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DIASTEREOSELECTIVE CONJUGATE ADDITION OF LITHIUM METHYLCYANOCUPRATE TO THE CHIRAL ISOPRENE UNITS 2-(R)- AND (S)-BENZYLOXY-2,5-DIHYDRO-4-FURANCARBOXALDEHYDE. TOTAL SYNTHESIS OF (-)- AND (+)-BOTRYODIPLODIN AND (+)- AND (-)-EPI-BOTRYODIPLODIN.

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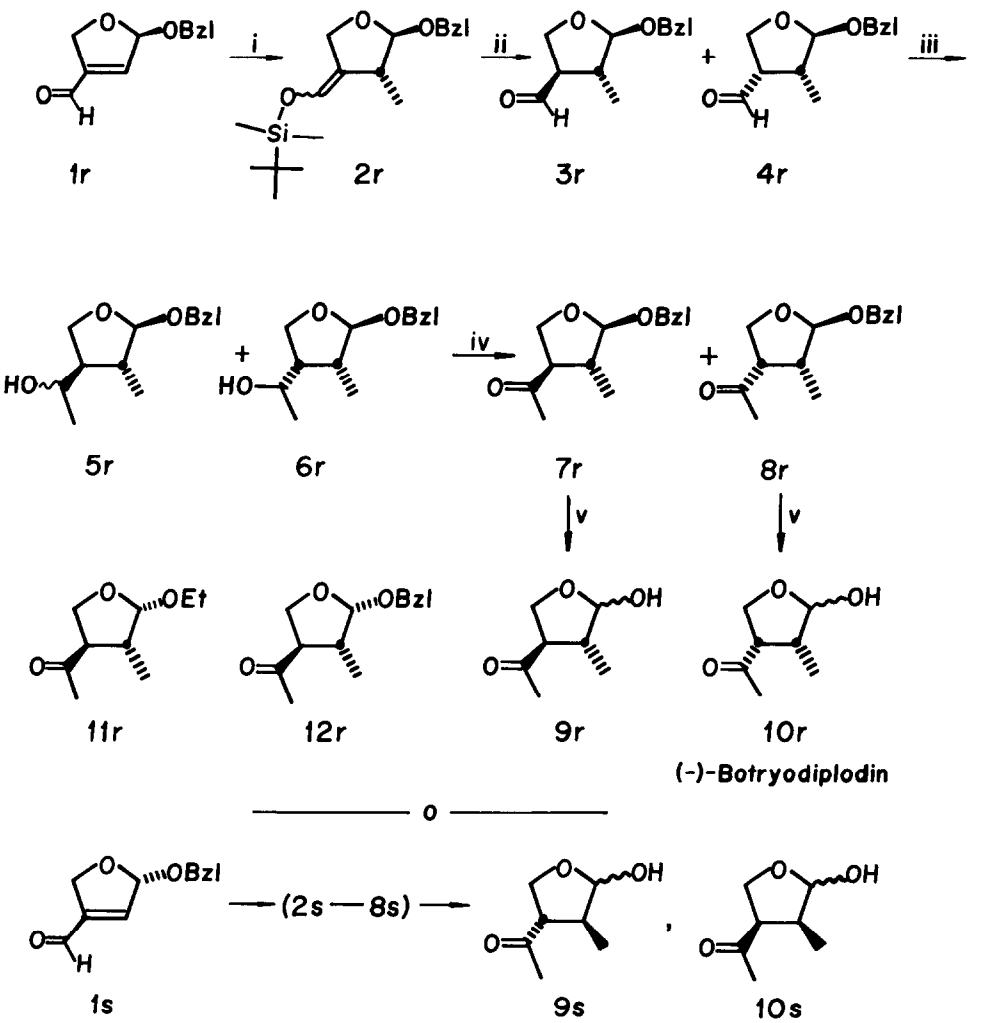
SUMMARY: Conjugate addition of lithium methylcyanocuprate to the title aldehydes proceeded with high diastereoselectivity (d.e. 94%). Methyl lithium 1,2-addition, followed by Swern oxidation of the resulting alcohols, gave benzyl botryodiplodin and benzyl epi-botryodiplodin. Hydrogenolysis of the benzyl groups gave the enantiomeric pairs of botryodiplodin **10r** and **10s** and epi-botryodiplodin (**9r** and **9s**).

Diastereoselective conjugate addition has been increasingly used for the synthesis of chiral compounds, and different approaches have been reported such as the utilisation of chiral auxiliary groups and chiral nucleophiles[1]. The chiral aldehydes **1r** and **1s**[2] carry an anomeric center of "disposable chirality", which was utilised to direct the incoming nucleophile in the conjugate addition step. These aldehydes were earlier used as chiral dienophiles in a Diels-Alder reaction with cyclopentadiene[3].

Reaction of **1r** and **1s** with lithium methylcyanocuprate in the presence of t-butyldimethylsilyl chloride[4] gave the silyl ethers **2r** and **2s** (chromatography gave the pure compounds in 87% yield) with an E/Z ratio of ~ 20:1. The crude product contained a small amount (~3%) of the anticipated 2,3-cis compound[5]. This high diastereofacial selectivity and the easy removal of the undesired isomer by chromatography made it possible to synthesise enantiomerically pure botryodiplodin (natural **10r**[6] and unnatural **10s**) and its epimer (**9r**[7] and **9s**). (-)-Botryodiplodin (**10r**) is a mycotoxin with antibiotic and antileukemic properties[8]. It has been prepared from natural methylenomycin[9] and the

racemate **10r/10s** was prepared by total synthesis[10]. The biosynthetic route of botryodiplodin (**10r**) has been determined[11].



Scheme 1. i) LiMeCNCu, t-BuMe$_2$SiCl, THF, -78-23°C; ii) Bu$_4$NF 3H$_2$O, THF/HOAc (19:1), 23°C; iii) MeLi, Et$_2$O, -78-23°C; iv) (COCl)$_2$, DMSO, (iPr)$_2$EtN, -60-23°; v) H$_2$, 1atm., 10% Pd/C, DME/H$_2$O, 3:1

Removal of the silyl group in **2r** and **2s** with $Bu_4NF \cdot 3H_2O$ in THF/HOAc (19:1) gave the aldehydes **3r/4r** and **3s/4s** (91%), respectively. Treatment of the aldehyde mixtures with MeLi in ether gave the alcohols **5r/6r** and **5s/6s** (91%). **5r** and **5s** were diastereomeric mixtures, whereas **6r** and **6s** were pure enantiomers. Swern oxidation of **5r/6r** and **5s/6s** gave the ketones **7r/8r** and **7s/8s** (94%; epimeric ratio ~ 9/1), which were all obtained in pure form by chromatography (SiO_2, heptane/EtOAc, 10/1). Treatment of **7r** or **8r** with methanolic sodium methoxide established the equilibrium **7r⇌8r** to be ~5:1. Hydrogenolysis (H_2, 1 atm, Pd/C, $H_2O/MeOCH_2CH_2OMe$, 1:3) of **7r**, **7s**, **8r**, and **8s** then gave essentially pure natural (**9r**) and unnatural (**9s**) epi-botryodiplodin and natural (**10r**) and unnatural (**10s**) botryodiplodin, as shown in Scheme 1. In our hands chromatography on silica gel led to severe deterioration of the products. Futhermore, the volatile nature of **9** and **10** resulted in loss of material on removal of the solvents (typical yields: 80-95%). Alternative conditions for hydrogenolysis (H_2, 1 atm, Pd/C, EtOH) and hydrolysis (HOAc/H_2O 3:1, 80°C) of **7r** gave **9r** and small amounts of **11r** and **12r**, respectively[5].

Table 1. Physical and spectral data[a]

Compound	$[\alpha]_D^{23}$(°)[b]	^{1}H-nmr data[c] (δppm/JHz)
2r	-88	4.85/0,8; 4,88/s[d]
2s	+87	4.85/0,8; 4,88/s
3r	-102	4.87/1.1
4r		4.89/s
3s	+103	4.87/1.1
4s		4.89/s
5r	-117	4.81/1.0; 4,80/1.1
5s	+118	4.81/1.0; 4.80/1.1
6r	-125	4.84/s
6s	+125	4.84/s
7r	-103	4.82/2.1
7s	+102	4.82/2.1
8r	-143	4.87/s
8s	+143	4.87/s
9r	+87	5.35/4.4; 5.05/1.0
9s	-83	5.35/4.4; 5.05/1.0
10r	-69[e]	5.18/s
10s	+69	5.18/s
11r		4.93/4
12r		5.03/4.6

[a] Correct elemental analyses were obtained for one enantiomer of each pair **2r/s-8r/s**; [b] (c~1, $CHCl_3$); [c] O-C<u>H</u>-O; [d] s=singlet [e] Lit.[12]: $[\alpha]_D^{25}$ -70.12° (c 0.124, MeOH) and Lit.[9]: $[\alpha]_D^{25}$ -69.1° (c 0.13, MeOH).

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References and notes

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5. The ^{1}H-nmr detection limit of **12r** in **7r** was shown to be ~0.3% by addition of 1% of **12r** to **7r** and recording the H-2 (anomeric proton) signals. **12r** could not be detected in the spectrum of **7r/8r** prepared according to Scheme 1. An anomeric proton doublet (5.00 ppm, 5.6 Hz) was detected in crude **2r**, indicating the presence of ca. 3% of a 2,3-cis isomer. This signal had disappeared in the spectrum of purified **2r**. We therefore conclude that the LiMeCNCu-addition gives **2r** (and **2s**) with a diastereomeric excess of 94% which increased to >99.4% after chromatography.

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