



## Stereoselective synthesis of (22Z)-25-hydroxyvitamin D<sub>2</sub> and (22Z)-1 $\alpha$ , 25-dihydroxyvitamin D<sub>2</sub>

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### ABSTRACT

Two new vitamin D<sub>2</sub> analogues, (22Z)-25-(OH)-D<sub>2</sub> and (22Z)-1 $\alpha$ ,25-(OH)<sub>2</sub>-D<sub>2</sub>, were serendipitously synthesized from vitamin D<sub>2</sub> and using the Julia–Kocienski olefination.

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The classical Julia olefination, also known as the Julia–Lythgoe olefination, was first described in 1973 by Julia and Paris.<sup>1</sup> Since then a variant of this reaction, the modified or one-pot Julia olefination,<sup>2</sup> also known as the Julia–Kocienski reaction, has emerged as a very powerful method for olefin synthesis. The stereochemical outcome of this reaction is generally predictable on the basis of the substrates and reaction conditions,<sup>2c,3</sup> although some exceptions have recently been reported.<sup>4</sup>

As part of our ongoing programme on the synthesis of vitamin D and its analogues, we decided to prepare 25-hydroxyvitamin D<sub>2</sub> (**1**) and 1 $\alpha$ ,25-dihydroxy vitamin D<sub>2</sub> (**2**) (Fig. 1); although considerable effort has been devoted to the synthesis of vitamin D<sub>3</sub> metabolites,<sup>5</sup> very few syntheses of 25-(OH)-D<sub>2</sub> and 1 $\alpha$ ,25-(OH)<sub>2</sub>-D<sub>2</sub> have been reported to date.<sup>6</sup>

Our approach was based on generation of the side chain by Julia–Kocienski reaction of an appropriate aldehyde with sulfones **3**, which bear a methyl ester group offering the possibility of easy modification at C-25 (Scheme 1).

It was anticipated that coupling of sulfones **3** with aldehyde **4** would lead stereoselectively to the formation of the *E* olefin. Much to our surprise, however, despite numerous changes in reaction conditions (cf. Table 1), only the *Z* olefin **5** could be isolated.

The optimized reaction conditions to synthesize *Z* olefin **5** were established to be reacting aldehyde **4** with sulfone **3a** (1.45 equiv) and LiHMDS (1.36 equiv) at –78 °C.

Benzothiazole **3a** was efficiently prepared from commercially available alcohol **6** and 2-mercaptobenzothiazole (**7**) using Mitsun-

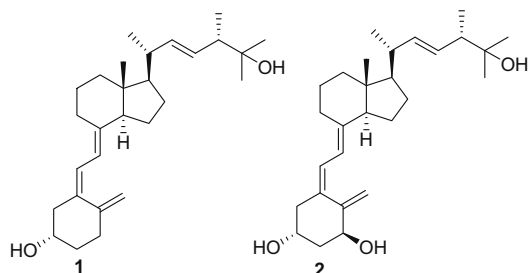
abu conditions<sup>7</sup> followed by oxidation of intermediate **8** (Scheme 2). Coupling of **3a** with aldehyde **4** gave exclusively *Z* olefin **5** in 75% yield.

This unexpected and unprecedented result prompted us to consider the synthesis of 22Z vitamin D<sub>2</sub> analogues. The analogue (22Z)-25-OH-D<sub>2</sub> was prepared as shown in Scheme 3 starting from the Inhoffen–Lythgoe diol (**9**), which is easily obtained by degradation of vitamin D<sub>2</sub>.<sup>8</sup> Protection of the hydroxyl groups of **9**, followed by selective deprotection of the primary alcohol, afforded compound **10** in 79% overall yield; and TPAP oxidation<sup>9</sup> of alcohol **10** then afforded aldehyde **4** in 93% yield. Julia–Kocienski olefination of **4** with sulfone **3a** was best carried out in THF at –78 °C using LiHMDS as base: under these conditions, the *Z* olefin **5** was obtained in 75% yield. Reaction of **5** with methyllithium, followed by removal of the silyl protecting group with TBAF, gave diol **11** in 78% overall yield; and TPAP oxidation of the C8 hydroxyl group, followed by protection of the C25 hydroxyl with TMS, afforded ketone **12** in 85% overall yield. Wittig–Horner coupling of ketone **12** with phosphine oxide **13**,<sup>10</sup> followed by removal of the silyl protecting group, then afforded the target vitamin D<sub>2</sub> analogue **14**<sup>11</sup> in almost quantitative yield.

For the synthesis of (22Z)-1 $\alpha$ ,25-(OH)<sub>2</sub>-D<sub>2</sub> (**20**) we decided to start from alcohol **15** (Scheme 4), which is readily obtained in large quantities from vitamin D<sub>2</sub> using the procedures described by Calverley<sup>12</sup> and later modified by Choudhry.<sup>13</sup>

TPAP oxidation of **15** afforded aldehyde **16** in 95% yield, and Julia–Kocienski olefination of **16** with sulfone **3a**, gave a 65% yield of ester **17**, which upon reaction with methyllithium in ether at –78 °C yielded alcohol **18**. Removal of the silyl protecting groups of **18** with TBAF in THF afforded a 93% yield of triol **19**, and

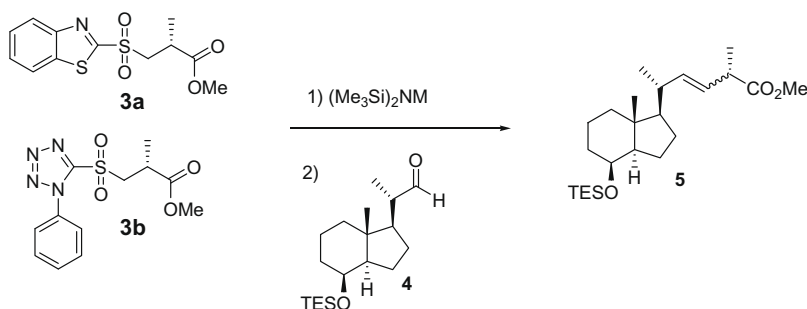
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**Figure 1.** Structures of 25-hydroxyvitamin D<sub>2</sub> (**1**) and 1α,25-dihydroxyvitamin D<sub>2</sub> (**2**).

photoisomerization of **19** using anthracene as sensitizer finally gave the target analogue **20**<sup>14</sup> in 85% yield.

In conclusion, we have synthesized two new vitamin D<sub>2</sub> analogues, (22*Z*)-25-OH-D<sub>2</sub> (**14**) and (22*Z*)-1α,25-(OH)<sub>2</sub>-D<sub>2</sub> (**20**), using a Julia–Kocienski olefination with an unexpected stereoselectivity. Compound **14** was synthesized from the Inhoffen–Lythgoe diol (**9**) in 10 steps and 33% overall yield, and compound **20** from readily accessible alcohol **15** in five steps and 41% overall yield. We are currently using our method to synthesize new vitamin D<sub>2</sub> analogues with modifications at C-25 for biological evaluation and SAR studies. Small samples of these new vitamin D<sub>2</sub> analogues (**14** and **20**) are available upon request for biological evaluation.

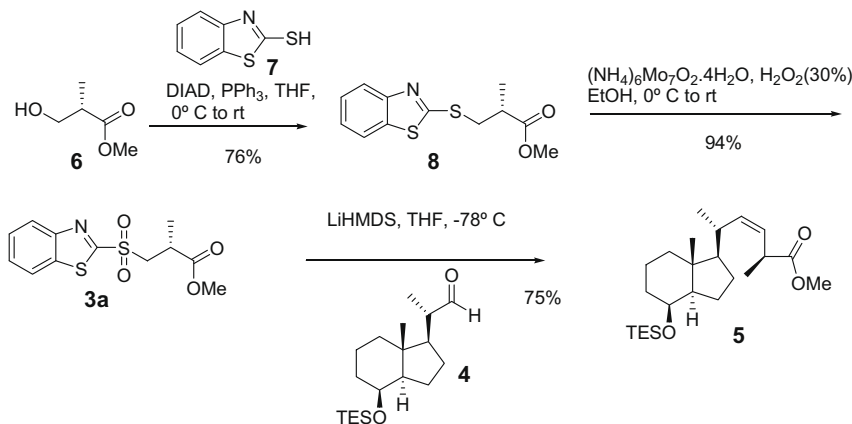


**Scheme 1.**

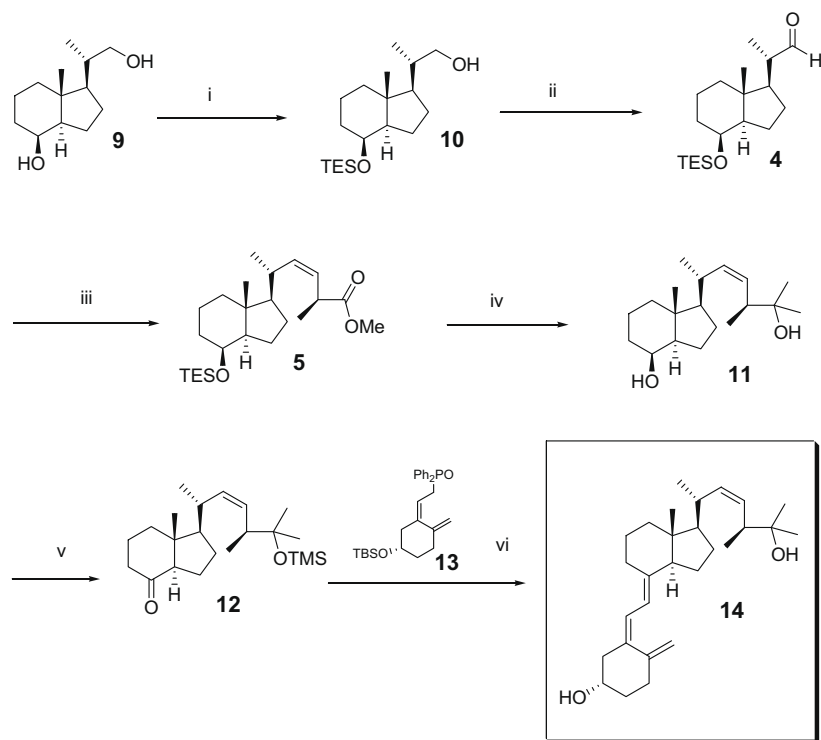
**Table 1**

| Entry | Solvent | M  | Phenyltetrazole (PT) |                     | Benzothiazole (BT) |                     |
|-------|---------|----|----------------------|---------------------|--------------------|---------------------|
|       |         |    | % Yield <b>5</b>     | <i>E</i> : <i>Z</i> | % Yield <b>5</b>   | <i>E</i> : <i>Z</i> |
| 1     | THF     | Li | 35 <sup>a</sup>      | 0:100               | 75 <sup>a</sup>    | 0:100               |
| 2     | THF     | K  | 0 <sup>b</sup>       |                     |                    |                     |
| 3     | THF     | Na | 57 <sup>a</sup>      | 0:100               |                    |                     |
| 4     | DME     | K  | 4 <sup>c</sup>       | 0:100               |                    |                     |
| 5     | DME     | Na | 0 <sup>b</sup>       |                     |                    |                     |

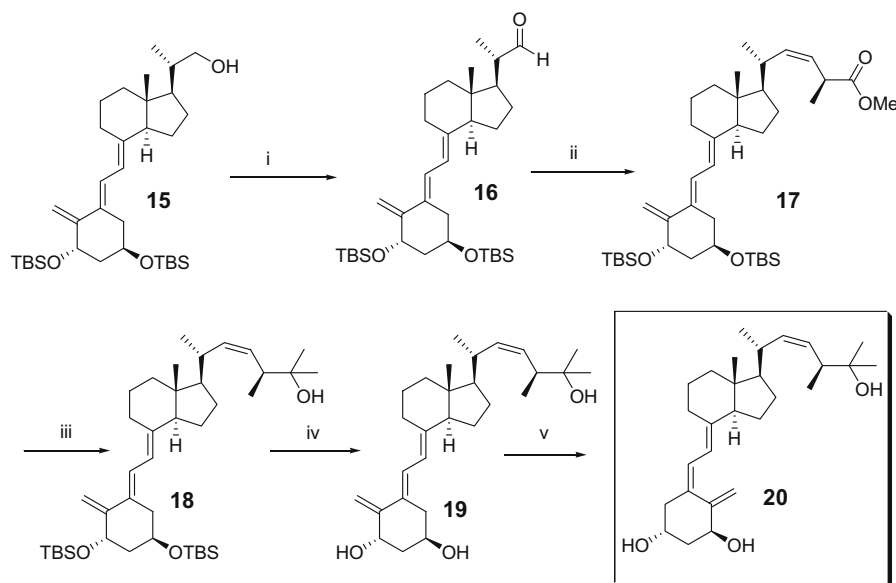
Conditions: <sup>a</sup> Aldehyde **4** (1 equiv), sulfone (1.45 equiv), base (1.36 equiv), –78 °C; <sup>b</sup> aldehyde **4** (1.5 equiv), sulfone (1 equiv), base (1.1 equiv), –55 °C; <sup>c</sup> aldehyde **4** (1 equiv), sulfone (1.45 equiv), base (1.36 equiv), –55 °C.



**Scheme 2.**



**Scheme 3.** Reagents and conditions: (i) (a) TESCl, imid,  $\text{CH}_2\text{Cl}_2$ , 0 °C (80%); (b) TBAF, THF (99%); (ii) TPAP, NMO,  $\text{CH}_2\text{Cl}_2$  (93%); (iii) **3a**, LiHMDS, THF, –78 °C (75%); (iv) (a) MeLi,  $\text{Et}_2\text{O}$ , –78 °C (79%); (b) TBAF, THF (99%); (v) (a) TPAP, NMO,  $\text{CH}_2\text{Cl}_2$  (98%); (b) TMS-imidazole (87%); (vi) (a) **13**, *n*-BuLi, THF, –78 °C (90%); (b) TBAF, THF (99%).



**Scheme 4.** Reagents and conditions: (i) TPAP, NMO,  $\text{CH}_2\text{Cl}_2$ , molecular sieves (95%); (ii) **3a**, LiHMDS, THF, –78 °C (65%); (iii) MeLi,  $\text{Et}_2\text{O}$ , –78 °C (85%); (iv) TBAF, THF (93%); (v) anthracene,  $\text{Et}_3\text{N}$ , *h\nu*,  $\text{CH}_2\text{Cl}_2$ , MeOH (85%).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.049.

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11. **Selected data for compound 14**: White solid; mp = 58–60 °C,  $R_f$  = 0.46 (50% EtOAc/hexane)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 6.12 (1H, d,  $J$  = 11.2 Hz, H-6), 5.9 (1H, d,  $J$  = 11.2 Hz, H-7), 5.19 (1H, dd,  $J$  = 2  $\times$  10.6 Hz, H-22 or 23), 5.09 (1H, dd,  $J$  = 2  $\times$  10.6 Hz, H-22 or 23), 4.92 (1H, s, H-19), 4.67 (1H, s, H-19), 3.78 (1H, m, H-3), 1.03 (6H, s, H-26 and 27), 0.87 (3H, d,  $J$  = 6.8 Hz, H-28 or 21), 0.84 (3H, d,  $J$  = 6.9, H-28 or 21), 0.46 (3H, s, H-18);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 145.8 (C-10), 142.0 (C-8), 138.0 (C-5), 122.3 (CH, C-6), 118.1 (CH, C-7), 112.4 (C-19), 72.8 (C-25), 69.5 (CH, C-3), 57.2 (CH, C-17), 56.7 (CH, C-14), 54.2 (CH<sub>2</sub>, C-1), 53.8 (CH, C-24), 46.4 (CH<sub>2</sub>), 43.2 (CH, C-20), 40.9 (CH<sub>2</sub>), 35.8 (CH<sub>2</sub>), 32.5 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 28.1 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>, C-26 and 27), 24.0 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>, C-28), 16.5 (CH<sub>3</sub>, C-21), 12.5 (CH<sub>3</sub>, C-18); MS (FAB<sup>+</sup>) [ $m/z$ , (%): 412.32 ([M<sup>+</sup>], 100), 396.32 (22), 395.31 (68), 393.30 (20), 377.30 (17), 271.19 (19), 269.18 (33), 253.19 (28), 251.18 (10), 211.19 (11), 202.26 (19), 197.20 (10), 187.27 (15), 186.31 (61), 185.23 (12), 183.23 (15); HRMS (EI<sup>+</sup>): calcd for C<sub>28</sub>H<sub>44</sub>O<sub>2</sub> 412.3341, found 412.3330.
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14. **Selected data for compound 20**: White solid; mp = 33–35 °C,  $R_f$  = 0.50 (100% EtOAc).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 6.35 (1H, d,  $J$  = 11.2 Hz, H-6), 6.00 (1H, d,  $J$  = 11.6 Hz, H-7), 5.31 (2H, m, H-19 and H-22 or 23), 5.17 (1H, dd,  $J$  = 2  $\times$  10.6 Hz, H-22 or 23), 4.98 (1H, s, H-19), 4.41 (1H, m, H-1), 4.21 (1H, m, H-3), 2.77 (1H, m), 2.45 (2H, m), 2.25 (1H, m), 1.85 (4H, m), 1.55 (5H, m), 1.45 (4H, m), 1.35 (4H, m), 1.17 (3H, s, H-26 or 27), 1.18 (3H, s, H-26 or 27), 0.98 (3H, d,  $J$  = 6.8 Hz, CH<sub>3</sub>-21 or 28), 0.94 (3H, d,  $J$  = 6.8 Hz, CH<sub>3</sub>-21 or 28), 0.57 (3H, s, H-18);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 147.7 (C-10), 142.9 (C-8), 138.2 (C-5), 133.0 (CH-23), 128.5 (CH-22), 124.9 (CH-6), 117.1 (CH-7), 111.7 (CH<sub>2</sub>-19), 72.7 (C-25), 70.8 (CH-1), 66.9 (CH-3), 56.7 (CH-14), 56.4 (CH-17), 45.3 (CH<sub>2</sub>), 45.9 (C-13), 42.8 (CH-24), 40.4 (CH<sub>2</sub>), 35.0 (CH-20), 29.1 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 27.0 (CH<sub>3</sub>-26 or 27), 26.7 (CH<sub>3</sub>-26 or 27), 23.6 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 21.3 (CH<sub>3</sub>-28), 16.4 (CH<sub>3</sub>-18), 12.4 (CH<sub>3</sub>-21); MS (EI<sup>+</sup>) [ $m/z$ , (%): 429.28 [(M+1)<sup>+</sup>, (6)], 428.27 [M<sup>+</sup>, (5)], 427.27 [(M-1)<sup>+</sup>, (3)], 411.27 (16), 277.09 (10), 269.14 (4), 230.20 (3), 199.15 (3); HRMS (EI<sup>+</sup>): calcd for C<sub>28</sub>H<sub>44</sub>O<sub>2</sub> 429.3369, found 429.3363.