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An efficient synthesis of the 25-hydroxy Windaus–Grundmann ketone

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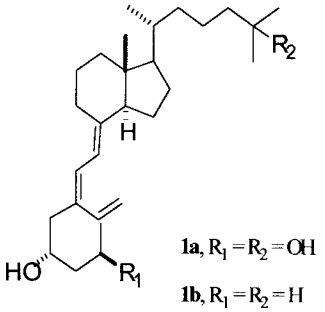
Abstract

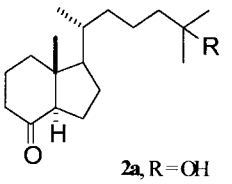
A short and efficient synthesis of the 25-hydroxy Windaus–Grundmann ketone from the Inhoffen–Lythgoe diol is described (seven steps, 70% overall). The most relevant feature of the synthesis is the preparation of the Wittig reagent **3** from cheap and commercially available starting materials. Pure **3** can be obtained in multigram quantities for achieving clean and efficient Wittig reactions.

1α,25-Dihydroxyvitamin D_3 [**1a**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3[1] (**1b**, calciferol), has a much broader spectrum of activities than originally thought and has been used together with its analogues in the treatment of a diverse range of human illnesses, including osteoporosis,[2] psoriasis,[3] cancer[4] and AIDS.[5] The 25-hydroxy Windaus–Grundmann ketone (**2a**) has proven useful in the convergent synthesis of **1a**.[6]



1a, $R_1 = R_2 = OH$

1b, $R_1 = R_2 = H$



2a, R = OH

2b, R = H

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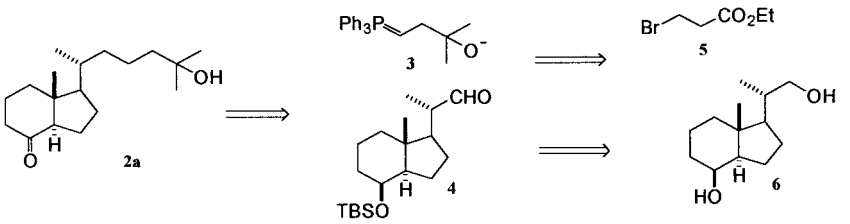
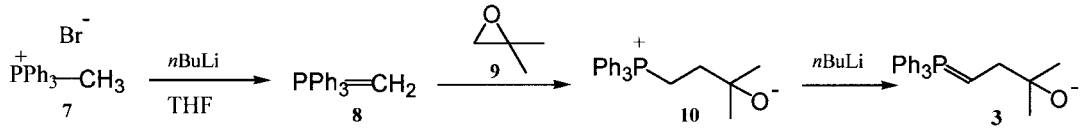
As outlined in Scheme 1, our synthetic approach takes advantage of the readily available Inhoffen–Lythgoe diol (**6**),[7] a direct precursor of the aldehyde **4**.[8] The Wittig reaction between the aldehyde **4** and the ylide **3**, followed by hydrogenation of the resulting olefin, would afford the target compound **2a**.



Scheme 1.

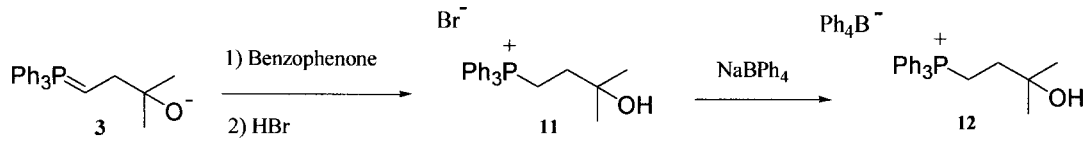
The use of the ylide **3** to perform the Wittig reaction is not unprecedented. Indeed, Salmond et al.[9] reported the first synthesis of **3** and its use for the preparation of 25-hydroxycholesterol. Salmond's synthesis of **3** is described in Scheme 2.

Methylenetriphenylphosphorane **8**, was prepared in tetrahydrofuran from methyltriphenylphosphonium bromide **7** and *n*-butyllitium. Reaction of **8** with isobutene oxide at 0°C gave the betaine **10**, which reacted with a further mol of *n*-butyllitium to yield the ylide **3**. Salmond and co-workers have already discussed the problems associated with the in situ preparation of the Wittig reagent **3** according to the sequence developed in Scheme 2, this in order to get the reagent **3** as pure as possible, and hence pointing out that this sequence might be quite tricky and difficult to achieve in order to get clean and efficient reactions with aldehydes.[9]



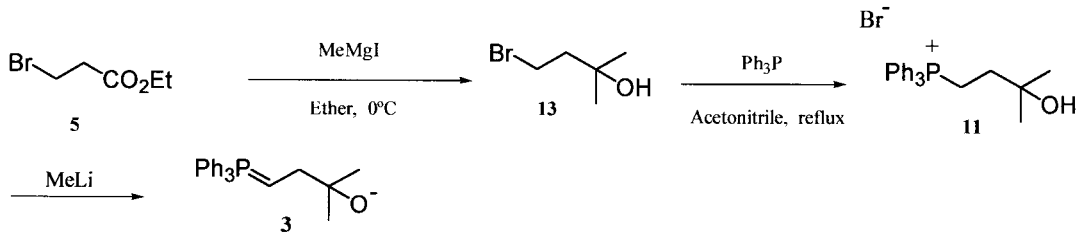
Scheme 2.

Indeed, Andrews et al.[10] reported the preparation of ylide **3** with low purity using Salmond's methodology (Scheme 3). They modified the method using phenyllithium as a base instead of *n*-butyllithium. The ylide **3** thus obtained was acidified with hydrogen bromide to give the hydroxyphosphonium salt **11** in a rather low yield (58%). The latter resisted all attempts at crystallization, and was then treated with a concentrated aqueous solution of sodium tetraphenyl borate to yield phosphonium tetraphenyl borate **12** as a pure stable salt which was used to generate a better quality ylide **3** by treatment with phenyllithium (2 equiv.).



Scheme 3.

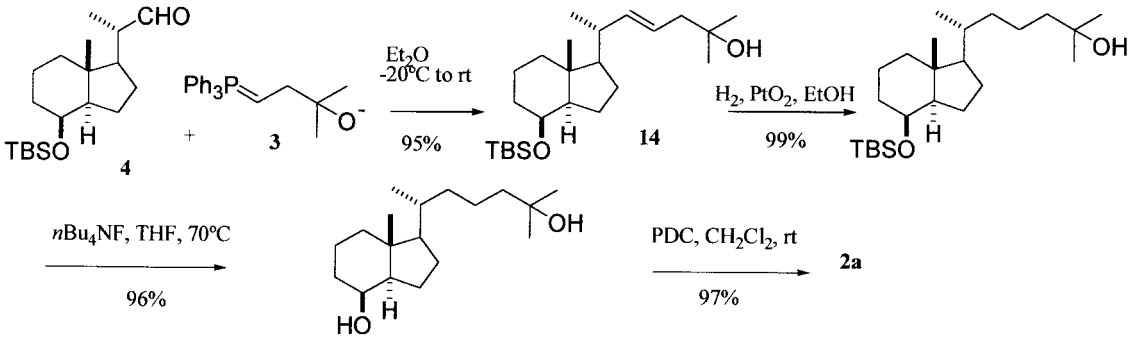
To overcome all of the problems associated with the preparation of **3**, we designed an alternative and straightforward synthesis using the cheap and commercially available ethyl 3-bromopropionate (Scheme 4).



Scheme 4.

Reaction of **5** with methyl magnesium iodide (2 equiv.) in ether at 0°C afforded the corresponding bromoalcohol **13**,[11] which was treated with triphenylphosphine in refluxing acetonitrile to yield quantitatively the phosphonium bromide **11** as a pure stable salt. Treatment of **11** with methyllithium (2 equiv.) in ether at –20°C provided the ylide **3**.[12]

Reaction of **3** with the aldehyde **4** (Scheme 5) gave the $\Delta^{22}E$-25-hydroxy compound **14** as the only detectable isomer, in 95% yield. Hydrogenation of **14** (H_2, PtO_2, EtOH), followed by desilylation and oxidation afforded the 25-hydroxy Windaus–Grundmann ketone (**2a**) (86% yield, four steps from the aldehyde **4**).



Scheme 5.

In conclusion, we have found an excellent method for the preparation of salt **11** as a pure and stable compound from the cheap and commercially available ethyl 3-bromopropionate. The usefulness of compound **11** is illustrated by the efficient and multigram synthesis of 25-hydroxy Windaus–Grundmann ketone. This method is useful for the preparation of calcitriol analogues modified at the rings or the triene system.

Acknowledgements

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12. The ylide **3** was prepared as follows: To a solution of the bromoalcohol **13** (3 g, 17.9 mmol) in acetonitrile (40 ml) was added triphenylphosphine (25g, 96 mmol). The mixture was refluxed for 24 h. The acetonitrile was evaporated to give a solid. Diethylether (300 ml) was added and the mixture stirred at rt for 3 h. After removal of the ether by filtration or decantation the resulting solid was stirred again with ether (300 ml) for 3 h and the ether removed. This procedure allows complete removal of excess of triphenylphosphine by dissolving it in ether and should be repeated until a fine powder was obtained. Filtration and drying yielded quantitatively the pure phosphonium salt **11** (7.7 g, mp: 164°C). An alternative to this procedure is to dissolve the solid mixture of the phosphonium salt **11** and triphenylphosphine in dichloromethane and reprecipitate **11** by adding ether. The ylide **3** was generated as follows: To a suspension of phosphonium salt **11** (7 g, 16.3 mmol) in ether (100 ml) at –20°C was added Methyllithium (2 equiv.) and the mixture was allowed to reach rt over 12 h. The resulting red solution of ylide **3** was recooled to –20°C and was ready to be used for the Wittig reaction.