Catalytic hydrogenolysis ($H_2$, Pd-C, AcOEt) of the benzyl groups of 14 afforded natural (-)-secoisolariciresinol 15 in 76% yield, mp 112-113.5°C, $[\alpha]_D$ -32° (c 0.8, $Me_2CO$). The literature[8] indicates mp 112-114°C, $[\alpha]_D$ -32° ($Me_2CO$). The diol 15 was dehydrated and cyclized by means of $HClO_4$ in refluxing acetone for 20 min, thus leading to natural (-)-anhydrosecoisolariciresinol 16, mp 120.5-121.5°C, $[\alpha]_D$ -62° (c 0.5, EtOH) in 74% yield after chromatography. The literature indicates mp 118-118.5°C and $[\alpha]_D$ -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 $H_2SO_4$, 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-3α ; (S)-(-) : H-3β

1 R,R' = $CH_2$
2 R = R' = Me
3 R = Me ; R' = H
6 R = Me ; R' = Bz



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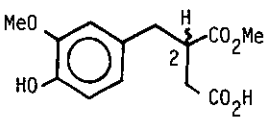
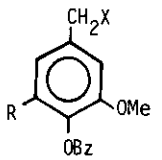
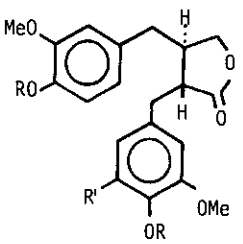


(R,S)-5
(R)-(+)-5 : H-2α
(S)-(-)-5 : H-2β

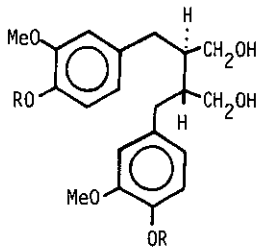
Bz = $-CH_2C_6H_5$



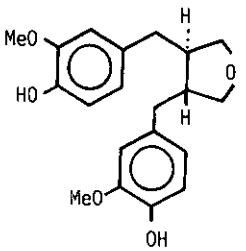
7 X = OH, R = MeO
8 X = Br, R = MeO
11 X = Br, R = H



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



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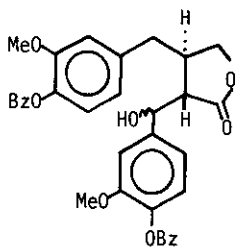
4 ⟶ (R,S)-5 ⟶ (R)-(+)-5 ⟶ (R)-(+)-3 ⟶ (R)-(+)-6
(R)-(+)-6 + 8 ⟶ 9 ⟶ 10
(R)-(+)-6 + 11 ⟶ 12 ⟶ 13 12 ⟶ 14 ⟶ 15



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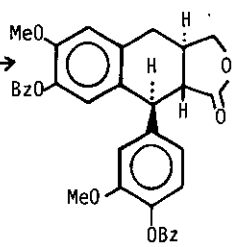

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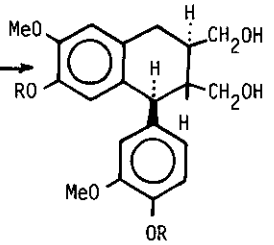

19 R = Bz 20 R = H

acid in AcOH/$CH_2Cl_2$ for 4 h 30 min at RT, thus affording O-dibenzylretrodendrin **18**, mp 178-180°C ($CH_2Cl_2$/MeOH), $[\alpha]_D$ -63° (c 1.15, $CHCl_3$) and in 78% yield after chromatography. $LiAlH_4$ reduction of the lactone ring of **18** in THF at RT for 1 h gave O-dibenzylisolariciresinol **19**, mp 122-123.5°C (AcOEt/$Et_2O$), $[\alpha]_D$ +1° (c 1, $CHCl_3$), and in 80% yield after chromatography. $^1$H-NMR ($CDCl_3$), 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 ($H_2$ 3 atm., Pd-C, AcOEt, RT, 18 h) of the benzyl groups of **19** furnished natural (+)-isolariciresinol **20**, mp 149-151°C ($CHCl_3$), $[\alpha]_D$ +68° (c 0.84, $Me_2CO$) and in 81% yield after chromatography. The literature indicates[9] mp 155-157°C ($CHCl_3$/MeOH) and $[\alpha]_D$ +68° (c 1, $Me_2CO$).

All the compounds described in this paper were characterized by IR and $^1$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,[1] we were able to obtain in a preparative fashion eighteen optically active lignoids, including ten natural lignans.

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