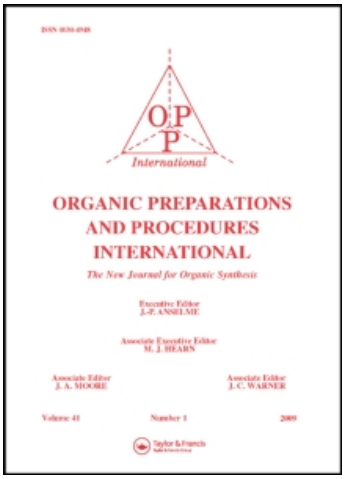

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A NOVEL AND CONVENIENT METHOD FOR THE SYNTHESIS OF PHENSTATIN

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A NOVEL AND CONVENIENT METHOD FOR THE SYNTHESIS OF PHENSTATIN

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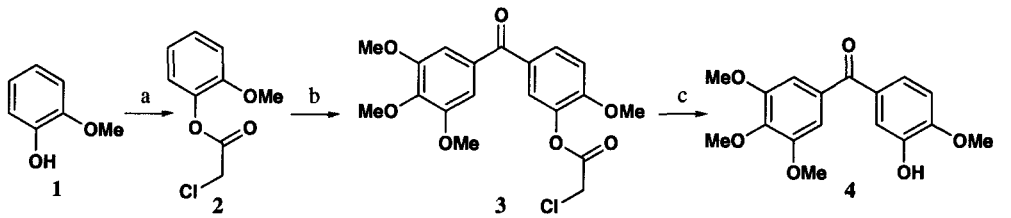
Phenstatin (**4**), a combretastatin A-4 (CA-4) derivative designed from the CA-4 skeleton by replacement of the olefin group with a carbonyl group, was found to be a potent anti-tubulin agent by the Pettit's group and displays excellent anticancer and antimitotic activities comparable to those of CA-4.[1] It is used as standard for antitublin test and is now under preclinical studies[2-9] with the potential to be developed as a drug.[10,11] Pettit's group reported the synthesis of phenstatin starting from 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde by

oxidation to the corresponding carboxylic acid, followed by conversion to the acid chloride and treatment with morpholine. Reaction of the amide with the lithium derivative prepared from 3,4,5-trimethoxybromobenzene and *tert*-butyllithium at –78°C followed by deprotection afforded phenstatin in 30% overall yield.[1] Another synthetic method was reported by Liou and coworkers starting from 3,4,5-trimethoxybromobenze and 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde in 3 steps (no yields given).[5]

This paper reports a new approach to **4** in a more economical and efficient route (60% overall yield) as shown in *Scheme 1*, in which the rarely used[12] but easily cleaved chloroacetyl function was selected as the protecting group of guaiacol and using polyphosphoric acid (PPA) as condensing agent.



a) Chloroacetyl chloride, 135°C, 4 h; b) 3,4,5-Trimethoxybenzoic acid, PPA, 85-90°C, 4 h; c) $CH_3COONa•3H_2O$, CH_3OH, 3 h, reflux, total yield 58%

Scheme 1

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 melting apparatus, and are not corrected. ^1H NMR spectra were recorded on Brucker-400 NMR spectrometer. Microanalyses were carried out on a Leco CHN-2000 Elemental Analyzer. Mass spectra were obtained on a MAT-95 spectrometer. All reagents were commercial products from China National Medicines Group Shanghai Chemical Reagents Company.

Preparation of 2-Methoxyphenyl Chloroacetate (2).- Guaiacol (10 g, 0.08 mol) and chloroacetyl chloride (13 g, 0.115 mol) were placed into a 100 mL flask. The mixture was heated to 135°C and refluxed for 4 hours[13] with stirring, then cooled to r.t. Cold water (10 mL) was added carefully to react with excess acid chloride. The mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was washed sequentially with water, saturated $NaHCO_3$, brine, then dried over anhydrous $MgSO_4$. The solvent was evaporated in *vacuo* and yielded a yellow oil, which was dissolved in hot ethanol (25 mL) and recrystallized to afford 11.5 g (71%) of pure **2**, mp 58-60°C (*lit.*[13] mp. 60°C). The mother liquor was purified by silica gel (eluted petroleum ether-ethyl acetate, 1: 10) to give another 3 g of **2**, resulting in an overall yield 90%. ^1H NMR ($CDCl_3$): δ 7.24 (1H, m, H-4), 7.07 (1H, dd, J = 1.6, J = 8, H-6), 6.98 (1H, dd, J = 1.2, J = 8, H-5), 6.96 (1H, m, H-3), 4.35 (2H, s, CH_2Cl), 3.83 (3H, s, $–OCH_3$).

Preparation of Phenstatin Choloroacetate (3).- 3,4,5-Trimethoxybenzoic acid (10 g, 0.047 mol) was mixed by means of a mechanical stirrer with 80 g of PPA[14] at 80°C and stirred for 1 hour, then **2** (3 g, 0.015 mmol) was added the mixture was stirred for an additional 4 hours. It was then added slowly into ice-water with vigorous stirring. The brown solid which precipitated was collected and washed with water (50 mL) and saturated $NaHCO_3$ (80 mL). Recrystallization from ethanol afforded 2.5 g (42%) of solid, mp. 150°C. The alcohol mother liquor was purified by silica gel (eluted petroleum ether-ethyl acetate, 1:1) to give an additional 1.3 g of **3**, resulting in an overall yield of 65%. Unreacted 3,4,5-trimethoxybenzoic acid (5.0 g) could be recovered from the filtrate above by acification to pH 5. ^{1}H NMR (CD_3COCD_3): δ 7.80 (1H, dd, $J_{6/2}$ = 2.1, $J_{6/5}$ = 8.7, H-6), 7.63 (1H, d, $J_{2/6}$ = 2.1, H-2), 7.31 (1H, d, $J_{5/6}$ = 8.7, H-5), 7.05 (2H, s, H-2',6'), 4.61 (2H, s, $-CH_2Cl$), 3.96 (3H, s, 4, $-OCH_3$), 3.85 (6H, s, 3',5'-OCH_3), 3.81 (3H, s, 4'-OCH_3). MS (*m/z, %*): 396 (27, M+2), 395 (18, M+1), 394 (83, M), 318 (100), 303 (24), 287 (20), 275 (24), 195 (33), 151 (32), 124 (48), 109 (22).

Anal. Calcd for $C_{19}H_{19}ClO_7$: C, 57.80; H, 4.85. Found: C, 57.74; H, 4.78

Preparation of Phenstatin (4).- Compound **3** (3 g, 0.008 mol) and sodium acetate trihydrate (5 g, 0.036 mol), were dissolved in 30 mL CH_3OH and refluxed for 3 hours. The solvent was evaporated and the residue was washed with water, dried in air, to give 2.37 g (98%) white solid, mp. 150°C, *lit.*[1] mp. 150°C. ^{1}H NMR ($CDCl_3$): δ 7.44 (1H, d, $J_{2/6}$ = 2.1, H-2), 7.39 (1H, dd, $J_{6/2}$ = 2.1, $J_{6/5}$ = 8.2, H-6), 7.03 (2H, s, H-2',6'), 6.92 (1H, d, $J_{5/6}$ = 8.2, H-5), 5.70 (1H, s, –OH), 3.99 (3H, s, 4-OCH_3), 3.93 (3H, s, 4'-OCH_3) 3.89 (6H, s, 3',5'-OCH_3); MS (*m/z, %*): 318 (100, M), 303 (18), 287 (14), 275 (25), 195 (24), 151 (32).

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.07; H, 5.76

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EXPLOITATION OF CO-OPERATIVE DIRECTED *ortho*-METALLATION (DoM) BY 1,3-RELATED –OMOM GROUPS IN THE DEVELOPMENT OF A FULLY REGIO-CONTROLLED SYNTHESIS OF ATRANOL FROM ORCINOL

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In connection with efforts to develop a total synthesis of the fungal metabolite diversonol[1] we required access to atranol (**5**, *Scheme 1*). The latter compound and its chloro derivative, both of which are powerful allergens, are themselves natural products and found as major components in oak moss absolute, an extract of the lichen *Everia prunatri* and an important ingredient in the perfumery industry.[2] Atranol also represents a key sub-structure associated with a wide-range of other lichen-derived natural products of polyketide origin. It has been prepared, albeit in very low yield, through Vilsmeier-Haack formylation of commercially available orcinol (**1**). The major product of this reaction is, in fact, the regioisomeric orcylaldehyde (**2**)[3] which we