

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

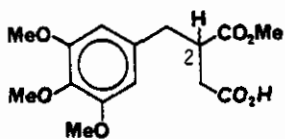
Khalid Lalami, Robert Dhal, and Eric Brown
Laboratoire de Synthèse Organique, Faculté des Sciences,
Route de Laval, BP 535, 72017 Le Mans Cedex, France

Abstract - Resolution of methyl α -(3,4,5-trimethoxybenzyl)hemisuccinate by means of (-)-ephedrine, followed by calcium borohydride reduction, afforded (R)-(+)- β -(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,β -dibenzylbutanolide series, such as isoyatein, cubebinone and dihydroclusin.

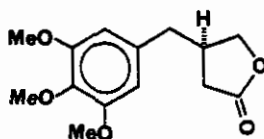
Amongst the natural lignans belonging to the α,β -dibenzylbutanolide series, very few examples are known in which the β -benzyl group is substituted by three methoxy groups in the 3,4 and 5 positions. We describe here the total syntheses of such lignans in optically active form, following a strategy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

Racemic methyl α -(3,4,5-trimethoxybenzyl)hemisuccinate (R,S)-1,² mp 127-129°C (CH₂Cl₂/Et₂O), was treated with (-)-ephedrine in acetone. Acidification of the least soluble salt afforded the dextrorotatory hemiester (R)-(+)-1, mp 95-97°C (CH₂Cl₂/Et₂O), [α]_D²⁵ +21° (c 1, MeOH) in 56% yield. Calcium borohydride reduction¹ of the latter gave the lactone (R)-(+)-2 (94% yield), mp 100-102°C (EtOH) and [α]_D²⁵ +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

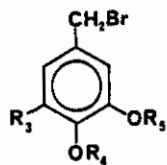
The lactone (R)-(+)-2 was treated with 1.3 equiv. of LiN(SiMe₃)₂ (LHDS) in a THF/hexane mixture at -70°C. After standing for 1 h at -50°C, the resulting anion reacted with the benzylic bromide 3 in THF at -78°C for 30 min, thus affording cordigerine 8 as an amorphous solid (85% yield), [α]_D²⁵ -36° (c 1, CHCl₃), in agreement with Bruneton's findings.⁵ However, Dhar and coworkers⁶ reported [α]_D²⁵ -42.4° (MeOH) and Mulchandani⁷ reported [α]_D²⁵ -17.6° (c 0.23, CHCl₃) for the same compound. The carbonyl group of cordigerine 8 was reduced with DIBAL in toluene at -78°C for 3 h, thus giving cubebinine 9 as an amorphous solid in 75% yield, [α]_D²⁵ -23° (c 1, CHCl₃) in agreement with the literature.⁷



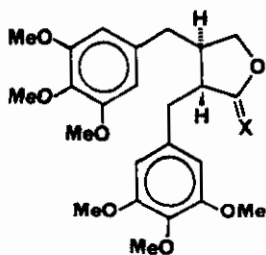
(R,S)-1
(R)-(+)-1, H₂-α



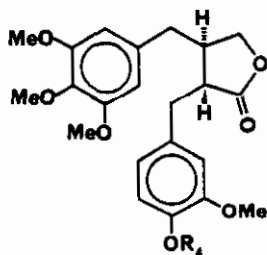
(R)-(+)-2



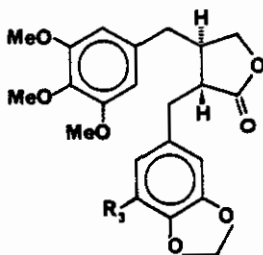
- 3 R₃ = OMe ; R₄ = R₅ = Me
4 R₃ = H ; R₄ = R₅ = Me
5 R₃ = H ; R₄ = Bz ; R₅ = Me
6 R₃ = H ; R₄ + R₅ = CH₂
7 R₃ = OMe ; R₄ + R₅ = CH₂



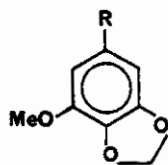
- 8 X = O
9 X = H, OH



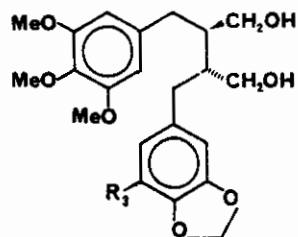
- 10 R₄ = Me
11 R₄ = Bz
12 R₄ = H



- 13 R₃ = H
16 R₃ = OMe



- 14 R = CHO
15 R = CH₂OH



- 17 R₃ = H
18 R₃ = OMe

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

Alkylation of the lactone (R)-(+)-2 with veratryl bromide 4 was carried out at low temperatures as above (1.3 equiv. LHDS/THF/hexane) and yielded the crystalline lignan 10 (82%), mp 117-119°C (EtOH) and $[\alpha]_D^{25} -34'$ (c 0.5, CHCl₃). Reported data : mp 120-121.5°C and $[\alpha]_D -17.8'$ (c 0.51, CHCl₃) for the natural compound,⁸ and mp 122-123°C (EtOH) and $[\alpha]_D^{10} -16.1'$ (c 0.81, CHCl₃) 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 equiv. 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 (H₂, 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.⁸ $[\alpha]_D^{10} -25.1'$ (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, CHCl₃) 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, CHCl₃) ; Lit.¹⁰ viscous mass, $[\alpha]_D^{25} -49.6'$ (c 0.035, CHCl₃).

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/CH₂Cl₂ 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 (Et₂O), on treatment with PBr₃ in Et₂O 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, CHCl₃) ; Lit.¹⁰ viscous mass, $[\alpha]_D^{25} -36.1'$ (c 0.083, CHCl₃).

On reduction with LiAlH₄ 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, CHCl₃). These data are in agreement with Mulchandani⁷ who reported mp 97-98°C and $[\alpha]_D^{25} -27.13'$ (c 0.24, CHCl₃) for dihydroclusin 17 isolated from *Piper cubeba*. Dhar and coworkers⁶ reported mp 68-70°C (EtOH) and $[\alpha]_D^{20} -48'$ (MeOH) for the lignan 17 isolated from *Piper clusii*. Koga¹² reported mp 95-96°C and $[\alpha]_D^{20} -29.9'$ (CHCl₃) for the lignan 17 of synthetic origin.

Finally, reduction of the lactone ring of cubebinone 16, using LiAlH₄ 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, CHCl₃). Dhar and coworkers⁶ reported mp 58-60°C (EtOH) and $[\alpha]_D^{26} -28'$ (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)-(+)- β -(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.)
<u>8</u>	-36°	-36° (5), -42.4° (34°C , MeOH)(6), -17.6° (7)
<u>10</u>	-34°	-17.8° (8), -16.1° (at 18°C)(9)
<u>12</u>	-33° (EtOH)	-25.1° (18°C , EtOH)(9)
<u>13</u>	-33°	-49.6° (10)
<u>16</u>	-37°	-36.1° (10)

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

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