A protecting group-free synthesis of the antineoplastic agent combretastatin A4

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The synthesis of combretastatin A4 (CA4) from commercially available inexpensive materials has been achieved via the Wittig reaction followed by irradiation of the (*Z*)/(*E*)-CA4 reaction mixture with sunlight. The method resulted in (*Z*)-CA4 in high yield. This method does not require protection of the phenolic hydroxy group. The synthesis is operationally simple and cost-efficient.

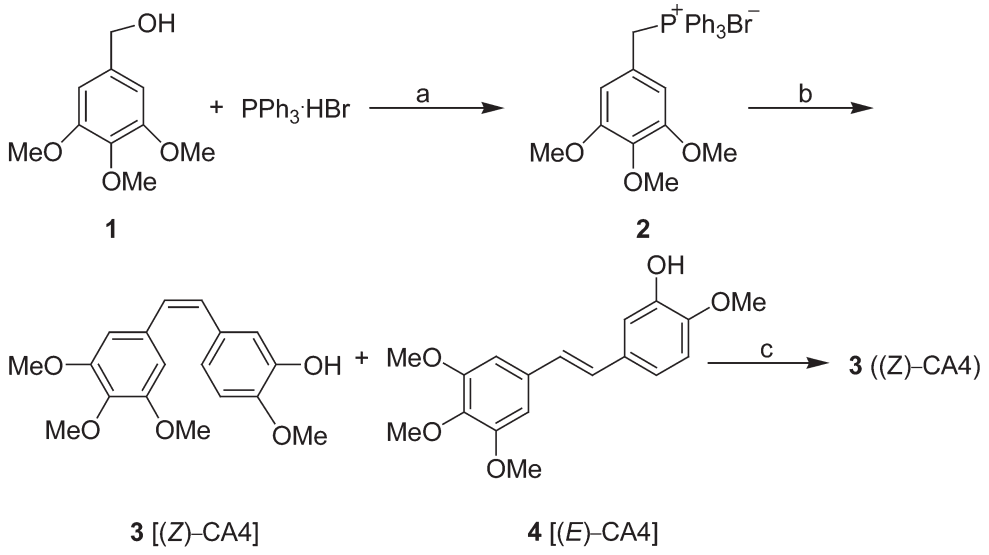
Keywords: antineoplastic agent, combretastatin A4, synthesis, Wittig reaction, irradiation

Combretastatin A4 (CA4) is one of the most potent antineoplastic agents[1,2] and its phosphate, CA4P, has produced positive results in clinical trials. CA4 is a natural product that comes from the bark of the African tree *Combretum caffrum*. The availability of CA4 is limited and therefore a practical synthesis of CA4 is needed to provide enough of the compound for further research and possible large scale production. Several reports have described the synthesis of CA4, such as, a Perkin condensation between 3,4,5-timethoxyphenylacetic acid and vanillin followed by elimination,[3] a one-pot hydrosilylation-protodesilylation of diaryl alkynes,[4] alkyne hydroboration,[5] partial alkyne hydrogenation using Lindlar's catalyst,[6] the Wittig reaction,[7,8] the Ramberg–Bäcklund reaction via a sulfone,[9] and hydrolysis of the Ti(II)-alkyne complexes formed from an alkyne and $Ti(OiPr)_4$/*n*-BuLi.[10]

In most of these methods, the hydroxyl group on the phenol ring must be protected or the reactions have to be conducted under harsh conditions, such as –78 °C,[11] 230 °C[3] or under anhydrous conditions.[12] These latter conditions would substantially add to the cost of production of CA4. In this work, CA4 has been synthesised from the commercially available isovanillin via the Wittig reaction without the need for protection and deprotection steps and the byproduct (*E*)-CA4 has been transformed into (*Z*)-CA4 in high yield.

The synthesis of CA4 is outlined in Scheme 1. Treatment of 3,4,5-trimethoxybenzyl alcohol **1** with triphenylphosphonium bromide in refluxing acetonitrile yielded phosphonium salt **2** in 92% yield. This step avoids the need to prepare unstable 3,4,5-trimethoxybenzyl bromide.[13] The Wittig reaction between isovanillin and the ylide derived from the phosphonium salt **2** was conducted in a series of solvents using different bases and the results are summarised in Table 1. Good yields were obtained for all the reactions (entries 1–13). EtOH/KOH (entry 1), EtOH/Cs_2CO_3 (entry 12), and EtOH/DBU (entry 13) gave almost quantitative yields of the (*E*)/(*Z*)-CA4 mixture and the latter two reactions were completed in shorter times (3 h). In other solvents (water, acetone, acetonitrile or THF), the yields were also high. In all the reactions, the *Z*:*E* ratios are roughly 1:1. Fortunately, part of the (*Z*)-CA4 can be crystallised from a mixture of ethyl acetate and *n*-hexane. The mother liquor was then concentrated and dissolved in ethanol in a Pyrex flask and irradiated by sunlight. This produced another batch of (*Z*)-CA4 which was then isolated via a second crystallisation. After repeating the process twice, an 84%yield of (*Z*)-CA4 was achieved. It has been reported that (*Z*)-CA4 is converted to (*E*)-CA4 in the presence of iodine.[3] However, this is the first report of the transformation of (*E*)-CA4 to (*Z*)-CA4 using sunlight. The possible reason is that (*E*)-CA4 can absorb sunlight and be converted to the excited state to become (*Z*)-CA4. This agrees with the UV spectra of (*E*)-CA4 (λ_{max} = 207 nm, 328 nm, c = 0.1 mmol L^{-1} in EtOH) and (*Z*)-CA4 (λ_{max} = 207 nm, 296 nm, c = 0.1 mmol L^{-1} in EtOH). The overall yield is similar to other synthetic routes in the literature,[3,14,15] but the present procedure is operationally simpler and more cost-efficient.

Following this route, a reaction starting with isovanillyl alcohol **5** lead to **6**,[12] which was reacted with 3,4,5-trimethoxybenzaldehyde to yield CA4 as outlined in Scheme 2. The



Scheme 1 Synthesis of (*Z*)-CA4 using 3,4,5-trimethoxybenzyl alcohol and isovanillin. Reagents and conditions: (a) acetonitrile, reflux, 10 h, 92%; (b) isovanillin (0.8 equiv.), see Table 1 for other details; (c) sunlight, 4 h, 84%.

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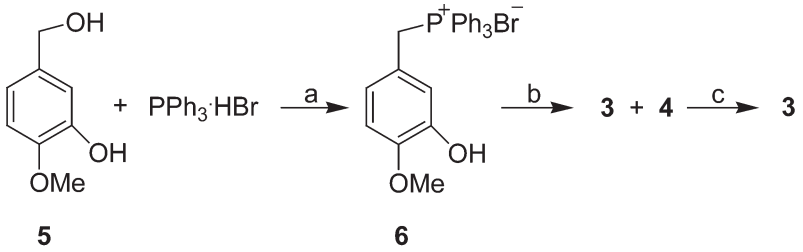

Scheme 2 Synthesis of (*Z*)-CA4 using isovanillyl alcohol and 3,4,5-trimethoxybenzaldehyde. Reagents and conditions: (a) acetonitrile, reflux, 6 h, 84%; (b) 3,4,5-trimethoxybenzaldehyde (0.67 equiv.), see Table 2 for other details; (c) sunlight, 4 h, 84%.

Table 1 Reaction conditions and results for the synthesis of CA4 using **2** and isovanilin

Entry	Reaction time/h	Solvent	Base	Z:E /%	Yield/%
1	6	Ethanol	KOH	55:45	97
2	6	Ethanol	NaOH	56:44	93
3	8	Ethanol	Na_2CO_3	52:48	90
4	8	Ethanol	K_2CO_3	53:47	96
5	8	Water	KOH	56:44	76
6	8	Water	NaOH	51:49	73
7	10	Water	K_2CO_3	54:46	71
8	10	Water	Na_2CO_3	58:42	70
9	7	Acetone	KOH	54:46	82
10	8	Acetonitrile	KOH	53:47	78
11	9	THF	KOH	52:48	74
12	3	Ethanol	Cs_2CO_3	56:44	98
13	3	Ethanol	DBU	57:43	99

Reaction conditions: **2** (1.0 equiv.), isovanilin (0.8 equiv.), base (1.2 equiv.), in refluxing solvents, under N_2.

Table 2 Reaction conditions and results for the synthesis of CA4 using **6** and 3,4,5-trimethoxybenzaldehyde

Entry	Reaction time /h	Solvent	Base	Z:E /%	Yield /%
1	5	Ethanol	KOH	26:74	90
2	5	Ethanol	NaOH	21:79	89
3	6	Ethanol	Na_2CO_3	49:51	85
4	6	Ethanol	K_2CO_3	40:60	88
5	6	Water	KOH	52:48	76
6	6	Water	NaOH	55:45	75
7	8	Water	K_2CO_3	56:44	72
8	8	Water	Na_2CO_3	59:41	70
9	7	Acetone	KOH	57:43	91
10	6	Acetonitrile	KOH	54:46	90
11	7	1,4-dioxane	KOH	56:44	79
12	8	THF	KOH	55:45	77
13	5	Methanol	KOH	52:48	86

Reaction conditions: **6** (1.0 equiv.), 3,4,5-trimethoxybenzaldehyde (0.67 equiv.), base (1.0 equiv.), in refluxing solvents, under N_2.

results are summarised in Table 2. All the yields were good (entries 1–13) and the reactions using stronger bases (entries 1,2,9,10) lead to higher yields and shorter reaction times. The resulting mixture of **3** and **4** was readily transformed into **3** [(*Z*)-CA4] in high yields via sunlight irradiation.

In summary, a new synthesis of CA4, starting from commercially available and inexpensive materials has been carried out. Protection and deprotection steps are not required in this synthesis. For the first time, the transformation of (*E*)-CA4 to (*Z*)-CA4 has been realised using sunlight irradiation. This is a cost-efficient and green method and all the steps involved are operationally simple. This method represents a practical synthesis for CA4.

Experimental

Synthesis of (Z)/(E)-CA4 and transformation of (E)-CA4 to (Z)-CA4

A mixture of acetonitrile (60 mL), 3,4,5-trimethoxybenzyl alcohol (4.531 g, 22.88 mmol) and triphenylphosphonium bromide (7.668 g, 22.36 mmol) was heated to reflux for 10 h. TLC indicated the completion of the reaction. After the evaporation of the solvents, the reaction mixture yielded a crude phosphonium salt. A mixture of the phosphonium salt (1.654 g, 3.162 mmol), isovanillin (0.400 g, 2.632 mmol), K_2CO_3 (0.545 g, 3.949 mmol) and ethanol (35 mL) was heated to reflux for 8 h, TLC indicated the completion of the reaction. After the evaporation of the ethanol, the product was distributed between aq. HCl (5%, 20 mL) and ethyl acetate (30 mL). The organic phase was separated and the aqueous phase re-extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give a crude product (2.054 g) which was subjected to flash chromatography (eluent: PE-EtOAc 5: 1) to give a (*Z*)/(*E*)-CA4 mixture (0.800 g). The mixture was crystallised from ethyl acetate and hexane to yield (*Z*)-CA4 (0.150 g). The mother liquor was concentrated and dissolved in EtOH (700 mL) in a 1000 mL round bottom flask. The EtOH solution was irradiated by outdoor sunlight at 10–14 °C for 4 h to provide another batch of (*Z*)-CA4 (0.200 g) after evaporation of the EtOH and crystallisation from ethyl acetate and hexane. Two further irradiation cycles of the residue after the evaporation of the mother liquor provided crops of (*Z*)-CA4 (0.145 g) and (*Z*)-CA4 (0.198 g). The total yield of (*Z*)-CA4 was 84%.

Electronic Supplementary Information

Detailed ^{1}H NMR assignments and IR data for both (*Z*)-CA4 and (*E*)-CA4 have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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