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Unexpected regioselectivity in the photocyclization of a chiral 2,3-bisbenzylidenesuccinate, leading to a podophyllotoxin related cyclolignan

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ABSTRACT

The Stobbe condensation between 3′,4′,5′-trimethoxyacetophenone and a benzylidenesuccinate derived from piperonal gave the *Z*,*E*-2,3-bisbenzylidenesuccinate as the only product. Such regioselectivity was explained by considering the Newman's projections of the transition states of this reaction. Introducing L-prolinol as a chiral auxiliary, macrolactonization and subsequent photocyclization of the atropoisomeric cyclic amide ester led to new cyclolignan analogue. By comparing the regioselectivity observed in this study with our previous results, some general rules regarding the photocyclization of chiral 2,3-bisbenzylidenesuccinates could be established.

1. Introduction

Podophyllotoxin (PPT, **1**) (Fig. 1) is the best known representative of lignans due to its antitumor properties [1]. Semisynthetic derivatives of podophyllotoxin, etoposide **2** and teniposide **3** are currently in clinical use [2]. However, their therapeutic potential is limited because of low water solubility, low selectivity [3] and a drug resistance [4]. New derivatives are being tested to overcome negative effects of those compounds [5,6].

In 2004 Charlton and co-workers presented the first asymmetric photocyclization approach to the synthesis of cyclolignans, using (-)-(1*R*,2*S*)-ephedrine as a chiral auxiliary [7]. This method allowed to obtain a *trans* configuration at C-1 and C-2 of the cyclolignan (+)-lyoniresinol dimethyl ether. In 2011 we demonstrated that the use of L-(+)-prolinol as a chiral auxiliary resulted in the formation of (1*R*,2*R*)-*cis*-dihydronaphthalene [8], which has the same configuration at C-1 and C-2 as in PPT, albeit the opposite absolute configuration. Interestingly, the cyclization was found to be initiated at the amide, and not the ester carbonyl, as would be predicted with regard to the reactivity of fulgenates. Later, using a similar methodology, a formal synthesis of PPT was completed [9]. In this case the cyclization occurred on the ester-bound fragment of the molecule, and thus the resulting cyclolignan had the same absolute configuration as **1**.

In this paper we describe our efforts in the stereoselective synthesis of (1*R*)-methylpodophyllotoxin, using the previously described methodology (Fig. 2). The methyl group at C-1 would influence the angle between trimethoxyphenyl and dihydronphathalene plane and, in consequence on binding of those compounds to the active side of tubuline/topoisomerase II [10]. Although a vast amount of cyclolignans were synthetized, C-1-methyl derivatives of PPT were not studied to date [11].

2. Experimental

All chemicals were purchased from Sigma-Aldrich and used as received. Piperonal, 3′,4′,5′-trimethoxyacetophenone and *t*-BuOK were flushed with dry argon and kept under inert atmosphere after every use. Toluene was dried by boiling for ca. 2 h with pieces of Na metal and subsequent distillation, and was stored over activated molecular sieves, 3 Å. Methanol was dried with KOH powder for 24 h, distilled and was stored over activated molecular sieves, 3 Å. Dichloromethane (DCM) was dried by storing it over activated molecular sieves, 3 Å, for at least 3 days. TLC analysis was performed on Merck TLC plates

(silica gel 60 F_{254} on glass plates). ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Bruker AVANCE 500/300 spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. High-resolution mass (ESI-TOF MS) spectra were run on the Micromass LCT spectrometer. Melting points were determined on a Melting Point Meter KSP1D and were uncorrected.

Diethyl 2*E*-(3,4-methylenedioxybenzylidene)butanedioate (6) was prepared in accordance with the procedure previously described

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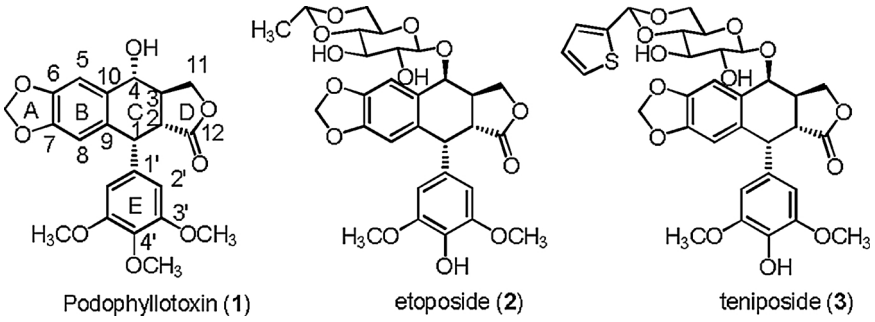

Fig. 1. Structures of podophyllotoxin, etoposide and teniposide.

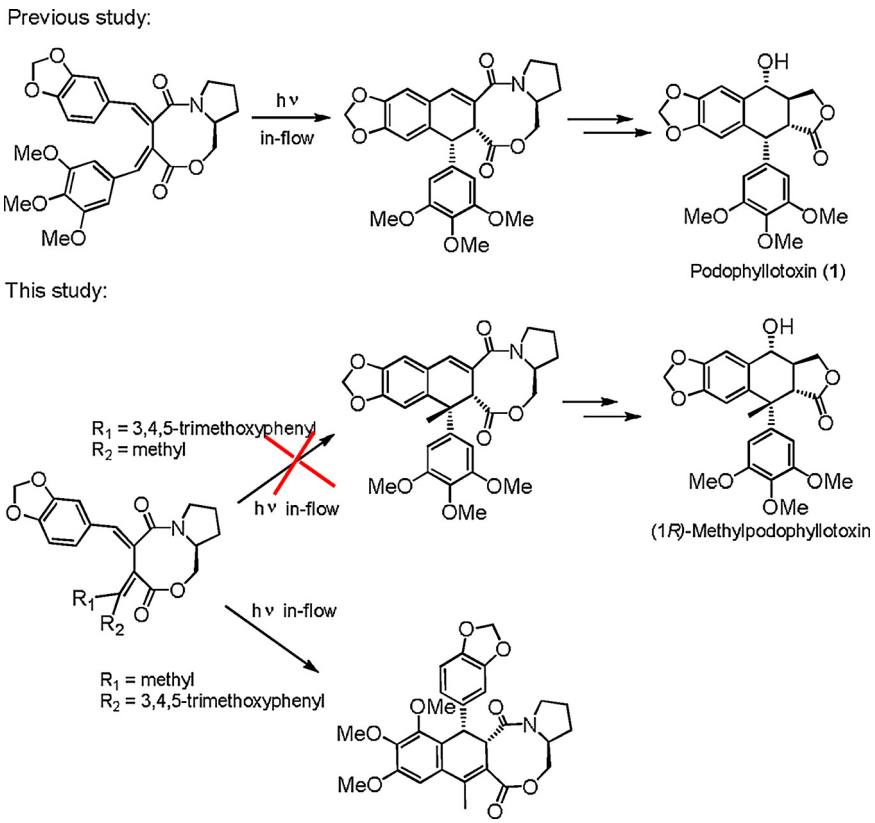

Fig. 2. Comparison of previous [9] and current studies.

[9], but starting from 35.0 g (1 eq, 140 mmol) of diacid **5** in 250 mL of dry ethanol and 50 mL of AcCl. 36.4 g (119 mmol, 60%, over 2 steps) of yellow oil of **6** was obtained. **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 200 MHz): δ 7.72 (s, 1 H), 6.91-6.81 (m, 3 H), 6.00 (s, *2*H), 4.27 (q, J = 7.2 Hz, 2 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.54 (s, 2 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 171.4, 167.7, 148.1, 148.1 141.7, 129.2, 125.1, 124.2, 109.3, 108.7, 101.6, 61.3, 61.2, 34.0, 14.4, 14.4. HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{18}O_6Na$ $[M + Na]^+$, 329.0996; found, 329.1010.

2*E*-(3,4-methylenedioxybenzylidene)-3*Z*-(3,4,5-trimethoxymethylbenzylidene)butanedioic acid monoethyl ester (7) was prepared in accordance with the procedure previously described [9], but starting from 403 mg (1.1 eq, 3.59 mmol) of t-BuOK in 15 mL of dry toluene and mixture of 686 mg (1.0 eq, 3.26 mmol) of 3′,4′,5′-trimethoxyacetophenone and 1.0 g (1.0 eq, 3.26 mmol) of diester **6** in 15 mL of dry toluene. The product (936 mg, 1.99 mmol, 61%) is a yellowish gum which foams upon solvent removal. **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 300 MHz): δ 7.89 (s, 1 H), 7.32 (s, 1 H), 7.06 (d, J = 7.5 Hz, 1 H), 6.79 (d, J = 7.5 Hz, 1 H), 6.43 (s, 2 H), 5.97 (s, 2 H), 3.94 (q, J = 6.9 Hz, 2 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 1.79 (s, 3 H), 0.90 (t, J = 6.9 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.2, 171.9, 168.6, 153.1, 153.0, 149.2, 148.0, 144.6, 138.5, 132.0, 128.9, 126.1, 108.7, 108.4, 108.4, 108.3, 105.7, 103.7, 101.6, 60.9, 60.7, 56.4, 56.1, 23.4, 13.7. HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{25}O_9$ $[M-H]-$, 469.1504; found, 469.1519.

Monoethyl (*S*)-(+)-2-pyrrolidinemethanol-2*E*-(3,4-methylenedioxybenzylidene)-3*Z*-(3,4,5-trimethoxymethylbenzylidene)butanediate amide ester (8) was prepared in accordance with the procedure previously described [9], but starting firstly from 1 g (1.0 eq, 2.13 mmol) of the monoester **7** in 40 mL of dry DCM and 195 µL (2.0 eq, 4.36 mmol) of oxalyl chloride and after first step oily residue was dissolved in 20 mL of dry DCM and added dropwise, under argon, to a stirring solution of 234 µL L-prolinol (1.1 eq, 2.40 mmol) and 914 µL of triethylamine (3.1 eq, 6.57 mmol) in 20 mL of dry DCM. 0.75 g (1.35 mmol, 64%) of product **8** was obtained. Crystals suitable for X-ray analysis were grown by slow evaporation of the ethanol solution. M.p. 155.7–156.9 °C. $[\alpha]_D^{25}$ = +215.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 300 MHz): δ 7.17 (d, J = 1.8 Hz, 1 H), 6.93 (ddd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, J_3 = 0.6 Hz, 1 H), 6.89 (s, 1 H), 6.79 (d, J = 8.1 Hz, 1 H), 6.35 (s, 2 H), 5.96 (dd, J_1 = 1.5 Hz, J_2 = 1.2 Hz, 2 H),