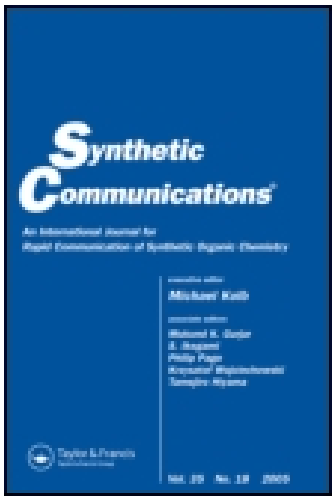

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A CONVENIENT AND EFFECTIVE SYNTHESIS OF 3-(3,5-DIMETHOXYPHENYL)PROPANAL

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ABSTRACT

A convenient and effective synthesis of 3-(3,5-dimethoxyphenyl) propanal, an important intermediate in the synthesis of various biologically active compounds is described.

3-(3,5-Dimethoxyphenyl)propanal **5** is an important intermediate for the synthesis of various isomeric tetrahydrocannabinols[1] and other related cannabinoids or cannabinoid-like compounds, for the stereoselective synthesis of 1-aryl-4a-methyloctahydrophenanthrenes[2] and for the introduction of stable isotopes (e.g. ^{2}H, ^{13}C) in different positions of the above compounds.

However, at present there are only two methods reported for its preparation. The first method[2] involves esterification[3] of trans-cinnamic acid followed by LAH reduction[2] to give 3-(3,5-dimethoxyphenyl)-1-propanol **4**, which is subsequently oxidized under Swern conditions to

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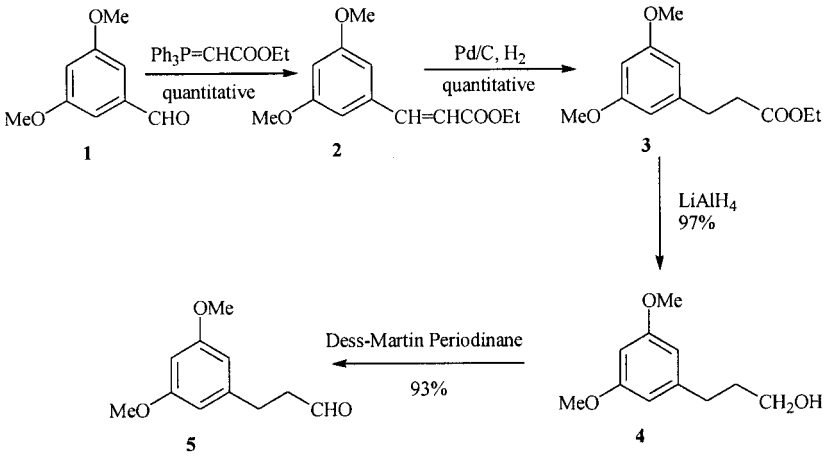

Scheme 1. Sequence of reactions for synthesis of aldehyde **5.**

give **5**. Reported yields are 60% for the combined reduction and oxidation steps and 57% overall yield. The second method[4] involves Perkin condensation of commercially available 3,5-dimethoxybenzaldehyde with acetic anhydride at high temperature to give dimethoxycinnamic acid in 72% yield. This is followed by LAH reduction using a Soxhlet apparatus to the corresponding alcohol **4**, which was then subjected to Swern oxidation with a reported, overall yield of 53%. Our interest in the synthesis of several functionalized cannabinoids required availability of aldehyde **5** on a larger scale. However, in our hands the first method led to inconsistent yields that were generally significantly lower than those reported. In addition, the disadvantages associated with second method such as low overall yield, requirement of high temperature, and long reaction time prompted us to develop a convenient method for the large scale synthesis of this useful intermediate. The present communication describes synthesis of compound **5** from 3,5-dimethoxybenzaldehyde in an overall 90% yield (Scheme 1).

RESULTS AND DISCUSSION

Treatment of 3,5-dimethoxybenzaldehyde with commercially available (carbethoxymethylene)triphenylphosphorane in dry THF afforded an isomeric mixture of ethyl 3,5-dimethoxycinnamate favoring the trans isomer (*cis* : *trans* = 3 : 97) in a quantitative yield. These isomers could be separated by flash column chromatography, thus also affording a convenient route for

the preparation of synthetically very useful but expensive trans-3,5-dimethoxycinnamic acid or its ester. Attempted direct reduction of a mixture of cinnamates using LAH[2] gave the required alcohol in only 55% yield with other by-products. A more effective modification involved, first, catalytic hydrogenation of **2** to give ethyl 3-(3,5-dimethoxyphenyl)propionate **3** in quantitative yields, followed by further reduction using LAH to give alcohol **4** in 97% isolated yield. The yields for both steps were consistent even when the reaction was carried out on 100 g scale. The crude product, which was more than 98% pure (by ^{1}H-NMR), was subjected to oxidation without further purification. The potential difficulties associated with the Swern oxidation[1,2] when used in large scale synthesis, namely the requirement of strictly anhydrous conditions and lower temperatures, led us to the use of pyridinium chlorocromate as oxidant. This afforded the required aldehyde in 79% isolated yield. However, the use of Dess-Martin Periodinane[5] at room temperature in wet dichloromethane led to **5** in excellent yield (93% after column chromatography) in just 1 h. The reaction was clean and was easily scaled up.

Dess-Martin Periodinane was prepared on a large scale by the reported procedure[5] and has a number of advantages such as good to excellent yields obtained, non-requirement of dry conditions and low temperatures. Moreover no toxic by products are formed when DMP is used as an oxidant.[6]

In summary, we have developed a convenient route for the large scale synthesis of 3-(3,5-dimethoxyphenyl)-propanal that offers several advantages over the earlier reported methods leading to higher overall yields while requiring simple reaction conditions and shorter reaction times.

EXPERIMENTAL

Melting points were determined on a micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC-E200 instrument, and chemical shifts are in δ (ppm) relative to internal TMS. All anhydrous solvents were obtained commercially and were used without further drying or purification.

Preparation of Ethyl 3,5-Dimethoxycinnamate (2)

To a stirred solution of (carbethoxymethylene) triphenylphosphorane (314 g, 903 mmol) in anhydrous THF (2.5 l) at 0°C under an argon atmosphere was added a solution of 3,5-dimethoxybenzaldehyde (100 g,

602 mmol) in anhydrous THF (500 ml) over a period of 30 min. Following the addition, the reaction was warmed to room temperature, stirred for an additional 2 h and was then quenched by addition of saturated ammonium chloride. The reaction mixture was diluted with diethyl ether, the organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an oil. The product was purified through a short column of silica gel using 17% Et_2O: petroleum ether as eluent to give compound **2** in quantitative yield (142 g) as a mixture of *cis* and *trans* isomer in 3 : 97 ratio, respectively.

***Cis*-isomer:** colorless viscous oil, ^{1}H-NMR (200MHz, $CDCl_3$): 1.25 (t, $J = 7.0$ Hz, 3H), 3.79 (s, 6H), 4.17 (q, $J = 7.0$ Hz, 2H), 5.93 (d, $J = 12.7$ Hz, 1H), 6.45 (t, $J = 2.2$ Hz, 1H), 6.78 (d, $J = 2.2$ Hz, 2H), 6.84 (d, $J = 12.7$ Hz, 1H).

***Trans*-isomer:** white crystalline solid, m.p. 45–46°C, (lit.[3] 45–46°C) ^{1}H-NMR (200 MHz, $CDCl_3$): 1.34 (t, $J = 7.0$ Hz, 3H), 3.81 (s, 6H), 4.27 (q, $J = 7.0$ Hz, 2H), 6.40 (d, $J = 16.0$ Hz, 1H), 6.49 (t, $J = 2.2$ Hz, 1H), 6.67 (d, $J = 2.2$ Hz, 2H), 7.60 (d, $J = 16.0$ Hz, 1H).

Preparation of Ethyl 3-(3,5-Dimethoxyphenyl)propionate (3)

To a solution of ethyl 3,5-dimethoxycinnamate (100 g, 424 mmol) in ethyl acetate (2.1 l) was added 10% Pd/C (17.0 g) and the resulting suspension was stirred vigorously under a hydrogen atmosphere for 4 h at room temperature. The catalyst was removed by filtration through celite and the filtrate was evaporated under reduced pressure to afford pure ester **3** as oil in a quantitative yield (100.5 g). B.p. 96–101°C (0.6 mm) (lit.[7] 125–130°C at 3.0 mm).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.25 (t, $J = 7.0$ Hz, 3H), 2.60 (t, $J = 7.7$ Hz, 2H), 2.90 (t, $J = 7.7$ Hz, 2H), 3.78 (s, 6H), 4.12 (q, $J = 7.0$ Hz, 2H), 6.31 (t, $J = 2.1$ Hz, 1H), 6.36 (d, $J = 2.1$ Hz, 2H).

Preparation of 3-(3,5-Dimethoxyphenyl)-1-propanol (4)

To a stirred suspension of LAH (18.7 g, 491 mmol) in anhydrous THF (900 ml) at 0°C under argon atmosphere was added a solution of ethyl 3,5-dimethoxyphenyl propionate (90 g, 378 mmol) in anhydrous THF (250 ml) over a period of 10 min. The reaction mixture was stirred vigorously for 2.5 h at the same temperature and then quenched by adding NaF (20.6 g, 491 mmol) followed by dropwise addition of 10% aqueous NaOH and water. The reaction mixture was then warmed to room temperature, diluted

with ethyl acetate and stirred for an additional 30 min. The suspension was filtered through celite and the organic layer was separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give compound **4** as colorless oil in 97% yield (71.8 g). B.p. 148–153°C at 0.6 mm. (lit.[3] 141°C at 0.4 mm).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.70 (s, OH), 1.88 (m, 2H), 2.65 (dd as t, $J = 7.5$ Hz, 2H), 3.67 (t, $J = 6.7$ Hz, 2H), 3.78 (s, 6H), 6.30 (t, $J = 2.1$ Hz, 1H), 6.37 (d, $J = 2.1$ Hz, 2H).

Preparation of 3-(3,5-Dimethoxyphenyl)propanal (5)

Procedure 1: Using Dess-Martin Periodinane: To a stirred solution of 3-(3,5-dimethoxyphenyl)-1-propanol (60 g, 306 mmol) in wet methylene chloride (1.1 l) at 0°C was added Dess-Martin Periodinane (169 g, 398 mmol) and the resulting suspension was warmed to room temperature and stirred for 1 h. The reaction was quenched by adding a mixture of $Na_2S_2O_3$ (10% in H_2O) and saturated $NaHCO_3$ (1 : 1), diluted with methylene chloride, and stirred vigorously for 30 min. The slurry was filtered through celite, the organic phase separated and the aqueous phase extracted with methylene chloride. Subsequently, the combined organic layer was washed with saturated $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the aldehyde was purified by flash column chromatography on silica gel using 45% Et_2O: petroleum ether as eluent afforded **5** as a pale yellow viscous oil in 93% yield (55.1 g)

^{1}H-NMR (200 MHz, $CDCl_3$): 2.76 (m, AA′BB′, 2H), 2.90 (m, AA′BB′, 2H), 3.78 (s, 6H), 6.31 (t, $J = 2.1$ Hz, 1H), 6.35 (d, $J = 2.1$ Hz, 2H), 9.80 (s, 1H).

Procedure 2: Using pyridinium chlorochromate: To a stirred suspension of pyridinium chlorochromate (13 g, 60.7 mmol) in anhydrous methylene chloride (100 ml) under an argon atmospere was added 3-(3,5-dimethoxyphenyl)propanal (7.0 g, 35.7 mmol) in anhydrous methylene chloride (20 ml) with constant stirring at room temperature. After 2.5 h anhydrous ether was added and the supernatant liquid was decanted from black gum. The insoluble residue was washed with anhydrous ether. The combined organic layer was passed through a short pad of silica gel and the solvent was removed under vacuo to give crude 3-(3,5-dimethoxyphenyl)-propanal. The crude aldehyde was purified by flash column chromatography on silica gel using 45% Et_2O: petroleum ether as eluent to give compound **5** in 79% yield (5.47 g).

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