Tetrahedron Letters,Vol.27,No.32,pp 3719-3722,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

(R)-(+)-β-VERATRYL-γ-BUTYROLACTONE, A NEW KEY-INTERMEDIATE FOR THE ASYMMETRIC SYNTHESIS OF VARIOUS LIGNANS

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Summary : Methyl α-veratrylhemisuccinate was resolved into its (R)-(+) and (S)-(-) antipodes by (S)-(-) and (R)-(+)-α-methylbenzylamine respectively. Calcium borohydride reduction of the (R)-(+)-hemiester afforded (R)-(+)-β-veratryl-γ-butyrolactone. The latter was used for the synthesis of various naturally occurring lignans such as (+)-dimethylisolariciresinol, (-)-kusunokinin and (-)-dimethylmatairesinol.

In a recent paper[1] we described a new and simple synthesis of (R)-(+) and (S)-(-)-β-piperonyl-γ-butyrolactones, which are key-intermediates for various lignans and biologically active lignan analogues.[2] Following a similar line, we describe here the synthesis of the hitherto unknown (R)-(+) and (S)-(-)-β-veratryl-γ-butyrolactones 2, and the synthesis of various optically active lignans starting from (R)-(+)-2.

The known racemic half-ester 1 is readily available in a one hundred gram scale by Stobbe condensation on veratraldehyde, followed by catalytic hydrogenation.[3] This racemic half-ester 1 was treated with (S)-(-)-α-methylbenzylamine (1 equivalent) in ethyl acetate. The least soluble salt was recrystallized four times, to reach constant m.p. 125-127.5°C and specific rotation $[\alpha]_D$ +17° (c 1, $CHCl_3$). This pure salt (obtained in 40% yield) was treated with dilute HCl, almost quantitatively affording the optically pure half-ester (R)-(+)-1, m.p. 99-101,5°C (ether), $[\alpha]_D$ +27° (c 1.2, ethanol). A partially resolved sample of (S)-(-)-1 having $[\alpha]_D$ -20° (obtained from the previous experiment) was treated with (R)-(+)-α-methylbenzylamine (1 equivalent) in AcOEt and the least soluble salt was recrystallized to reach constant m.p. 125-129°C and $[\alpha]_D$ -17° ($CHCl_3$). This pure salt was acidified as above, quantitatively yielding the half-ester (S)-(-)-1, m.p. 99.5-101.5°C, $[\alpha]_D$ -28° (c 0.92, EtOH).

A sample of (S)-(-)-1 was racemized without decomposition or side-reactions by refluxing with 2 equivalents of sodium methoxide in dry methanol for 24 hours.

The half-ester (R)-(+)-1 was reduced with calcium borohydride in ethanol, as described in the racemic series,[3] affording the β-veratryllactone (R)-(+)-2 as a colourless oil, $[\alpha]_D$ +8° (c 2.69, $CHCl_3$) and in nearly quantitative yield after molecular distillation. The enantiomeric lactone (S)-(-)-2, $[\alpha]_D$ -8° (c 1.95, $CHCl_3$) was similarly obtained from the half-ester (S)-(-)-1.

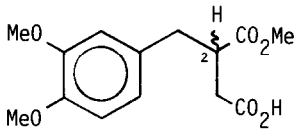
The lactone (R)-(+)-2 was next hydroxyalkylated with veratraldehyde using hexamethyldisilazide as a base[4] (benzene solution, room temperature, 4 min), thus affording the epimeric mixture of alcohols 3 in 88% yield. This mixture was intramolecularly cyclized with CF_3CO_2H in

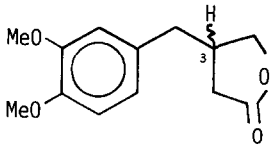
CH_2Cl_2 at RT for 4 hours,[4] giving (-)-α-dimethylretrodendrin 4, m.p. 188-189°C, $[\alpha]_D$ -58° (c 1, acetone) in about 90% yield. Lit.[5] m.p. 189.5-191.5°C, $[\alpha]_D$ -58° (acetone). The lactone ring of 4 was reduced with $LiAlH_4$ in THF at RT for 2 h 30 min, affording (+)-dimethylisolariciresinol 5, m.p. 176-178°C (MeOH), $[\alpha]_D$ +12° (c 0.64, $CHCl_3$), in 84% yield after recrystallization. Lit.[5] m.p. 175-177°C and $[\alpha]_D$ +12° ($CHCl_3$).

The lactone (R)-(+)-2 was alkylated with piperonyl bromide in dry THF, using lithium diisopropylamide as a base (-80°C, 3 h), giving (-)-kusunokinin 6 as an amorphous solid, $[\alpha]_D$ -36° (c 1.1, $CHCl_3$), in 81% yield after chromatography. Lit.[6] $[\alpha]_D$ -31.4°. A sample of (-)-kusunokinin 6 was reduced with diisobutyl aluminium hydride in toluene at -80°C for 2 hours, giving (-)-3,4-dimethoxy-3,4-desmethylenedioxycubebin 7, m.p. 88-90°C (needles from ether), $[\alpha]_D$ -53° (c 0.86, $CHCl_3$), in 82.5% yield after recrystallization. The literature[7] indicates m.p. 89-91°C (no optical rotation is reported).

In a similar fashion, the lactone (R)-(+)-2 was alkylated with veratryl bromide in dry THF using LDA as a base, at -78°C for 3 hours. (-)-Dimethylmatairesinol 8, m.p. 128.5-130.5°C (AcOEt/cyclohexane), $[\alpha]_D$ -35° (c 1.95, $CHCl_3$), was thus obtained in 62% yield after chromatography and recrystallization. The literature[8] indicates m.p. 127-128°C (MeOH) and $[\alpha]_D$ -35.6° (c 3.7, $CHCl_3$). Partial reduction of the lactonic carbonyl of (-)-dimethylmatairesinol 8 using DIBAL in toluene at -80°C for 2 hours, gave (-)-9 as a sharp-melting solid, m.p. 146-148°C (needles from CH_2Cl_2/Et_2O), $[\alpha]_D$ -41° (c 0.76, $CHCl_3$), in 88% yield after recrystallization. The literature[6] indicates m.p. 147-148°C, $[\alpha]_D$ -19.8° (solvent unknown) for (-)-kusunokinol 9 (stereochemistry at C-2 unspecified). However, the specific rotation $[\alpha]_D$ -41° we observed for (-)-9 is in good agreement with the corresponding data observed for the following two very closely related lignans, compound 7, $[\alpha]_D$ -53° (see above) and (-)-cubebin 10, $[\alpha]_D$ -45.9° (c 2, $CHCl_3$).[9] *On the other hand, reduction of (±)-dimethylmatairesinol 8, m.p. 107.5-109.5°C* (Et_2O), using DIBAL in toluene at -78°C, afforded (±)-9 as a sharp-melting solid, m.p. 145-147°C (needles from Et_2O). The ^{1}H-NMR spectrum of (±)-9 in $CDCl_3$ solution showed a broad peak at δ 5.25 ppm ascribed to the hemiacetalic proton at C-2. The ^{13}C-NMR of (±)-9 in $CDCl_3$ solution showed a splitting of various signals, and especially of the signal of the C-2 hemiacetalic carbon which appeared at δ 103.45 ppm and δ 98.47 ppm, thus affording a proof of the presence of two C-2 epimers in solution, in the ratio ca 60:40 respectively. The chemical shift of the C-2 of the major epimer is very close to the corresponding value (δ 103.5 ppm) reported for (-)-cubebin 10.[10] By comparison of the ^{13}C-NMR data was observed for (±)-9 with those reported by CAMBIE and coworkers[11] for similar compounds, α- and β-intermedianols, whose structure was unambiguously established by X-ray, we can ascribe to the major epimer of (±)-9 (in solution) a 2-OH group in the β position corresponding to the more stable trans C-2, C-3 stereochemistry. *Moreover it can be inferred that crystalline synthetic (-)-9 as well as (-)-cubebin 10 have a β-OH.* The discrepancy between the $[\alpha]_D$ values of (-)-9 (2β-OH) and (-)-kusunokinol 9[6] might be due to the fact that the latter is the 2α-OH epimer.

Finally, treatment of (-)-dimethylmatairesinol 8 with $LiAlH_4$ in THF at room temperature for 3 hours afforded (-)-dimethylsecoisolariciresinol 11, m.p. 122,6-124°C (CH_2Cl_2/ether),

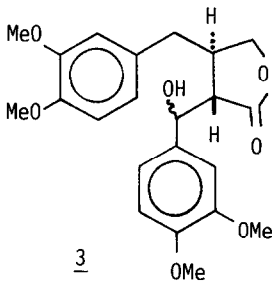




(R)-(+)-1 H-2α ⟶ (R)-(+)-2 H-3α

(S)-(-)-1 H-2β ⟶ (S)-(-)-2 H-3β

(R)-(+)-2 ⟶ 3



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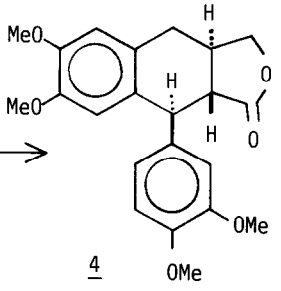

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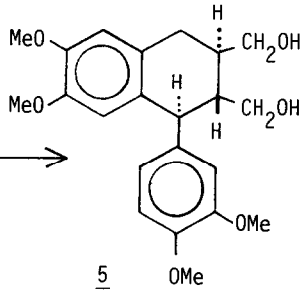

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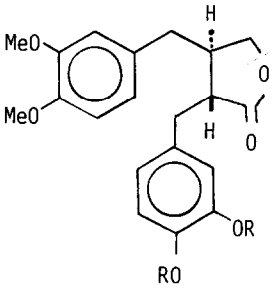
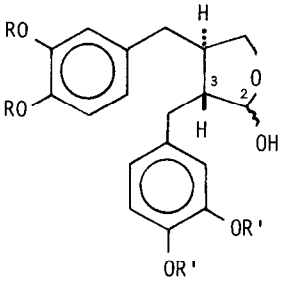
(R)-(+)-2 ⟶ 6 ⟶ 7



6 R,R = -CH_2-

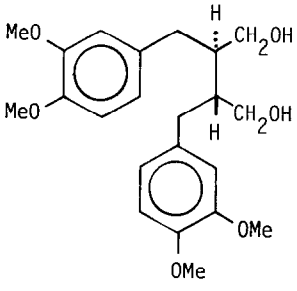
8 R = Me



7 R = Me ; R',R' = -CH_2-

9 R = R' = Me (α- and β-OH)

10 R,R = R',R' = -CH_2-



11

(R)-(+)-2 ⟶ 8 ⟶ 9

8 ⟶ 11

$[\alpha]_D$ - 33° (c 1, $CHCl_3$) in 88 % yield after recrystallization. The literature[12] indicates m.p. 121-123°C, $[\alpha]_D$ - 33°.

All the compounds described in this paper were characterized by IR and ^{1}H-NMR spectrometry. The new compounds (R)-(+)-1, (S)-(-)-1, (R)-(+)-2 and (S)-(-)-2 also gave good microanalytical results.

Conclusion

We have prepared (R)-(+)-β- veratryl-γ-butyrolactone 2 in four steps from veratraldehyde, including resolution of the intermediate methyl α-veratrylhemisuccinate (R,S)-1 by means of (S)-(-)-α-methylbenzylamine. The "non natural" antipode (S)-(-)-1 can be racemized and recycled in view of further resolution, which makes the whole synthetic process both economical and preparative.

We used the lactone (R)-(+)-2 as a starting material for the asymmetric synthesis of the seven lignans 4-9 and 11. This is the first time the natural compounds 5-9 and 11 are obtained in optically active form by total synthesis.

Aknowledgements

We thank Dr. R. DHAL for useful discussions.

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(Received in France 7 June 1986)