

ORIGINAL PAPER

Total synthesis of cannabisin F

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A practical eight-step synthesis of lignanamide cannabisin F starting from vanillin is reported for the first time. This synthetic strategy applies the aldol reaction followed by the Wittig reaction to afford the key 8-*O*-4'-neolignan intermediate diacid. The diacid was condensed with *N,O*-protected tyramine giving, after deprotection, cannabisin F.

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Introduction

Cannabis sativa is an annual plant (Sakakibara et al., 1995; Jiang et al., 2006) whose fruit has been used as anti-asthma, anti-constipation, and anti-helminthic drug. As research proceeds, some of the secondary metabolites have been isolated in *Cannabis sativa* such as cannabinoids, flavonoids, stilbenoids, terpenoids, alkaloids, and lignanamides (Flores-Sanchez & Verpoorte, 2008), among which the lignanamide family exhibited interesting and diverse biological activities, including feeding deterrent activity, insecticidal effects, antitumour-promoting effect, and anti-inflammatory activity (Li et al., 2012). However, only the synthesis of one lignanamide, cannabisin G, has been reported (Xia et al., 2010). Li et al. (2010) have also successfully synthesised cannabisin G by oxidative coupling as a key step.

Cannabisin F belongs to the lignanamides, and it was first isolated from cannabis fruits and roots in 1995 (Sakakibara et al., 1995). It has been suggested that cannabisin F exhibited cytotoxic activity (Chen et al., 2006), cell-growth inhibitory activities against human lung cancer lines A549 and human cervical cancer lines HeLa (Li et al., 2012). In this paper, the first total synthesis of cannabisin F is reported.

Experimental

Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. IR spectra of the compounds in KBr pellets were obtained in the range of 400–4000 cm⁻¹ on a Nicolet NEXUS 670 FTIR spectrometer (Thermo Fisher Scientific, USA). ¹H (500 MHz) and ¹³C (125 MHz) NMR spectra were recorded on a Bruker AM-500 spectrometer. HRMS spectra were obtained on a Bruker Daltonics APEXII47e spectrometer. Flash column chromatography and TLC were performed on silica gel (200–300 mesh) (Qingdao Haiyang Chemical Co., China) and silica gel GF254 plates (Qingdao Haiyang Chemical Co., China), respectively.

All chemicals were used as supplied without further purification unless otherwise specified. Vanillin (4-hydroxy-3-methoxybenzaldehyde), chloroacetic acid, lithium diisopropylamide (LDA), triethylamine (Et₃N), benzenesulfonyl chloride, 4-toluenesulfonic acid (TsOH), 3,4-dihydro-2*H*-pyran (DHP), triphenylphosphine (Ph₃P), pyridinium *p*-toluenesulfonate (PPTS), trifluoroacetic acid (TFA), *N,N'*-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), hydrazine hydrate, chloromethyl methyl ether (methoxymethyl chloride, MOMCl), thionyl chloride (SOCl₂), trimetoxymethane (HC(OCH₃)₃),

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