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A simple, enantiospecific approach to both enantiomers of 1α,25-dihydroxyvitamin D_3 A-ring precursors from *R*-carvone†

A. Srikrishna,* Santosh J. Gharpure and P. Praveen Kumar

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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Abstract

A simple and direct approach to both enantiomeric series of A-ring derivatives of 1α,25-dihydroxyvitamin D_3 and the corresponding 1α,3α-derivatives, starting from the abundantly available *R*-carvone, is described.

Research activity in the synthesis of vitamin D_3 (**1**) and its analogues has grown exponentially owing to the discovery that 1α,25-dihydroxyvitamin D_3 (calcitriol, **2**), the hormonally active metabolite of vitamin D_3, 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 D_3 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 1α,25-dihydroxyvitamin D_3 analogues. Several research groups[3] 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 1α,25-dihydroxyvitamin D_3 and its analogues starting from the more abundantly available *R*-carvone.

* Corresponding author. E-mail: ask@orgchem.iisc.ernet.in (A. Srikrishna)

† 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.

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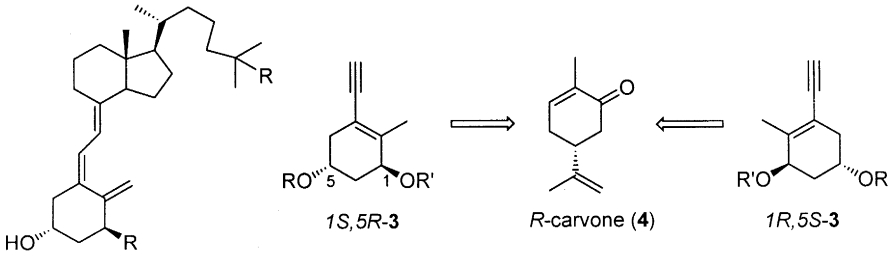
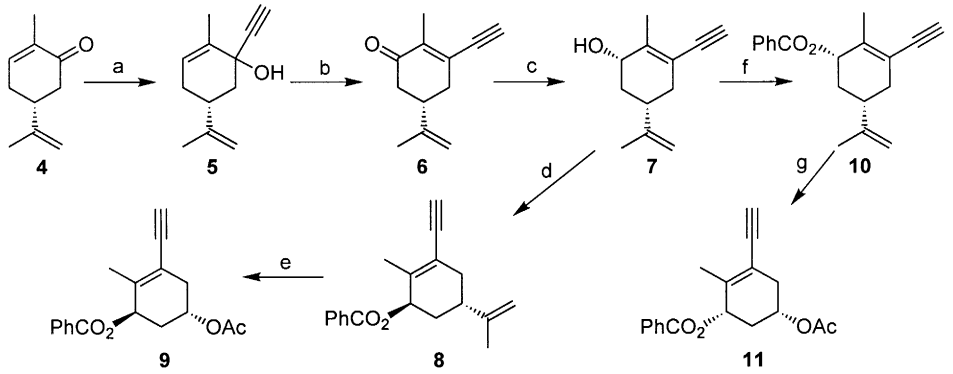


1. R = H (vitamin-D_3)
2. R = OH (calcitriol)

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 D_3. 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**, $[\alpha]_D^{24}$ 40.3 (*c* 3.6, $CHCl_3$). Regio- and stereoselective reduction of the enone **6** with lithium aluminium hydride in ether furnished the *syn*-allylic alcohol 1*S*,5*S*-**7**, $[\alpha]_D^{25}$ 22.2 (*c* 5.4, $CHCl_3$), 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 reaction[6] 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**, $[\alpha]_D^{25}$ 125.5 (*c* 10, $CHCl_3$). Finally, controlled ozonolysis in a methylene chloride–methanol medium followed by Criegee rearrangement[7] 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

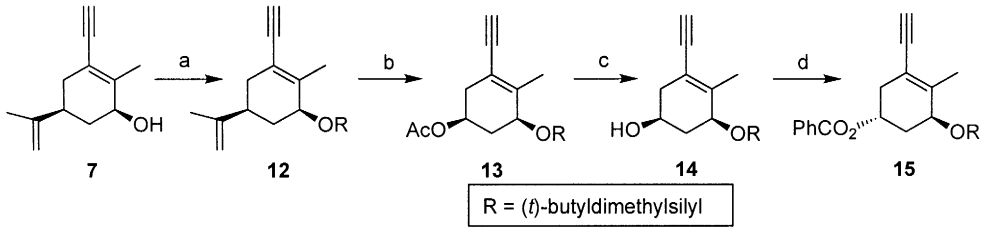
‡ All the compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds and are not optimised. Selected spectral data for the acetoxy benzoate **9**: $[\alpha]_D^{24}$ 13.0 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3280, 1735, 1715. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): 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). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, 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 (CH_2), 33.6 (CH_2), 21.2 (CH_3), 18.5 (CH_3). For the *syn*-acetoxy benzoate **11**: $[\alpha]_D^{25}$ −63.0 (*c* 1.27, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3270, 1720. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): 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). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, 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 (CH_2), 33.0 (CH_2), 21.1 (CH_3), 18.0 (CH_3). For the acetate **13**: $[\alpha]_D^{20}$ 30.7 (*c* 1.14, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3300, 1740. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): 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). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, 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 (CH_2), 35.4 (CH_2), 25.9 (3 C, CH_3), 21.3 (CH_3), 18.2 (C), 17.9 (CH_3), −4.1 (CH_3), −4.8 (CH_3). For the benzoate **15**: m.p. 98–99°C. $[\alpha]_D^{23}$ −41.7 (*c* 1.15, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3300, 1720. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): 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 (1 H, 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). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, 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 (CH_2), 35.2 (CH_2), 25.9 (3 C, CH_3), 18.9 (CH_3), 18.2 (C, Si*C*(CH_3)$_3$), −4.2 (CH_3), −4.7 (CH_3).

chloride, pyridine and DMAP in methylene chloride led to the benzoate **10**, $[\alpha]_D^{24}$ 18.4 (*c* 2.5, $CHCl_3$), m.p. 74°C, which on ozonolysis followed by Criegee rearrangement furnished the diastereomeric A-ring synthon 1*S*,5*S*-**11**.[8‡]



Scheme 1. Reagents, conditions and yields:[‡] (a) HC≡C–Li·ethylenediamine, THF, sonification, 1.5 h; (b) PCC, silica gel, CH_2Cl_2, 10 h; 70%; c) LAH, Et_2O, −40°C, 1 h, 98%; (d) Ph_3P, PhCOOH, DEAD, THF, rt, 10 h, 97%; (e) (i) O_3/O_2, CH_2Cl_2:MeOH (5:1), $NaHCO_3$, −70°C; (ii) Ac_2O, Et_3N, DMAP, C_6H_6, 1 h rt, 6 h reflux; 37%;[8] (f) PhCOCl, DMAP, Py, CH_2Cl_2, 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 1*S*,5*R*-**3**, Scheme 2. Even though repetition of the same sequence with *S*-carvone will provide the shortest route to the A-ring synthon 1*S*,5*R*-**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, $CHCl_3$). 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 1*S*,5*S*-**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, $CHCl_3$), 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 1*S*,5*R*-**15**[‡] of calcitriol (**2**), in which the two hydroxy groups are differentially protected.



Scheme 2. Reagents, conditions and yields:[‡] (a) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 4 h, rt, 96%, (b) (i) O_3/O_2, CH_2Cl_2:MeOH (5:1), $NaHCO_3$, −70°C; (ii) Ac_2O, Et_3N, DMAP, C_6H_6, 1 h rt, 6 h reflux; 38%;[8] (c) K_2CO_3, MeOH, rt, 2 h, 92%; (d) Ph_3P, 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 1α,25-dihydroxyvitamin D_3 analogues and also the corresponding 1α,3α-derivatives **11**, **13** and **14**.

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8. In addition to the Criegee product, varying amounts of starting material and 10–20% of simple ozonolysis products (easily separable) were also obtained.