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TOTAL SYNTHESIS OF THE LIGNANS (-)- AND (+)-BURSERAN, (-)-CUBEBIN, AND (-)-HINOKININ BY DIASTEREOSELECTIVE CONJUGATE ADDITION OF BENZYL ANIONS TO 2-(R)- AND (S)-BENZYLOXY-2,5-DIHYDRO-4-(3,4-METHYLENEDIOXYBENZOYL)FURAN.

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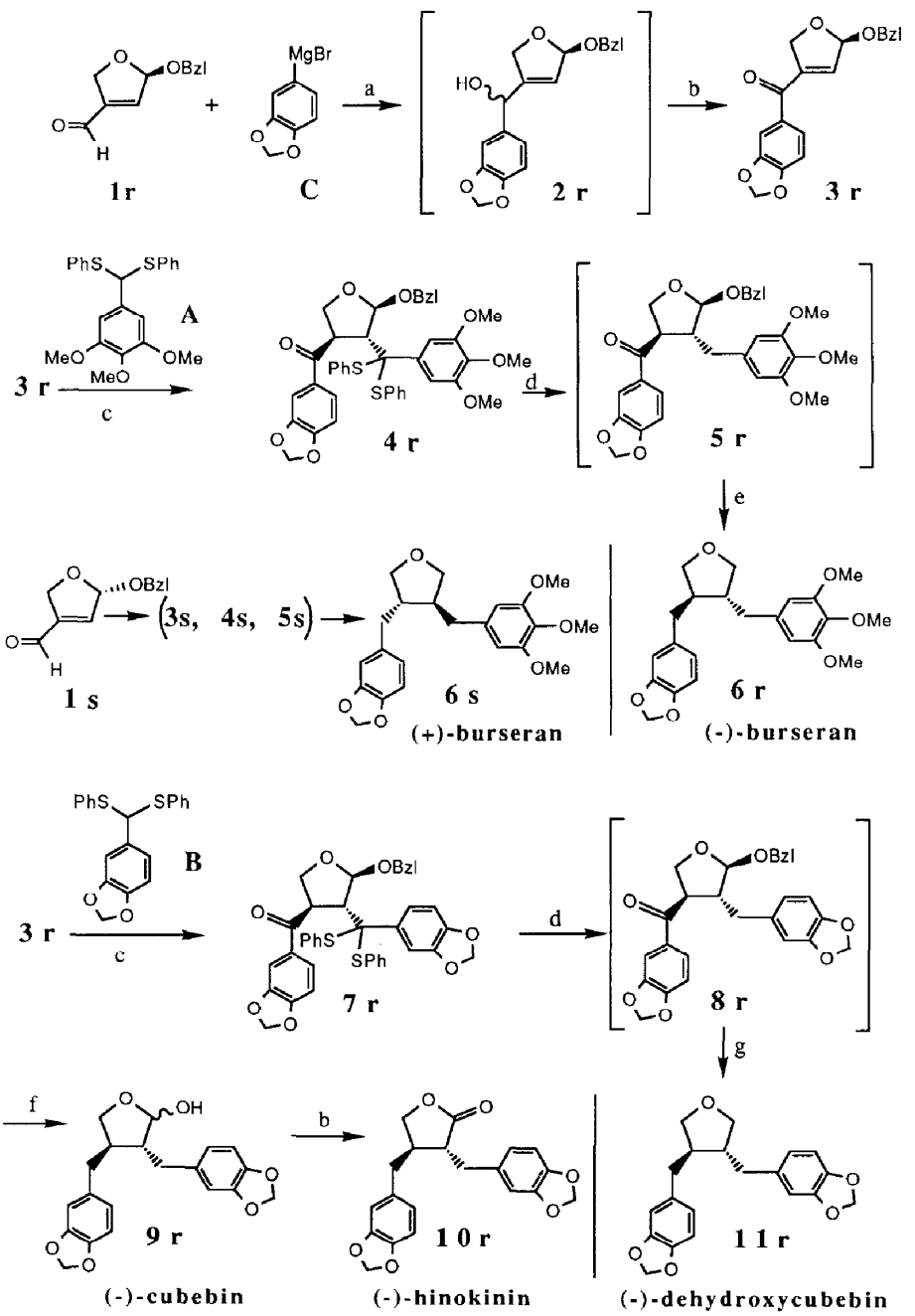
SUMMARY: 1,2-Addition of 3,4-methylenedioxymagnesium bromide to 2-(R) and (S)-benzyloxy-2,5-dihydro-4-furancarboxaldehyde, followed by oxidation, gave the title ketones (**3r** and **3s**). Conjugate addition of the anions of 3,4,5-trimethoxy- and 3,4-methylenedioxybenzaldehyde diphenylthioacetal to **3r** and **3s** and Raney-nickel desulfurisation, followed by hydrogenolysis under various conditions, gave the title lignans. (-)-Burseran was prepared in >98% diastereomeric excess.

Plant lignans[1] with dibenzylbutane-, podophyllotoxin-, and steganin-related skeleta are being used for the development of chemotherapeutic agents[2]. Crude plant material has been used in folk medicine by the North American indians[3] and by the Chinese[4]. Recently, enterolactone and enterodiol, both lignans of the dibenzylbutane class, were isolated from human urine[5].

A large number of total syntheses of these natural products, including racemic hinokinin[6] have been reported and reviewed[7]. In the dibenzylbutyrolactone class, pure enantiomers have been synthesised in only a few cases including burseran[8] and (-)-podhorizon[9]. The absolute configuration of natural burseran has not been determined.

We recently reported[10] the synthesis of both enantiomers of the γ-lactol mycotoxin botryodiplodin *via* 1,4-addition of lithium methylcyanocuprate to the chiral isoprene units **1r** and **1s** respectively[11]. We now report the total synthesis of natural (-)-cubebin[12] (**9r**) and (-)-hinokinin[6] (**10r**), as well as (+) (**6s**) and (-) (**6r**)-burseran[8] by 1,4-addition of the anions of the benzylic dithioacetals **A** and **B** to the chiral α,β-unsaturated ketones **3r** and **3s** (Scheme 1).



Scheme 1. a: tetrahydrofuran, 0°. b: CrO_3/pyridine, dichloromethane, 22°, 15 min. c: **A** or **B**, n-butyllithium, tetrahydrofuran, -78°, 20 min; **3r** or **3s**, then -78°--22°. d: Raney-nickel, dimethoxyethane, 0°. e: H_2, 1 atm., 10% Pd/C, acetic acid/water, 9:1, 6.5 h. f: H_2, 4 atm., 10% Pd/C, dimethoxyethane/water/N-ethyldiisopropylamine, 85:15:0.05, 20 h. g: H_2, 1 atm., 10% Pd/C, acetic acid/dimethoxyethane/water, 5:4:1, 24h,

Treatment of **1r** and **1s**[11] with the Grignard reagent **C** in tetrahydrofuran at 0° gave the alcohols **2r** and **2s** , which, after extractive work-up, were oxidised with chromium trioxide/pyridine in dichloromethane at room temperature[13]. Chromatography on silica gel gave the ketones **3r** and **3s** in 90% over-all yield. Addition of the anion of **A**[14] (generated by addition of n-butyllithium in tetrahydrofuran) to **3r** and **3s**, followed by chromatographic purification gave **4r** and **4s** (60%), respectively. Similarly, the anion of **B**[14] was added to **3r** to give **7r** (78%). Desulfurisation of **4r**, **4s**, and **7r** with Raney nickel in dimethoxyethane gave the crude ketones **5r**, **5s**, and **8r** respectively. These ketones were used in the following step without purification. However, **8r** was purified for structure confirmation by ^{1}H-nmr spectroscopy. Hydrogenation (H_2, 1 atm., Pd/C, acetic acid/water, 9:1) of **5r** and **5s** gave (-)- and (+)-burseran (**6r** and **6s**, 52%), respectively. Hydrogenation (H_2, 4 atm., Pd/C) of **8r** in a slightly basic solvent mixture (dimethoxyethane/water/N-ethyldiisopropylamine, 85:15:0.05) gave natural (-)-cubebin (**9r**, 36%). Oxidation of **9r** with chromium trioxide/pyridine in dichloromethane at room temperature gave natural (-)-hinokinin (**10r**, 83%). Hydrogenation of **8r** in acidic medium (cf. the preparation of **6r** and **6s** above) gave (-)-dehydroxycubebin[15] (**11r**, 43% from **7r**). The final products (**6r**, **6s**, **9r**, **10r**, and **11r**) were purified by chromatography on silica gel. Physical and spectroscopic data are presented in Table 1.

The ^{1}H-nmr detection limit of **6s** in **6r** was shown to be approx. 1% by addition of a suitable amount of the chiral shift reagent tris-[3-(heptafluoropropylhydroxy-methylene)-d-camphorato]-europium to a solution of **6r/6s** (97:3) and recording the methylenedioxy proton signals. **6s** could not be detected in the spectrum of synthetic **6r**; therefore, the enantiomeric excess (e.e.) of **6r** in the synthetic sample was >98%. This high e.e. emanates from the high degree of diastereoselectivity in the conjugate addition of **A** to **3r** (Scheme 1). It is probable that the reaction of **B** with **3r** resulted in equally high optical purities for **9r**, **10r**, and **11r** (cf. Table 1).

Table 1. Physical and Spectral Data[a]

Compound	M.p. (°C)	$[\alpha]_D^{23}$ (°)[b]	^{1}H-nmr data[c] (δ ppm/J Hz)
3r	49-52	-49	6.12/s
3s		+47	6.12/s
4r	60.5-64	+97	5.61/d, 0.5
4s		-91	5.61/d, 0.5
6r		-45 (Lit[8]: -35)	5.93/q, 1.3
6s		+44 (Lit[8]: +38)	5.93/q, 1.3
7r	65-68	+45	5.38/d, 1.0
8r		-87	4.95/d, 2.0
9r	125-128	-69[d] (Lit[16]: -68)	5.13/d, 4.6; 5.11/d, 2.4
10r		-35 (Lit[17]: -34)	4.13/dd, 6.9, 9.2; 3.86/dd, 7.0, 9.1
11r		-55 (Lit[15]: -45, -37)	3.90/dd, 6.8, 8.7; 3.50/dd, 6.1, 8.7

a) Correct elemental analyses were obtained for the crystalline compounds **3s**, **4r**, **7r**, and **9r**; ^{13}C-nmr data for **6r**, **10r**, and **11r** were in agreement with published data[8,6,15]. b) c~1, $CHCl_3$. c) $CDCl_3$/Me_4Si. **3r/s**, **4r/s**, **7r**, **8r**, **9r**: "anomeric" (O-C<u>H</u>-O) signal; **6r/s**: O-C<u>H</u>$_2$-O signal; **10r**: CH_2-OCO signal; **11r**: C<u>H</u>$_2$-O-C<u>H</u>$_2$-signal. d) c~0.5, CD_3OD.

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14. Compounds **A** and **B** were prepared (M. Tazaki and M. Takagi. Chem. Lett., **1979**, 767) by treating the corresponding aldehyde with diphenyl disulfide and tributylphosphine followed by aqueous work-up and chromatography. **A** had: mp 100-101°; ^{1}H-nmr δ 7.26-7.39 (m, 10 H, PhS), 6.54 (s, 2 H, arom.), 5.35 [s, 1 H, $(PhS)_2CH$], 3.83 (s, 3 H, OMe), 3.73 (s, 6 H, OMe). **B** had: ^{1}H-nmr δ 7.24-7.38 (m, 10 H, PhS), 6.99 (d, 1 H, J 1.8 Hz, arom.), 6.78 (dd, 1 H, J 8.0, 1.8 Hz, arom.), 6.66 (d, 1 H, J 8.1 Hz, arom.), 5.95 (s, 2 H, OCH_2O), 5.36 [s, 1 H, $(PhS)_2CH$].
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