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A simple, enantiospecific approach to both enantiomers of 1 α ,25-dihydroxyvitamin D₃ A-ring precursors from *R*-carvone[†]

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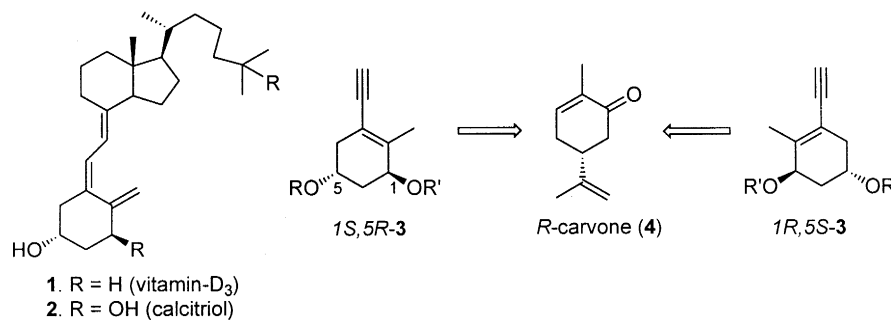
Abstract

A simple and direct approach to both enantiomeric series of A-ring derivatives of 1 α ,25-dihydroxyvitamin D₃ and the corresponding 1 α ,3 α -derivatives, starting from the abundantly available *R*-carvone, is described. © 2000 Elsevier Science Ltd. All rights reserved.

Research activity in the synthesis of vitamin D₃ (**1**) and its analogues has grown exponentially owing to the discovery that 1 α ,25-dihydroxyvitamin D₃ (calcitriol, **2**), the hormonally active metabolite of vitamin D₃, and its analogues have a much broader spectrum of activity than originally thought, in addition to the classical roles of regulating calcium and phosphorous metabolism.¹ Calcitriol **2** and its derivatives have been used recently in treating a diverse range of human diseases such as osteoporosis, cancer, AIDS and psoriasis. An attractive convergent synthetic approach to vitamin D₃ analogues is based on the coupling of a CD-ring fragment with a suitable A-ring fragment,² as originally developed by Lythgoe.¹ The palladium(II)-mediated coupling of the A-ring synthon enyne 1*S*,5*R*-**3** with an enol triflate of the CD ring fragment has become one of the most convenient methods for the large scale generation of 1 α ,25-dihydroxyvitamin D₃ analogues. Several research groups³ have employed *S*-carvone as the chiral starting material for the synthesis of enyne derivatives 1*S*,5*R*-**3**. Herein, we report a simple and straightforward enantiospecific approach to both enantiomeric forms of the A-ring **3** of 1 α ,25-dihydroxyvitamin D₃ and its analogues starting from the more abundantly available *R*-carvone.

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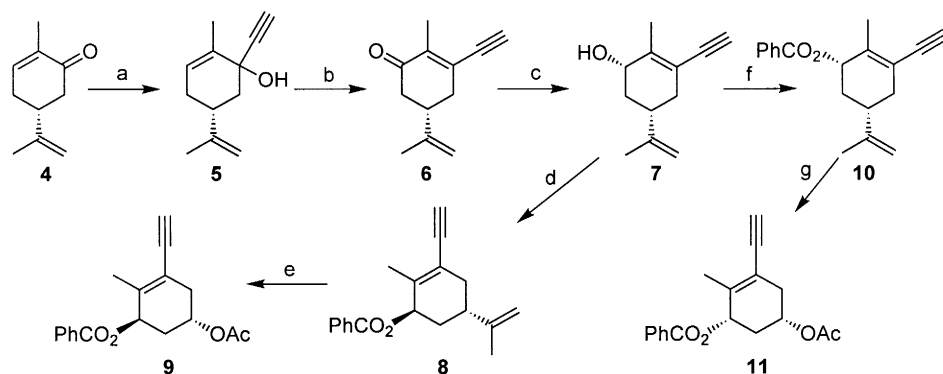
[†] Chiral synthons from carvone. Part 40. For part 39, see: Srikrishna, A.; Dinesh, C. *Indian J. Chem.* **1999**, *38B*, 1151; Part 38 see: Srikrishna, A.; Gharpure, S. J. *Tetrahedron Lett.* **1999**, *40*, 1035.



To begin with, we have addressed the synthesis of the 1*R*,5*S* enantiomeric enyne, Scheme 1. It was anticipated that the isopropenyl group could serve as the masked hydroxy group corresponding to the C-3 hydroxy of vitamin D₃. The acetylenic side chain was conveniently introduced employing a 1,3-enone-transposition methodology.⁴ Thus, sonochemical irradiation of a solution of *R*-carvone (**4**) and lithium acetylide–ethylenediamine complex in THF yielded the tertiary alcohol **5**, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the enynone **6**, $[\alpha]_{\text{D}}^{24}$ 40.3 (*c* 3.6, CHCl₃). Regio- and stereoselective reduction of the enone **6** with lithium aluminium hydride in ether furnished the *syn*-allylic alcohol 1*S*,5*S*-**7**, $[\alpha]_{\text{D}}^{25}$ 22.2 (*c* 5.4, CHCl₃), whose stereochemistry was based on the well established reduction of carvone derivatives.⁵ For the conversion of the alcohol **7** into 1*R*,5*S*-**3**, inversion at the C-1 carbon atom is required in addition to degradation of the isopropenyl group. A Mitsunobu reaction⁶ was contemplated for simultaneous inversion and protection of the alcohol group. Thus, reaction of the alcohol **7** with diethyl azodicarboxylate (DEAD), triphenylphosphine and benzoic acid in THF furnished the benzoate 1*R*,5*S*-**8**, $[\alpha]_{\text{D}}^{25}$ 125.5 (*c* 10, CHCl₃). Finally, controlled ozonolysis in a methylene chloride–methanol medium followed by Criegee rearrangement⁷ using acetic anhydride and triethylamine in the presence of a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in refluxing benzene transformed the benzoate **8** into the calcitriol analogue A-ring 1*R*,5*S*-enantiomeric synthon **9**.^{8†} In another direction, instead of the Mitsunobu inversion, protection of the alcohol in **7** with benzoyl

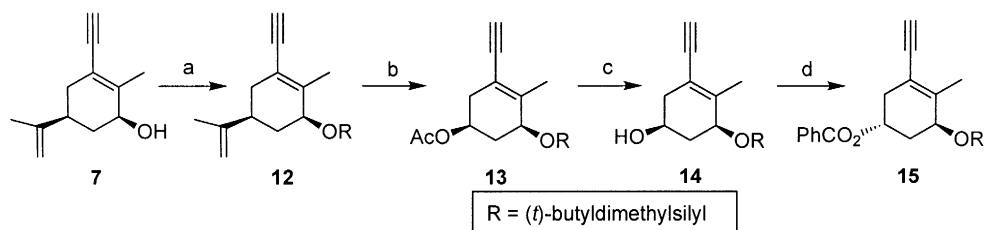
† All the compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds and are not optimised. Selected spectral data for the acetoxy benzoate **9**: $[\alpha]_{\text{D}}^{24}$ 13.0 (*c* 1.0, CHCl₃). IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3280, 1735, 1715. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 8.07 (2H, d, *J* 7.5 Hz), 7.61 (1H, t, *J* 7.5 Hz), 7.44 (2H, t, *J* 7.5 Hz), 5.73 (1H, t, *J* 4.8 Hz), 5.20 (1H, m), 3.14 (1H, s), 2.72 (1H, dd, *J* 17.4 and 3.9 Hz), 2.26 (1H, dd, *J* 17.4 and 7.8 Hz), 2.20–2.00 (2H, m), 2.05 (3H, s), 1.97 (3H, s). ¹³C NMR (75 MHz, CDCl₃+CCl₄, DEPT): δ 170.1 (C), 165.9 (C), 139.5 (C), 133.1 (CH), 130.1 (C), 129.9 (2 C, CH), 128.5 (2 C, CH), 116.7 (C), 82.4 (C), 81.7 (CH), 70.6 (CH), 66.4 (CH), 35.1 (CH₂), 33.6 (CH₂), 21.2 (CH₃), 18.5 (CH₃). For the *syn*-acetoxy benzoate **11**: $[\alpha]_{\text{D}}^{25}$ –63.0 (*c* 1.27, CHCl₃). IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3270, 1720. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 8.04 (2H, d, *J* 7.5 Hz), 7.55 (1H, t, *J* 7.5 Hz), 7.43 (2H, t, *J* 7.5 Hz), 5.68 (1H, t, *J* 4.0 Hz), 5.15 (1H, m), 3.13 (1H, s), 2.59 (1H, d with fine splitting, *J* 16.8 Hz), 2.45–2.00 (3H, m), 1.99 (3H, s), 1.96 (3H, s). ¹³C NMR (75 MHz, CDCl₃+CCl₄, DEPT): δ 169.7 (C), 165.5 (C), 139.9 (C), 133.0 (CH), 130.1 (C), 129.7 (2 C, CH), 128.3 (2 C, CH), 115.6 (C), 82.4 (C), 81.7 (CH), 69.9 (CH), 65.9 (CH), 34.9 (CH₂), 33.0 (CH₂), 21.1 (CH₃), 18.0 (CH₃). For the acetate **13**: $[\alpha]_{\text{D}}^{20}$ 30.7 (*c* 1.14, CHCl₃). IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3300, 1740. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 4.87 (1H, m), 4.29 (1H, m), 3.02 (1H, s), 2.49 (1H, dd, *J* 16.2 and 4.2 Hz), 2.35–2.10 (2H, m), 2.04 (3H, s), 1.90 (3H, s), 1.72 (1H, d of t, *J* 11.7 and 9.3 Hz), 0.90 (9H, s), 0.10 (3H, s), 0.09 (3H, s). ¹³C NMR (75 MHz, CDCl₃+CCl₄, DEPT): δ 170.1 (C), 145.3 (C), 112.6 (C), 83.1 (C), 80.3 (CH), 69.9 (CH), 67.2 (CH), 38.1 (CH₂), 35.4 (CH₂), 25.9 (3 C, CH₃), 21.3 (CH₃), 18.2 (C), 17.9 (CH₃), –4.1 (CH₃), –4.8 (CH₃). For the benzoate **15**: m.p. 98–99°C. $[\alpha]_{\text{D}}^{23}$ –41.7 (*c* 1.15, CHCl₃). IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3300, 1720. ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 8.01 (2H, d, *J* 7.5 Hz), 7.54 (1H, t, *J* 7.5 Hz), 7.43 (2H, t, *J* 7.5 Hz), 5.41 (1H, m), 4.31 (1H, m), 3.03 (1H, s), 2.73 (1H, d with fine splitting, *J* 18.0 Hz), 2.35 (1H, dd, *J* 18.0 and 6.0 Hz), 2.05–1.95 (2H, m), 1.98 (3H, s), 0.93 (9H, s), 0.12 (6H, s). ¹³C NMR (75 MHz, CDCl₃+CCl₄, DEPT): δ 165.6 (C), 143.9 (C), 132.8 (CH), 130.6 (C), 129.7 (2 C, CH), 128.3 (2 C, CH), 113.2 (C), 83.2 (C), 80.3 (CH), 68.8 (CH), 67.5 (CH), 37.0 (CH₂), 35.2 (CH₂), 25.9 (3 C, CH₃), 18.9 (CH₃), 18.2 (C, SiC(CH₃)₃), –4.2 (CH₃), –4.7 (CH₃).

chloride, pyridine and DMAP in methylene chloride led to the benzoate **10**, $[\alpha]_D^{24}$ 18.4 (*c* 2.5, CHCl₃), m.p. 74°C, which on ozonolysis followed by Criegee rearrangement furnished the diastereomeric A-ring synthon **1S,5S-11**.^{8‡}



Scheme 1. Reagents, conditions and yields:[‡] (a) HC≡C–Li·-ethylenediamine, THF, sonification, 1.5 h; (b) PCC, silica gel, CH₂Cl₂, 10 h; 70%; (c) LAH, Et₂O, –40°C, 1 h, 98%; (d) Ph₃P, PhCOOH, DEAD, THF, rt, 10 h, 97%; (e) (i) O₃/O₂, CH₂Cl₂:MeOH (5:1), NaHCO₃, –70°C; (ii) Ac₂O, Et₃N, DMAP, C₆H₆, 1 h rt, 6 h reflux; 37%;⁸ (f) PhCOCl, DMAP, Py, CH₂Cl₂, rt, 10 h, 98%; (g) same as (e), 33%⁸

After successfully developing a short route to the calcitriol A-ring synthon **9**, attention was turned to the natural series **1S,5R-3**, Scheme 2. Even though repetition of the same sequence with *S*-carvone will provide the shortest route to the A-ring synthon **1S,5R-9**, we have conceived a strategy from *R*-carvone itself via inversion at C-5 instead of at C-1. Consequently, reaction of the alcohol **7** with *t*-butyldimethylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP in methylene chloride furnished the TBDMS ether **12**, $[\alpha]_D^{21}$ 32.0 (*c* 1.0, CHCl₃). As earlier, ozonolysis in a methylene chloride–methanol medium followed by Criegee rearrangement using acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP in refluxing benzene transformed the TBDMS ether **12** into the acetate **1S,5S-13**.^{8‡} Hydrolysis of the acetate in **13** using potassium carbonate in methanol furnished the alcohol **14**, $[\alpha]_D^{22}$ –25.0 (*c* 1.24, CHCl₃), m.p. 81–82°C. Finally, Mitsunobu reaction of the alcohol **14** using triphenylphosphine and DEAD in the presence of benzoic acid furnished the A-ring **1S,5R-15**[‡] of calcitriol (**2**), in which the two hydroxy groups are differentially protected.



Scheme 2. Reagents, conditions and yields:[‡] (a) TBDMSCl, imidazole, DMAP, CH₂Cl₂, 4 h, rt, 96%, (b) (i) O₃/O₂, CH₂Cl₂:MeOH (5:1), NaHCO₃, –70°C; (ii) Ac₂O, Et₃N, DMAP, C₆H₆, 1 h rt, 6 h reflux; 38%;⁸ (c) K₂CO₃, MeOH, rt, 2 h, 92%; (d) Ph₃P, PhCOOH, DEAD, THF, rt, 4 h, 80%

In conclusion, we have developed a short and simple enantiospecific approach to both enantiomeric forms of **9** and **15** building blocks to 1 α ,25-dihydroxyvitamin D₃ analogues and also the corresponding 1 α ,3 α -derivatives **11**, **13** and **14**.

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