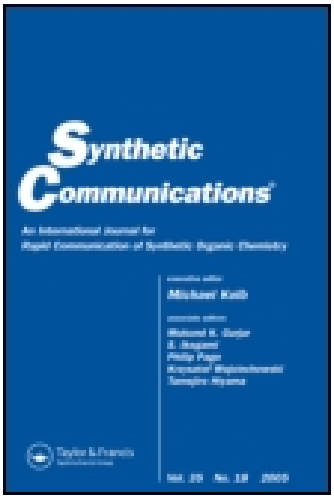

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Vitamin D_3 Synthetic Studies. A Three-Step Procedure for the Preparation of (+)-(1R,5R,6R,9R,2′R)-1-Methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nona from Windaus-Grundmann Ketone

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VITAMIN D_3 SYNTHETIC STUDIES. A THREE-STEP PROCEDURE FOR THE PREPARATION OF (+)-(1*R*,5*R*,6*R*,9*R*,2'*R*)-1-METHYL-9-(6-METHYLHEPT-2-YL)-5-(PHENYLSULFONYL)BICYCLO[4.3.0]NONANE FROM WINDAUS-GRUNDMANN KETONE

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ABSTRACT: A procedure is described for the preparation of vitamin D_3 key fragment (+)-(1*R*,5*R*,6*R*,9*R*,2'*R*)-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nonane **3** in three steps and 55% overall yield from Windaus-Grundmann ketone **5**.

Since the pioneering work of Lythgoe,[1] synthetic interest in the vitamin D family of molecules has been rekindled by the discovery that oxidized congeners of vitamin D_3 **1** such as 1α,25-dihydroxyvitamin D_3 **2** are active against certain cancer cell lines, and as anti-psoriatic agents.[2]

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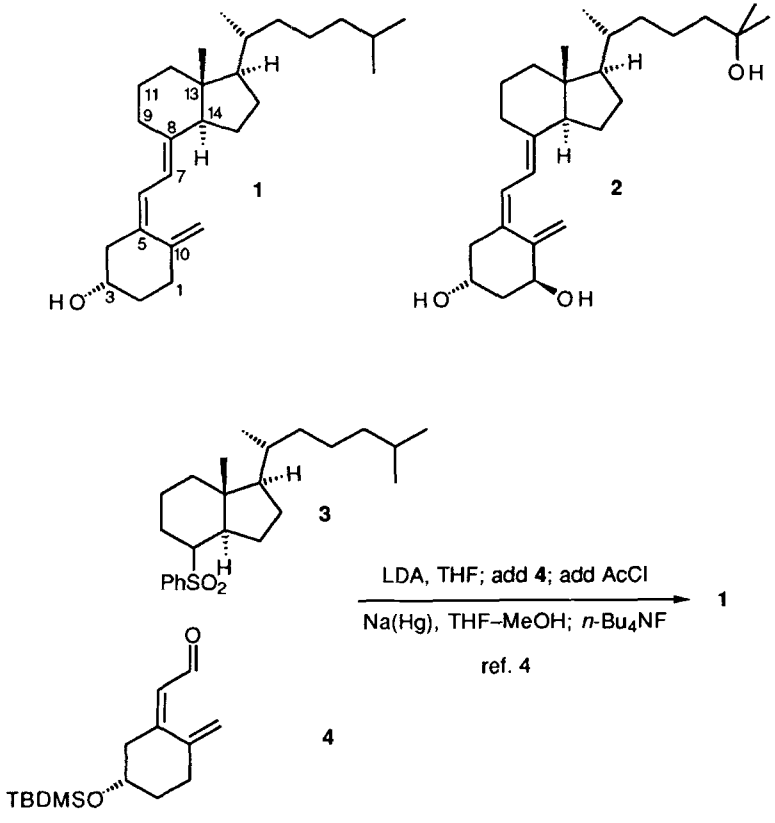
The most commonly employed preparative approach towards these compounds involves disconnection of the C7–C8 bond in **1**. This establishes 'A-ring' and 'CD-ring' fragments such as **4** and **3** which are joined using standard alkene-forming reactions. In this context, the Julia olefination procedure[3] has been deployed by Kametani[4] and Lythgoe[5] for the stereoselective assembly of vitamins D_3 and D_4 (Scheme 1).



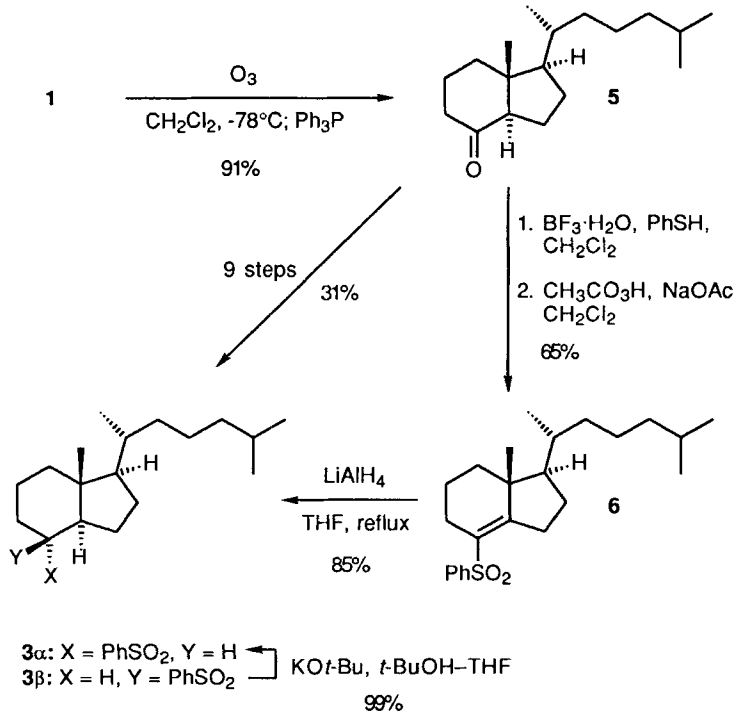
Scheme 1

In the search for therapeutically useful analogues of vitamin D_3, CD-ring fragments such as **3** are becoming important building-blocks for the

preparation of semi-synthetic drug candidates.[6] We have started a synthetic programme which aims to construct the CD-ring system via the intramolecular Diels–Alder (IMDA) reaction of a sulfonyl-substituted triene.[7] Our approach differs from existing IMDA-based strategies,[8] in that the C8–C9 and C13–C14 bonds rather than the C11–C12 and C13–C14 bonds are formed in the cycloaddition process. In order to confirm unambiguously the stereochemistry of the IMDA cycloadducts, and to provide relay compounds on which to assess modified coupling reactions with A-ring fragments, we required access to compound **3**. A published procedure[5] for the synthesis of an analogue of **3** from the product of ozonolysis of vitamin D_4 required nine steps, and we sought a shorter, more direct alternative. We report herein a three-step, two-column method for the preparation of **3** from Windaus-Grundmann ketone **5**.[9]

We reasoned that CD-ring fragments possessing C-8 sulfur substituents would be accessible via direct nucleophilic attack of sulfur nucleophiles on **5** and its derivatives. Initial attempts to introduce the phenylthio group reductively by treatment of **5** with thiophenol–boron trifluoride hydrate–diethylmethylsilane[10] gave complex product mixtures. However, carrying out the reaction *in the absence of the reducing agent* gave a single regioisomeric bicyclic vinylic sulfide, which was oxidized *crude* to give the corresponding vinylic sulfone **6** in good overall yield for the two steps from **5**. Sulfone **6** was inert to catalytic hydrogenation under a variety of conditions. However, brief treatment with lithium aluminium hydride in tetrahydrofuran under reflux gave a *ca.* 9:1 mixture of **3**α and **3**β in high yield (Scheme 2). The structure of **3**β was *confirmed by its*

essentially quantitative conversion into **3**α on treatment with potassium *tert*-butoxide in *tert*-butanol–tetrahydrofuran. Sulfone **3**α prepared in this way had ^{1}H nmr, ir, ms, tlc and mp characteristics identical with those of material prepared using a slight modification of the established degradation sequence.[11]



Scheme 2

In summary, we have developed a short, efficient and practical route for the preparation of the vitamin D_3 building-block **3** from readily available Windaus-Grundmann ketone **5**. The use of the reduction step for the conversion of **6** to **3** will allow the preparation of vitamin D_3 analogues

specifically deuterated at C-14. The successful realization of the IMDA strategy[7] will enable access to materials functionalized in the C-ring, by elaboration of the C11–C12 double bond resulting from the cycloaddition process.[13] The results of these investigations will be reported shortly.

Procedure for the preparation of 3α**:** To a solution of Windaus-Grundmann ketone **5** (1.23 g, 4.67 mmol) in CH_2Cl_2 (18.7 mL) at 0°C was added thiophenol (4.8 mL, 10 eq.) followed by $BF_3{\cdot}H_2O$ (0.554 mL, 1.2 eq.). The resulting solution was stirred at 0°C for 6 h, whereupon tlc showed complete consumption of starting material. The mixture was poured into water (25 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with aq. NaOH (1M; 3 x 30 mL), water (3 x 30 mL), and dried ($MgSO_4$). Concentration under reduced pressure gave a pale yellow oil which was redissolved in CH_2Cl_2 (45 mL), and the mixture cooled to 0°C. The solution was buffered with anhydrous NaOAc (421 mg, 1.1 eq.) and peracetic acid (3.24 mL of a 33% solution in dilute acetic acid, 3.3 eq.) added dropwise. The resulting solution was stirred at r.t. for 16 h when tlc showed complete consumption of starting material. The mixture was then added to water (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with NaOH (1M; 3 x 60 mL), water (3 x 60 mL) and dried ($MgSO_4$). Concentration under reduced pressure followed by silica gel chromatography (20% ether–hexanes) gave (+)-(1*R*,9*R*,2'*R*)-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]non-5-ene **6** as a colourless oil (1.17 g, 65% over 2 steps).[14] To a solution of **6** prepared in this way (1.14 g, 2.94 mmol) in THF (19 mL) under Ar at r.t. was added $LiAlH_4$ (2.94 mL of a 1M

solution in THF, 1 eq.). The pale yellow solution was heated to reflux for 20 min and the resulting deep orange solution allowed to cool to r.t. Water (114 μL) was added dropwise, followed by aq. NaOH (3M; 114 μL), and finally water (342 μL). The solution was stirred at r.t. for 20 min and the resultant white precipitate removed by filtration, washing the residue thoroughly with ether. Evaporation of the combined ethereal layers under reduced pressure followed by chromatography on silica gel (20% ether–hexanes) gave, in order of elution, (1*R*,5*S*,6*R*,9*R*,2'*R*)-1-methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nonane **3**β (0.103 g, 9%) followed by (+)-(1*R*,5*R*,6*R*,9*R*,2'*R*)-1-methyl-9-(6-methyl-hept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nonane **3**α (0.874 g, 76%).[15]

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(11) In this modified route the axial alcohol prepared via DIBAL-H reduction of **5** was converted to the xanthate (*n*-BuLi, THF–DMPU, CS_2, MeI) prior to thermally-induced *syn*-elimination[12] (215°C, 6 min) to give the $\Delta_{8,9}$ alkene.

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(14) (+)-(1*R*,9*R*,2'*R*)-1-Methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]non-5-ene **6**: δ_H (500 MHz, $CDCl_3$) *inter alia* 0.86,

0.87 (both 3H, d, *J* 6.5 Hz, $CH(CH_3)_2$), 0.91 (3H, s, C-1 CH_3), 0.93 (3H, d, *J* 6.5 Hz, C-2' CH_3), 2.10–2.15, 2.34–2.39, 2.72–2.78, 2.98–3.06 (4H, m, 2 x H-4, 2 x H-7); δ_C (68 MHz, $CDCl_3$) 18.4, 18.8, 19.1, 22.6, 22.8, 23.9, 24.6, 27.0, 27.8, 28.0, 34.1, 35.5, 35.8, 39.5, 46.9, 55.0, 127.2, 128.8, 129.0, 132.9, 141.5, 163.5; $[\alpha]_D^{20}$ +8.4 (*c* 1.1, $CHCl_3$).

(15) (+)-(1*R*,5*R*,6*R*,9*R*,2'*R*)-1-Methyl-9-(6-methylhept-2-yl)-5-(phenylsulfonyl)bicyclo[4.3.0]nonane **3**α: mp 117–118°C (hexanes–ether) (lit.[4] mp, 116.5–118°C); δ_H (500 MHz, $CDCl_3$) *inter alia* 0.69 (3H, s, C-1 CH_3), 0.86 (6H, d, *J* 6.5 Hz, $CH(CH_3)_2$), 0.89 (3H, d, *J* 6.5 Hz, C-2' CH_3), 3.03 (1H, td, *J* 12.0, 3.5 Hz, H-5); δ_C (68 MHz, $CDCl_3$) 12.0, 18.8, 21.3, 22.9, 23.9, 25.5, 27.5, 28.1, 35.6, 36.2, 38.9, 39.5, 44.8, 48.3, 55.2, 63.9, 128.9, 129.0, 133.4, 138.6.

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