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In Situ Alcohol Oxidation-Wittig Reactions

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Abstract: Allylic, propargylic and benzylic alcohols can be oxidised with activated manganese dioxide in the presence of stabilised Wittig reagents to generate α,β–unsaturated esters directly. This simple procedure, which can also be utilised with diols to give double homologation, is generally useful and particularly valuable if the intermediate aldehydes are difficult to isolate, toxic or prone to isomerisation.

The oxidation of primary alcohols and homologation of the corresponding aldehydes using stabilised Wittig reagents is a commonly used synthetic procedure (Equation 1). Problems can arise, however, if the intermediate aldehyde is difficult to isolate due to volatility, toxicity or high reactivity (*e.g.* to hydration or polymerisation). Such problems can often be overcome using the procedure developed by Ireland and Norbeck[1] in which the aldehyde is generated using the Swern oxidation conditions and then the Wittig reagent (or other nucleophilic species) is added directly to the reaction mixture. This sequential "one-pot" oxidation-aldehyde addition procedure has proved to be of great synthetic value.[2]

Equation 1 (E = CO_2Et, *etc.*)

$$RCH_2OH \xrightarrow{[O]} RCHO \xrightarrow{Ph_3P=CHE} RCH{=}CHE$$

In our research programme concerned with the synthesis of members of the manumycin family of antibiotics[3] and related compounds[4] we have utilised an even more direct variant of this sequence in which allylic, propargylic and benzylic alcohols are oxidised to the corresponding aldehyde using activated manganese dioxide in the presence of a stabilised Wittig reagent (Equation 2). Thus, as the aldehyde is trapped as it is formed, this procedure is especially valuable for problematic aldehydes of the types referred to above. A recent publication by Barrett's group[5] on the use of the Dess-Martin periodinane in a similar process prompts us to disclose our own preliminary studies in this area.

Equation 2 (R = vinyl, alkynyl, phenyl; E = CO_2Et, *etc.*)

$$RCH_2OH \xrightarrow[Ph_3P=CHE]{MnO_2,\ CH_2Cl_2,\ RT} RCH{=}CHE$$

This development arose from our search for efficient synthetic routes to the side chains of alisamycin (**1**) and colabomycin (**2**) (Figure 1). In particular, an improved route to bromodienamide (**3**), the key coupling partner in the synthetic approach to the lower side chains,[3,4] was required, as was a stereoselective procedure for the preparation of *E,Z*-dienes for the construction of the upper side chain of colabomycin.

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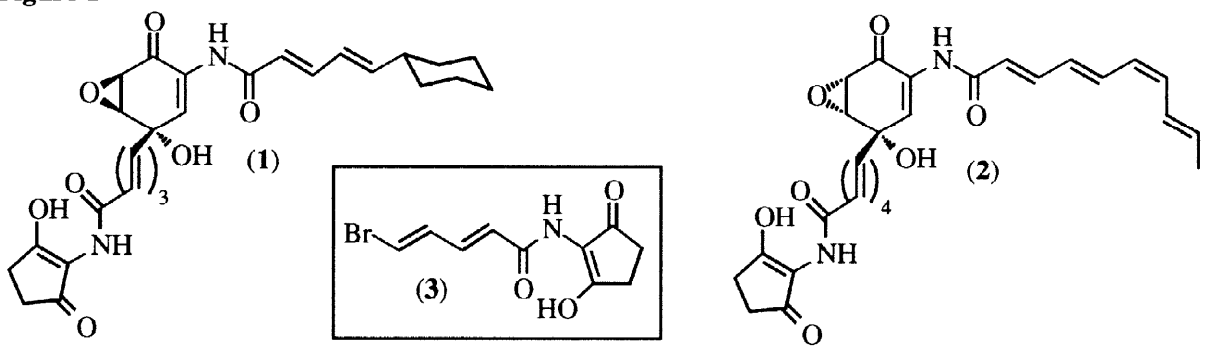
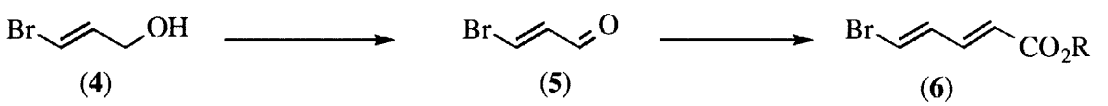
Figure 1

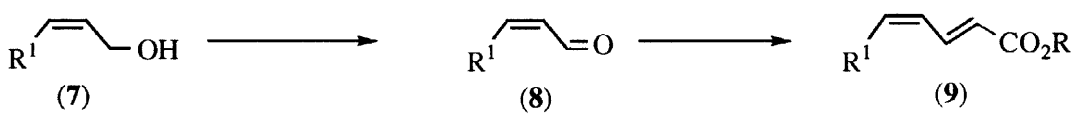


In principle, both of these requirements could be met by a stabilised Wittig approach (Equations 3 and 4). Thus (Equation 1), oxidation of bromovinyl alcohol (**4**) to bromoacrolein (**5**) followed by Wittig homologation would give bromodienoate (**6**), the ideal precursor to bromodienamide (**3**). This approach appears to be jeopardised by the reported[6] ease of decomposition of aldehyde (**5**). This was confirmed when the stepwise oxidation (MnO_2)-Wittig reaction [(carboethoxymethylene)triphenylphosphorane] of alcohol (**4**) gave adduct (**6**, R = Et) in yields of only 10-30%. Similarly, *Z*-allylic alcohols (**7**) are readily available but *Z*-enals (**8**) are known to undergo rapid isomerisation[7] and this approach to *E,Z*-dienoates (**9**) (Equation 4) appears unlikely to proceed with a high degree of stereocontrol.

Equation 3

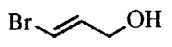
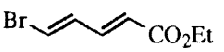
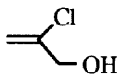
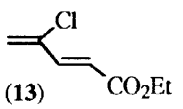
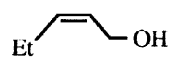
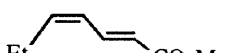
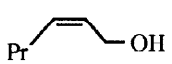
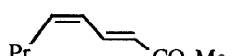
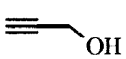
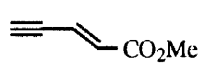
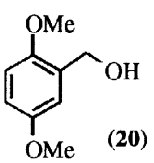
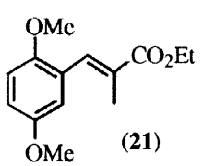
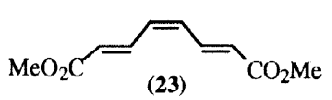
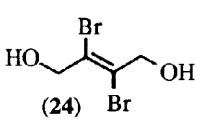
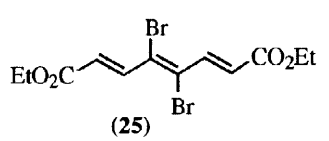
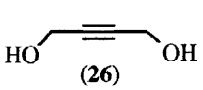
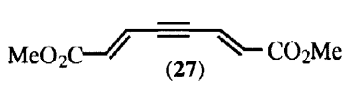
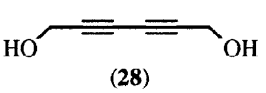
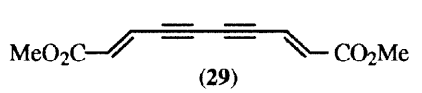


Equation 4



We therefore decided to carry out the oxidation reactions in the presence of (carboethoxymethylene)triphenylphosphorane to trap the intermediate aldehydes before they had time to decompose/isomerise. Activated manganese dioxide was chosen as oxidant as it seemed likely to be compatible with the phosphorane and is also extremely easy to use and can be removed by simple filtration at the completion of the reaction. We were delighted to find that this procedure worked efficiently with a range of substrates (Table 1).[8,9] Thus, the problematic elaboration of bromopropenol (**10**) proceeded in 81% yield when the *in situ* trapping procedure was employed, and although the reaction was slower, the chloro allylic alcohol (**12**) also underwent clean oxidation-homologation. Product (**13**) is of potential value as a side chain precursor for spongistatins/altohyrtins/cinachyrolides.[10] In a similar manner, the *Z*-allylic alcohols (**14**) and (**16**) were elaborated to dienoates (**15**) and (**17**), respectively, this time using (carbomethoxymethylene)-triphenylphosphorane.

Table MnO_2 oxidation-stabilised Wittig reactions in dichloromethane[a]

 **(10)**, *E*:*Z* = 3:1	 **(11)**	RT, 2 d 81% (*E*,*E*:*E*,*Z*:*Z*,*E*:*Z*,*Z* = 18:6:3:1)[b]
 **(12)**	 **(13)**	40°C, 16 h 51% (*E*:*Z* = 8:1)[c]
 **(14)**	 **(15)**	RT, 2 d 81% (*E*,*Z*:*Z*,*Z* = 9:1)
 **(16)**	 **(17)**	RT, 2 d 81% (*E*,*Z*:*Z*,*Z* = 9:1)
 **(18)**	 **(19)**	RT, 2.5 d 82% (*E*:*Z* = 4:1)
 **(20)**	 **(21)**	35°C, 5 h 80% (> 98% *E*)
 **(22)**	 **(23)**	RT, 2 d 65% (*E*,*E*,*E*:*E*,*Z*,*E*:*E*,*E*,*Z*:*E*,*Z*,*Z* = 2.5:2.5:1:1)
 **(24)**	 **(25)**	RT, 15 h 84% (>98% *E*,*E*,*E*)
 **(26)**	 **(27)**	RT, 1.5 d 70% (*E*,*E*:*E*,*Z* = 2.5:1)
 **(28)**	 **(29)**	RT, 2 d 55% (*E*,*E*:*E*,*Z* = 2:1)

[a]Activated MnO_2 (Aldrich, *ca.* 10/20 equiv. for alcohols/diols) was added in 4-5 portions over 4-24 h to the alcohol and specified stabilised Wittig reagent (1.2/2.4 equiv.) in dichloromethane at the specified temperature.

[b]The reaction of (**10**) in Et_2O and $CHCl_3$ gives similar yields.

[c]Reaction carried out using technical grade (90%) starting material.

These reactions proceeded with total retention of the pre-existing *Z*-alkene unit. The success of these transformations led to additional studies to establish the scope of this new process. Thus, propargyl alcohol (**18**) gave the ynenoate (**19**) in good yield: the intermediate aldehyde, propynal, is a lachrymator which is reported to polymerise on exposure to pyridine bases and alkalies "with almost explosive force".[11] The benzylic alcohol (**20**) also underwent oxidation-Wittig reaction, in this case using (carboethoxyethylidene)-triphenylphosphorane. Extension of the methodology to diols (**22**), (**24**),[9] (**26**) and (**28**) was also successful producing the corresponding double adducts (**23**), (**25**), (**27**) and (**29**) respectively, in fair to excellent yields. Most reactions were carried out at RT and took 15 hours to several days to go to completion. However, the oxidation-Wittig reaction of alcohol (**12**), which was extremely slow at RT (3.5 d, 42%), proceeded much faster when the temperature was raised to 40°C (16 h, 51%).

We are currently exploring the use of other oxidants (PDC, CrO_3, Magtrieve™, Ag_2CO_3 *etc.*) and nucleophilic reagents in this domino[12] reaction, as well as evaluating its synthetic potential.

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References and Notes

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8. All new compounds were fully characterised by high field ^1H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.
9. Representative procedure: At RT, manganese dioxide (Aldrich, activated, 0.87 g, 10 mmol) was added in 5 portions over 5 h to a stirred solution of 2,3-dibromobuten-1,4-diol (**24**) (123 mg, 0.5 mmol) and (carboethoxymethylene)triphenylphosphorane (418 mg, 1.2 mmol) in dichloromethane (25 ml). The resulting reaction mixture was stirred for *ca.* 15 h until t.l.c. indicated that the reaction was complete. The manganese dioxide was removed by filtration, washed well with dichloromethane, and the combined organic portions were concentrated to *ca.* 1-2 ml. Column chromatography (PE-ether, 7:1) gave *E,E,E*-triene (**25**) (160 mg, 84%) as a white crystalline solid, m.p. 145-147°C, which was fully characterised.
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