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Furan approach to the synthesis of the A-ring of Vitamin D analogues

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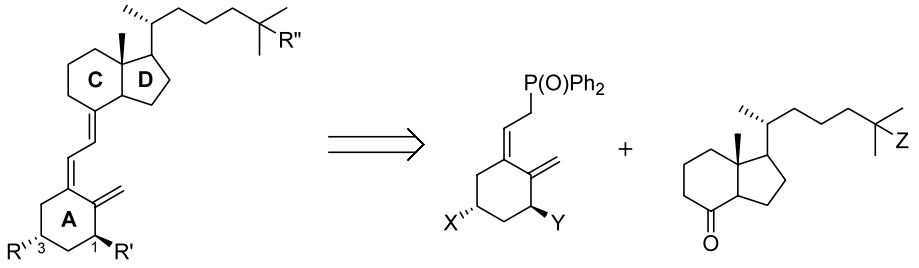
Dedicated to Professor Charles P. Casey on the occasion of his 60th birthday

Abstract—The efficient transformation of 2,3-disubstituted furan (**3**) into (*Z*)-dienol (**2**) illustrates a useful strategy for the synthesis of the A-ring of Vitamin D analogues.

Calcitriol (**1a**), the active metabolite of Vitamin D_3 (**1b**), has an extraordinary range of biological activity, including inhibition of tumor cell proliferation.[1] The clinical utility of **1a**, however, is restricted due to dose-limiting hypercalcemia. In an effort to reduce calcemetic effects and improve desired therapeutic activity, hundreds of analogues of Vitamin D_3 have been prepared.[2,3] One of the most successful synthetic strategies for the synthesis of Vitamin D_3 analogues, initially developed by Lythgoe,[4] has been based on the coupling of A-ring phosphine oxides with C, D-ring ketones (Fig. 1). The Hoffmann–La Roche chemists used this strategy for the synthesis of **1a**.[5] The continued interest in the synthesis of analogues and labeled compounds for biological studies has stimulated efforts to develop new synthetic methods and strategies in this field.[6–8] This paper describes a new synthetic approach to the A-ring of Vitamin D_3 based on furan chemistry.

The diverse chemistry of the furan ring is the focal point of many syntheses.[9] The oxidation of the furan ring, for example, has been exploited in the synthesis of macrolides[10] and carbohydrates.[11] Previous work by Jennings[12] has demonstrated the facile peracid oxidation of a 2,3-disubstituted annulated furan to the corresponding unsaturated 1,4-dicarbonyl compound. We reasoned that the selective reduction of the aldehyde and the methylenation of the ketone would provide the desired (*Z*)-dienol moiety of the A-ring of Vitamin D_3 compounds. Since most Vitamin D_3 analogues have a stereogenic center at C-1, typically a hydroxyl group, we chose as our first synthetic target (*Z*)-dienol **2** (Fig. 2).[13,14] The furan precursor **3** required for this synthetic



R,R',R"=OH (Calcitriol, **1a**)
R=OH; R',R"=H (Vitamin D_3, **1b**)

Figure 1.

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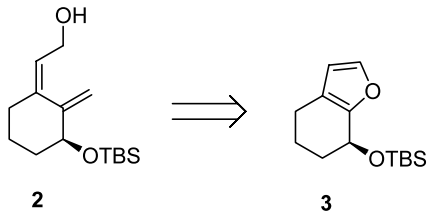
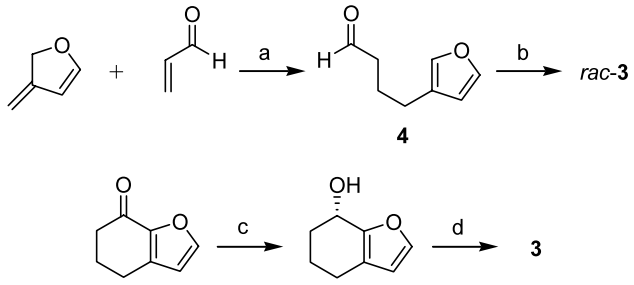


Figure 2.

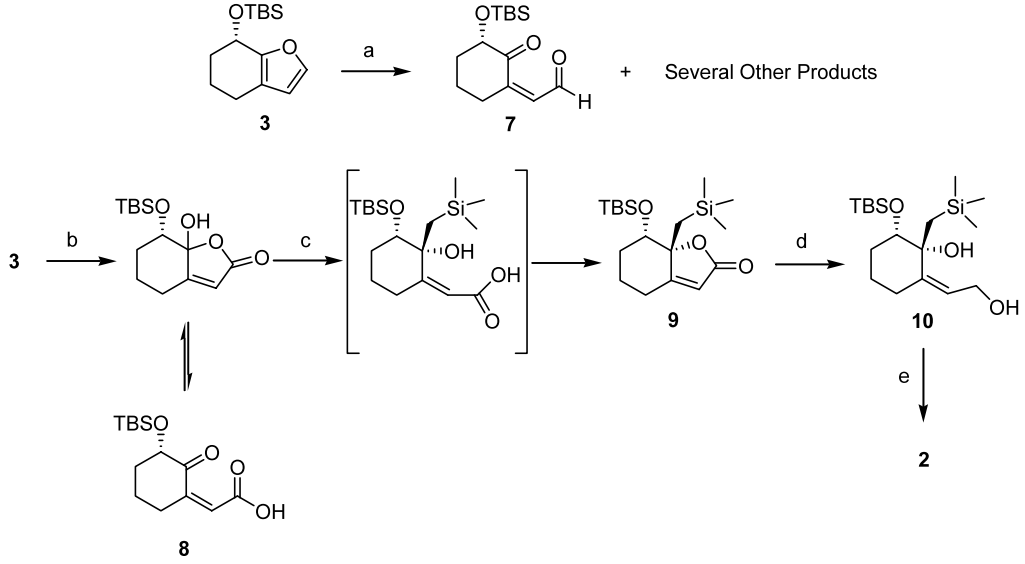


Scheme 1. *Reagents and conditions*: (a) CH_2Cl_2, 40°C, 20 h; (b) TBSOTf, 2,6-lutidine, 0°C, 1 h; (c) (*R*)-RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene) (0.5 mol%), HCO_2H/NEt_3, 6 days; (d) TBSCl, imidazole, 16 h.

target has been previously prepared in racemic form,[15] and we envisioned a simple modification of the literature procedure for the asymmetric synthesis of **3**. This paper describes our preliminary results for the conversion of non-racemic furan **3** into **2**.

The synthesis of racemic TBS-protected **3** in three steps from 1,2-cyclohexadione has been previously reported in the literature.[15] We developed an alternative two-step procedure starting with 3-methylene-2,3-dihydrofuran, an exceptionally reactive ene in the ene reaction.[16] The ene reaction of 3-methylene-2,3-dihydrofuran with acrolein gave furanyl aldehyde **4** (80% yield), which cyclized with TBSOTf in a Friedel–Crafts alkyation reaction to give *rac*-**3** in 71% yield (Scheme 1). There is some precedent for Friedel–Crafts cyclization reactions of aldehydes to give α-hydroxy/alkoxy products,[17,18] but usually there are further Friedel–Crafts reactions of the initial product.[19] The ready access to racemic material facilitated our initial oxidation studies, but the synthesis of non-racemic **3** was necessary for testing the durability of the C-1 chiral center during our synthetic protocol. Furanyl ketone **5**,[20] available from either the condensation of 1,2-cyclohexadione with chloroacetaldehyde[15] or in three steps from 3-methylene-2,3-dihydrofuran and ethyl acrylate,[16] was reduced using Noyori's ruthenium(II) asymmetric transfer hydrogenation[21] to give alcohol **6** in 91% yield and 96% ee. The assignment of the stereochemistry as *S* was determined by ^{1}H NMR studies of the corresponding Mosher ester of **6** and is consistent with the previous sense of stereochemistry found in the reduction of other aromatic ketones.[21] Conversion of alcohol **6** into the corresponding silyl ether **3** using standard procedures proceeded in 81% yield.

The oxidation of **3** with MCPBA gave the desired acid- and base-sensitive unsaturated 1,4-dicarbonyl compound **7** in moderate yields along with several other products (Scheme 2). When the reaction was buffered with NaOAc, the product distribution changed dramatically, giving γ-hydroxybutenolide **8** as the sole product. The separation of **8** and *m*-chlorobenzoic acid was difficult, so the preferred oxidation conditions employ peracetic acid buffered with NaOAc (87% yield). The clean oxidation of **3** to **8** was not unwelcome; Sato has recently demonstrated that the ethyl ester of a similar γ-hydroxybutenolide could be converted into the desired (*Z*)-dienol moiety.[8] The methylenation of **8** or its ethyl ester with Tebbe's reagent, however, gave low yields of the desired alkene, so we developed an alterna-



Scheme 2. *Reagents and conditions*: (a) *m*-$ClC_6H_5CO_3H$, 2 h; (b) CH_3CO_3H (2.1 equiv.), NaOAc, CH_2Cl_2, 6.5 h; (c) $CeCl_3$ (3 equiv.), $LiCH_2SiMe_3$ (2.4 equiv.), −78°C (1 h) to −42°C (1 h); (d) DIBAL, −78 to −42°C, 1 h; CH_3OH, $NaBH_4$, 16 h; (e) aq. HF, CH_3CN, 12 min.

tive strategy based on the Peterson olefination.[22,23] The reaction of $LiCH_2SiMe_3/CeCl_3$[24] with **8** gave lactone **9** as a single diastereomer (76% yield), with the carboxylic acid/alcohol precursor as an observable intermediate. Lactone **9** was reduced to diol **10** in two steps (89% yield). When $LiAlH_4$ was used for the reduction of **9**, there was significant cleavage of the TBS ether. Brief treatment of diol **10** with aqueous HF in acetonitrile gave the desired (*Z*)-dienol **2** in 68% yield and 96% ee.

The conversion of furan **3** into (*Z*)-dienol **2** in 40% overall yield without racemization of the stereogenic center demonstrates the viability of the furan approach for the synthesis of the A-ring of Vitamin D_3 compounds. The (*Z*)-stereochemistry is inherent in the furan precursor, so no photochemical isomerization step is necessary, unlike many other syntheses of A-ring precursors. We are exploring the applicability of this approach for the synthesis of the A-ring precursors of both **1a** and **1b** using the asymmetric carbonyl-ene reaction of 3-methylene-2,3-dihydrofuran for the formation of the C-3 stereogenic center.[25] These results will be reported in due course.

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