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A SIMPLE PREPARATION OF (R)-(+)-ß-(3,4,5-TRIMETHOXYBENZYL)-BUTANOLIDE, AND ITS USE IN THE TOTAL SYNTHESES OF NATURALLY OCCURRING DIBENZYLBUTANOLIDE LIGNANS.

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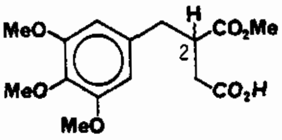
Abstract - Resolution of methyl α-(3,4,5-trimethoxybenzyl)hemisuccinate by means of (-)-ephedrine, followed by calcium borohydride reduction, afforded (R)-(+)-ß-(3,4,5-triméthoxybenzyl)butanolide. This lactone was used as a starting material for the optically active syntheses of 8 recently discovered lignans belonging to, or deriving from the α,ß-dibenzylbutanolide series, such as isoyatein, cubebinone and dihydroclusin.

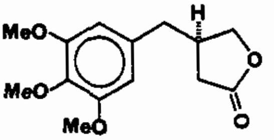
Amongst the natural lignans belonging to the α,ß-dibenzylbutanolide series, very few examples are known in which the ß-benzyl group is substituted by three methoxy groups in the 3,4 and 5 positions. We describe here the total syntheses of such lignans in optically active form, following a strategy similar to the one we used for the syntheses of other more widespread α,ß-dibenzylbutanolide lignans.[1]

Racemic methyl α-(3,4,5-trimethoxybenzyl)hemisuccinate (R,S)-1,[2] mp 127-129°C (CH_2Cl_2/Et_2O), was treated with (-)-ephedrine in acetone. Acidification of the least soluble salt afforded the dextrorotatory hemiester (R)-(+)-1, mp 95-97°C (CH_2Cl_2/Et_2O), $[\alpha]_D^{25}$ +21° (c 1, MeOH) in 56% yield. Calcium borohydride reduction[1] of the latter gave the lactone (R)-(+)-2 (94% yield), mp 100-102°C (EtOH) and $[\alpha]_D^{25}$ +7° (c 1, MeOH). This compound had been synthesized in our laboratory some years ago,[3] in nine steps from (S)-glutamic acid according to KOGA's method.[4]

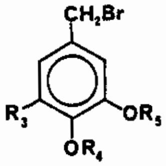
The lactone (R)-(+)-2 was treated with 1.3 equv. of $LiN(SiMe_3)_2$(LHDS) in a THF/hexane mixture at -70°C. After standing for 1 h at -50°C, the resulting anion reacted with the benzylic bromide 3 in THF at -78°C for 30 min, thus affording cordigerine 8 as an amorphous solid (85% yield), $[\alpha]_D^{25}$ -36° (c 1, $CHCl_3$), in agreement with Bruneton's findings.[5] However, Dhar and coworkers[6] reported $[\alpha]_D^{34}$ -42.4° (MeOH) and Mulchandani[7] reported $[\alpha]_D^{25}$ -17.6° (c 0.23, $CHCl_3$) for the same compound. The carbonyl group of cordigerine 8 was reduced with DIBAL in toluene at -78°C for 3 h, thus giving cubebinin 9 as an amorphous solid in 75% yield, $[\alpha]_D^{25}$ -23° (c 1, $CHCl_3$) in agreement with the literature.[7]



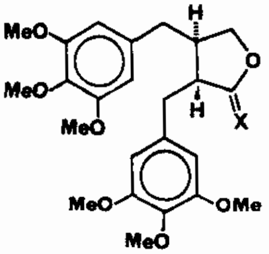
(R,S)-1
(R)-(+)-1, H2-α



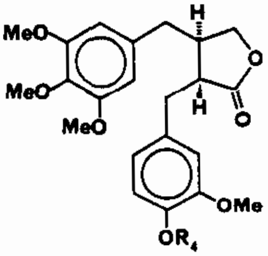
(R)-(+)-2



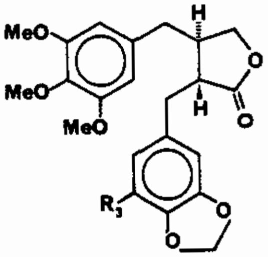
3 R_3 = OMe ; R_4 = R_5 = Me
4 R_3 = H ; R_4 = R_5 = Me
5 R_3 = H ; R_4 = Bz ; R_5 = Me
6 R_3 = H ; R_4 + R_5 = CH_2
7 R_3 = OMe ; R_4 + R_5 = CH_2



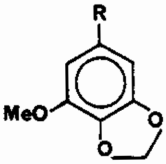
8 X = O
9 X = H,OH



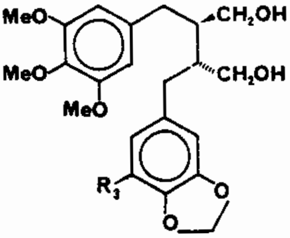
10 R_4 = Me
11 R_4 = Bz
12 R_4 = H



13 R_3 = H
16 R_3 = OMe



14 R = CHO
15 R = CH_2OH



17 R_3 = H
18 R_3 = OMe

2 + 3 → 8 → 9
2 + 4 → 10
2 + 5 → 11 → 12 → 10
2 + 6 → 13 → 17
2 + 7 → 16 → 18
14 → 15 → 7

Alkylation of the lactone (R)-(+)-2 with veratryl bromide 4 was carried out at low temperatures as above (1.3 equv. LHDS/THF/hexane) and yielded the crystalline lignan 10 (82%), mp 117-119°C (EtOH) and $[\alpha]_D^{25}$ -34°(c 0.5, $CHCl_3$). Reported data : mp 120-121.5°C and $[\alpha]_D$ -17.8° (c 0.51, $CHCl_3$) for the natural compound,[8] and mp 122-123°C (EtOH) and $[\alpha]_D^{18}$ -16.1° (c 0.81, $CHCl_3$) for the hemisynthetic compound.[9]

Alkylation of the lactone (R)-(+)-2 with O-benzylvanillyl bromide 5 was carried out at low temperatures, as above (1.3 equv. LHDS/THF/hexane) and gave the compound 11 as an amorphous solid in 88% yield, and having $[\alpha]_D^{25}$ -24° (c 0.5, MeOH). Catalytic hydrogenolysis (H_2, 4 bar/ 10% Pd-C/AcOEt/RT/20 h) of the benzyl ether group of 11 afforded the lignan 12 (amorphous solid, 89%), $[\alpha]_D^{25}$ -33° (c 0.5, EtOH) ; Lit.[9] $[\alpha]_D^{18}$ -25.1° (c 0.55, EtOH). The phenol group of 12 was methylated, using a large excess of diazomethane in ether at room temperature, thus giving the lignan 10 in 97% yield, mp 117-119°C (EtOH) and $[\alpha]_D^{25}$ -34° (c 0.5, $CHCl_3$) in agreement with our findings above.

Alkylation of the lactone (R)-(+)-2 with piperonyl bromide 6 in the usual conditions, yielded the lignan 13 (isoyatein) as an amorphous solid (80%) which slowly crystallized from ethanol, having mp 113-116°C and $[\alpha]_D^{25}$ -33° (c 1, $CHCl_3$) ; Lit.[10] viscous mass, $[\alpha]_D^{25}$ -49.6° (c 0.035, $CHCl_3$).

The known aldehyde 14 was obtained in three steps from vanillin according to Stevenson's method.[11] Reduction of 14 with sodium borohydride in MeOH/CH_2Cl_2 gave the crystalline benzylic alcohol 15, mp 64.4-65.7°C in 99% yield. The latter was next transformed into the unstable benzylic bromide 7 (70%), mp 96-100°C (Et_2O), on treatment with PBr_3 in Et_2O at 20°C for 1 h. Alkylation of the lactone (R)-(+)-2 with the bromide 7 was performed in the usual conditions, and the expected lignan 16 (cubebinone) was thus obtained as an amorphous solid (81% yield) which slowly crystallized from ethanol, having m.p. 108-110°C and $[\alpha]_D^{25}$ -37° (c 1, $CHCl_3$) ; Lit.[10] viscous mass, $[\alpha]_D^{25}$ -36.1° (c 0.083, $CHCl_3$).

On reduction with $LiAlH_4$ in THF at room temperature for 3 h, isoyatein 13 afforded the diarylbutane lignan 17 (dihydroclusin) in 92% yield, m.p. 95-97°C (EtOH) and $[\alpha]_D^{25}$ -29° (c 1, $CHCl_3$). These data are in agreement with Mulchandani[7] who reported mp 97-98°C and $[\alpha]_D^{25}$ -27.13° (c 0.24, $CHCl_3$) for dihydroclusin 17 isolated from *Piper cubeba*. Dhar and coworkers[6] reported mp 68-70°C (EtOH) and $[\alpha]_D^{20}$ -48° (MeOH) for the lignan 17 isolated from *Piper clusii*. Koga[12] reported mp 95-96°C and $[\alpha]_D^{20}$ -29.9° ($CHCl_3$) for the lignan 17 of synthetic origin.

Finally, reduction of the lactone ring of cubebinone 16, using $LiAlH_4$ in THF at room temperature for 3 h, gave the diarylbutane lignan 18 (90% yield), mp 150-154°C and $[\alpha]_D^{25}$ -31° (c 1, $CHCl_3$). Dhar and coworkers[6] reported mp 58-60°C (EtOH) and $[\alpha]_D^{36}$ -28° (MeOH) for the lignan 18 isolated from *Piper clusii*.

Conclusion - In this paper we have described the optically active total syntheses of 8 recently discovered lignans deriving from (R)-(+)-ß-(3,4,5-trimethoxybenzyl)butanolide 2. The present, and the previously reported $[\alpha]_D$ values for the dibenzylbutanolide lignans 8, 10, 12, 13 and 16 are displayed in the following table. It can be seen that $[\alpha]_D$ values consistently remain in a narrow range (from -32° to -35°), which is not surprising since the corresponding lignans 8, 10, 12, 13 and 16 only differ from each other by minor variations in the substitution pattern at the 3, 4 and 5 positions of the α-benzyl group. Therefore we believe that our $[\alpha]_D$ values are correct and correspond to optically pure compounds. Although the spectral data (IR, ^1H- and ^{13}C-NMR) of our synthetic compounds always matched well with those reported in the literature for the same compounds of natural origin, the above table shows some striking discrepancies in the $[\alpha]_D$ values. This may be due to the fact that some of those natural products, as being very often minor components, were not isolated in a chemically or optically pure form.

	$[\alpha]_D$ values*	
Lignan	Found	Lit. (Ref.)
8	-36°	-36°(5), -42.4°(34°C,MeOH)(6), -17.6°(7)
10	-34°	-17.8°(8), -16.1°(at 18°C)(9)
12	-33°(EtOH)	-25.1°(18°C,EtOH)(9)
13	-33°	-49.6°(10)
16	-37°	-36.1°(10)

* Measured at 25°C in $CHCl_3$ unless otherwise stated.

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