

Desymmetrization of diols by a tandem oxidation/Wittig olefination reaction

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Diols are desymmetrized by a tandem oxidation/Wittig olefination to give α,β -unsaturated hydroxy esters without the requirement for protecting group strategies; the α,β -unsaturated hydroxy esters are transformed into dienyl diesters using a second oxidation/Wittig olefination sequence using PCC.


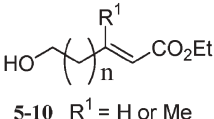

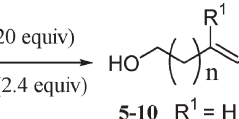












The Wittig reaction remains one of the most effective synthetic methods for the introduction of a double bond and the versatility of this reaction is demonstrated by its extensive use in natural product chemistry.^{1,2} However, the utility of this approach is limited when applied to carbonyl compounds that are difficult to isolate due to their instability, toxicity or volatility. Aldehydes can be particularly problematic and several research groups have described *in situ* oxidation/Wittig procedures utilizing primary alcohols that circumvent the requirement to isolate unstable products. A number of oxidizing reagents have been employed, including manganese dioxide,³ barium permanganate,⁴ Dess–Martin periodinane,⁵ tetrapropylammonium perruthenate (TPAP)⁶ and iodobenzoic acid⁷ and the range of alcohols investigated admirably demonstrates the generality of this synthetic approach. The application of tandem reaction sequences to the homologation of diols, however, is problematic due to competing elimination reactions, oxidative cleavage and oxidative degradation^{5,8,9} or is limited to activated diols.¹⁰

We required an efficient route for the synthesis of dienyl diesters, and were attracted to the potential simplicity and flexibility of this approach provided that undesirable elimination and degradation reactions could be avoided. Recent studies have demonstrated that there is considerable variation in the oxidizing capacity of manganese dioxide and that this property is related to the morphology of the crystallites.¹¹ With this in mind, we investigated a range of commercially available grades of manganese dioxide and were delighted to observe that reactions involving Wittig reagents **1a** ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$) and **2** ($\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{CO}_2\text{Et}$) with 1,2-ethanediol and manganese dioxide (Aldrich, 10 μm , 90%) produced the dienyl diesters **3** and **4** in good yields (Table 1, entries 1 and 2). Surprisingly, however, application of these conditions to reactions involving 1,3-propanediol furnished only small quantities of the dienyl diester. Instead, these reactions produced high yields of the intermediate α,β -unsaturated hydroxy esters **5** and **6**. The oxidation proceeds with impressive selectivity to give the mono-oxidized material as the major product regardless of the quantity of oxidant used.¹² With this realization, we extended our studies to assess the generality of this reaction, and were gratified to find that

good yields of α,β -unsaturated hydroxy esters were produced from a series of diols.[†]

α,β -Unsaturated hydroxy esters are highly versatile intermediates and have found widespread use in a number of synthetic pathways and in natural product synthesis.¹³ This protocol for the generation of these compounds is notable as no protection/deprotection strategy is required, and no air sensitive reagents are employed.

Table 1 Synthesis of α,β -unsaturated hydroxy esters

Entry	Diol	Product ^a	Yield (%) ^b
1		 3	67
2		 4	62
3		 5	79 ^c
4		 6	66 ^c
5		 7	71 ^{c,d}
6		 8	66 ^c
7		 9	52 ^c
8		 10	52 ^c

^a Reactions at room temperature in CH_2Cl_2 for 24 hours using Aldrich 10 μm MnO_2 . ^b Reactions produced $\sim 5\%$ *Z*-isomer.

^c Reactions produced $< 5\%$ diester. ^d 91% obtained after 48 hours at room temperature.

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While the α,β -unsaturated hydroxy esters **5–10** were produced in good yields, the yields of dienyl diesters were poor and could not be improved using this one-pot approach. Indeed, when the α,β -unsaturated hydroxy esters were isolated and subjected to a second oxidation/Wittig protocol under our standard conditions, only traces of the dienyl diesters were isolated. Additional experiments utilizing activated manganese dioxide, extended reaction times or elevated temperatures furnished only moderate (20–25%) yields with the balance of material being unreacted alcohol. The desired dienyl diesters could, however, be obtained by oxidation of the α,β -unsaturated hydroxy esters using silica supported pyridinium chlorochromate (PCC)¹⁴ followed by trapping of the intermediate aldehydes with Wittig reagents **1a** and **1b** ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$) in a sequential one-pot procedure.

Initial one-pot reactions involving the addition of silica supported PCC at the start of the reaction followed after two hours by Wittig reagent **1a** or **1b** resulted in efficient generation of the intermediate aldehyde, however, this was not converted to significant yields of the diester even after protracted reaction times (up to 48 hours). This is presumably due to the reprotonation of the Wittig reagent due to the acidic nature of the oxidant. We therefore sought to control the acidity of the reaction conditions by the addition of a buffering agent which would effectively suppress the reprotonation of the Wittig reagent.¹⁵ Our initial studies showed that oxidation over a two hour period followed by simultaneous addition of two equivalents of imidazole and Wittig

reagent followed by 22 hours of stirring produced reasonable yields of diester. Further improvements in yields were obtained by leaving the oxidation step for four hours and adding the imidazole one hour prior to introduction of the Wittig reagent followed by an additional 19 hours stirring. Under these conditions, the desired diester products **11–16** were produced in good yields (Table 2).¹⁶

In summary, the *in situ* oxidation/Wittig homologation protocol has been successfully extended to include the reaction of unactivated diols and leads to an efficient desymmetrization. The competing oxidative degradation and elimination reactions previously observed are avoided by moderation of the oxidative capacity of the oxidant achieved by judicious choice of crystallite morphology. This methodology provides an effective and convenient direct protocol for the synthesis of α,β -unsaturated hydroxy esters without the requirement for prior protecting group manipulation. The intermediate α,β -unsaturated hydroxy esters were resistant to further oxidation by manganese dioxide but were converted to dienyl diesters in good yields on oxidation with silica supported pyridinium chlorochromate and subsequent trapping of the intermediate aldehydes, providing access to both symmetrical and unsymmetrical dienyl compounds.

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Table 2 PCC mediated synthesis of dienyl diesters

Entry	Ester ^a	Product ^b	Yield (%) ^c
1			64
2			73
3			65
4			69
5			74
6			70

^a Contains ~ 5% Z-isomer. ^b Reactions at room temperature in CH_2Cl_2 for 24 hours. ^c Reactions produced ~ 5% E,Z-isomer.

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Notes and references

† **Typical procedure for the oxidation of diols with manganese dioxide: preparation of 7.** A mixture of 1,4-butanediol (200 mg, 2.22 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (2.4 equivalents, 5.33 mmol, 1.86 g) and manganese dioxide (20 equivalents, 44.40 mmol, 3.86 g) in dichloromethane (80 ml) was stirred for 24 hours at room temperature. At this time the manganese dioxide was removed by filtration through a Celite pad, which was then washed with additional dichloromethane (2×10 ml). The solvent was then removed *in vacuo* to give an orange oil which was purified by column chromatography (petrol \rightarrow 20% ethyl acetate : petrol) to give **7** (249 mg, 71%) as a colorless oil; $^1\text{H NMR}$ (400 MHz; CDCl_3) δ = 1.25 (3H, t, J = 7 Hz), 1.65 (2H, pent, J = 7 Hz), 2.25 (2H, dq, J = 7, 1 Hz), 2.55 (br s, 1H, OH), 3.60 (2H, t, J = 7 Hz), 4.15 (2H, q, J = 7 Hz), 5.85 (1H, dt, J = 16, 1 Hz), 6.95 (1H, dt, J = 16, 7 Hz); $^{13}\text{C NMR}$ (100 MHz; CDCl_3); δ = 167.2, 149.0, 122.0, 62.1, 60.7, 31.2, 28.9, 14.6; MS (CI, NH_3) m/z 176, (M + NH_4) $^+$, 159 (M + H) $^+$; exact mass (CI, NH_3) calculated for $\text{C}_8\text{H}_{18}\text{O}_3\text{N}$ (M + NH_4) $^+$, 176.1281, found (M + NH_4) $^+$ 176.1279; ν_{max} (film)/ cm^{-1} (neat) 3419, 1715, 1699, 1269, 1195, 1037.

‡ **Typical procedure for the oxidation of α,β -unsaturated hydroxy esters using PCC: preparation of 11.** A mixture of *E*-6-hydroxy-hex-2-enoic acid ethyl ester (300 mg, 1.90 mmol) **7** and pyridinium chlorochromate (2 equivalents, 3.80 mmol, 0.82 g, ground with 2 weight equivalents of silica, 1.64 g) was stirred for 4 hours at room temperature in dichloromethane (80 ml). Imidazole (2 equivalents, 3.80 mmol, 0.26 g) was added and the reaction mixture stirred for a further 1 hour. The addition of (ethoxycarbonylmethylene)triphenylphosphorane (2.4 equivalents, 4.56 mmol, 1.59 g) was followed by 19 hours of stirring. At this time the silica supported pyridinium chlorochromate was removed by filtration through a Celite pad, which was then washed with additional dichloromethane (2×50 ml). The solvent was then removed *in vacuo* to give an orange/brown oil which was purified by column chromatography (petrol \rightarrow 10% ethyl acetate : petrol) to give **11** (275 mg, 64%) as a colorless oil; $^1\text{H NMR}$ (400 MHz; CDCl_3) δ = 1.28 (6H, t, J = 7 Hz), 2.35–2.40 (4H, m), 4.18 (4H, q, J = 7 Hz), 5.84 (2H, d, J = 16 Hz), 6.90–6.95 (2H, m); $^{13}\text{C NMR}$ (100 MHz; CDCl_3); δ = 166.7, 147.3, 123.0, 60.7, 30.8, 14.6; MS (CI, NH_3) m/z 244, (M + NH_4) $^+$, 227 (M + H) $^+$; exact mass (CI, NH_3) calculated for $\text{C}_{12}\text{H}_{22}\text{O}_4\text{N}$ (M + NH_4) $^+$, 244.1543, found (M + NH_4) $^+$ 244.1542; IR ν_{max} (film)/ cm^{-1} (neat) 2982, 1714, 1654, 1368, 1265, 1095.

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