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Stereoselective synthesis of (22*Z*)-25-hydroxyvitamin D_2 and (22*Z*)-1α,25-dihydroxyvitamin D_2

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ABSTRACT

Two new vitamin D_2 analogues, (22*Z*)-25-(OH)-D_2 and (22*Z*)-1α,25-$(OH)_2$-D_2, were serendipitously synthesized from vitamin D_2 and using the Julia–Kocienski olefination.

The classical Julia olefination, also known as the Julia–Lythgoe olefination, was first described in 1973 by Julia and Paris.[1] Since then a variant of this reaction, the modified or one-pot Julia olefination,[2] 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,[2c,3] although some exceptions have recently been reported.[4]

As part of our ongoing programme on the synthesis of vitamin D and its analogues, we decided to prepare 25-hydroxyvitamin D_2 (**1**) and 1α,25-dihydroxy vitamin D_2 (**2**) (Fig. 1); although considerable effort has been devoted to the synthesis of vitamin D_3 metabolites,[5] very few syntheses of 25-(OH)-D_2 and 1α,25-$(OH)_2$-D_2 have been reported to date.[6]

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 Mitsunobu conditions[7] 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 22*Z* vitamin D_2 analogues. The analogue (22*Z*)-25-OH-D_2 was prepared as shown in Scheme 3 starting from the Inhoffen–Lythgoe diol (**9**), which is easily obtained by degradation of vitamin D_2.[8] 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[9] 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**,[10] followed by removal of the silyl protecting group, then afforded the target vitamin D_2 analogue **14**[11] in almost quantitative yield.

For the synthesis of (22*Z*)-1α,25-$(OH)_2$-D_2 (**20**) we decided to start from alcohol **15** (Scheme 4), which is readily obtained in large quantities from vitamin D_2 using the procedures described by Calverley[12] and later modified by Choudhry.[13]

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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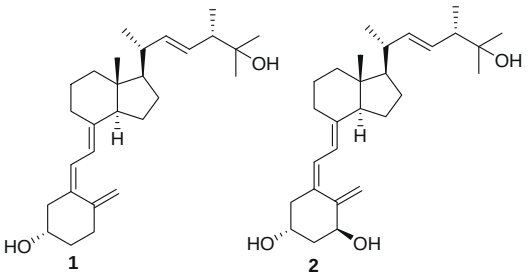
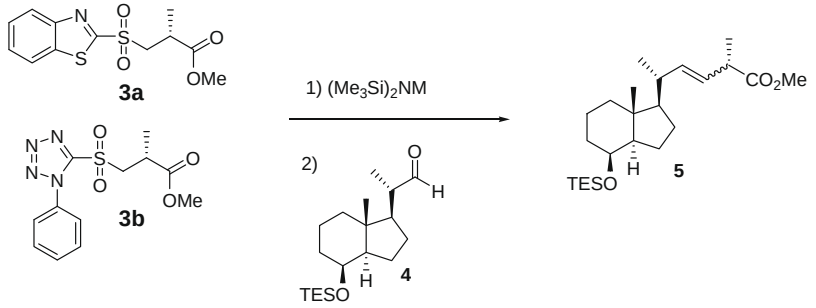


Figure 1. Structures of 25-hydroxyvitamin D_2 (**1**) and 1α,25-dihydroxyvitamin D_2 (**2**).

photoisomerization of **19** using anthracene as sensitizer finally gave the target analogue **20**[14] in 85% yield.

In conclusion, we have synthesized two new vitamin D_2 analogues, (22*Z*)-25-OH-D_2 (**14**) and (22*Z*)-1α,25-$(OH)_2$-D_2 (**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_2 analogues with modifications at C-25 for biological evaluation and SAR studies. Small samples of these new vitamin D_2 analogues (**14** and **20**) are available upon request for biological evaluation.

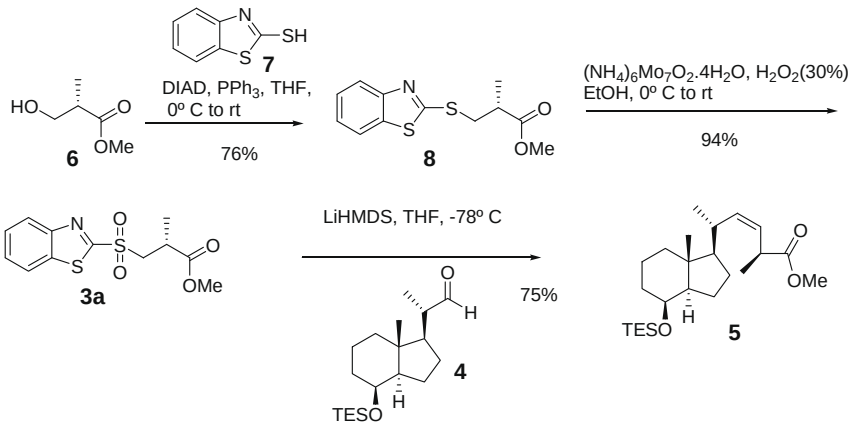


Scheme 1.

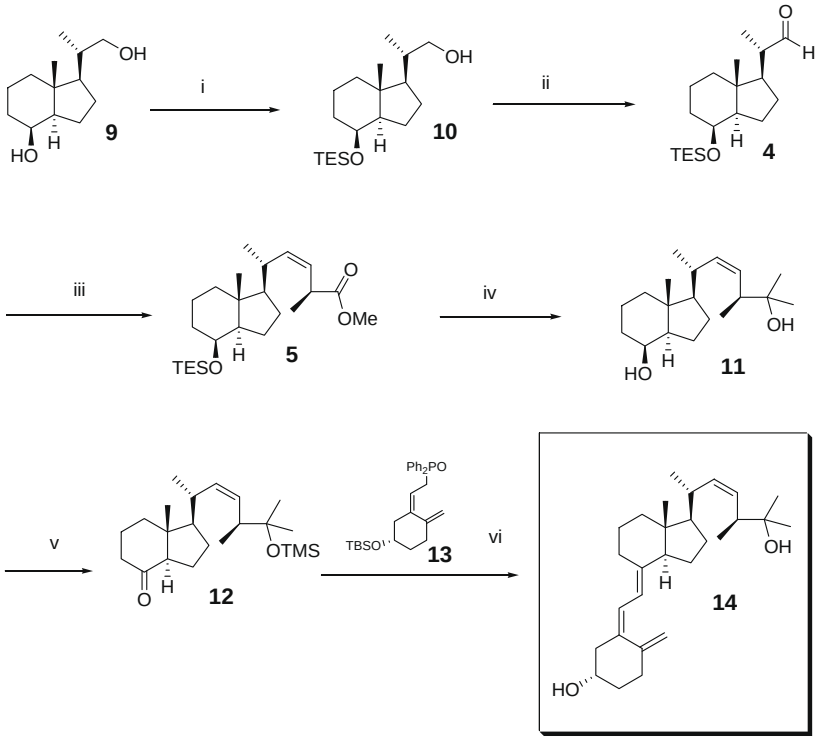
Table 1

Entry	Solvent	M	Phenyltetrazole (PT)		Benzothiazole (BT)	
			% Yield **5**	*E*:*Z*	% Yield **5**	*E*:*Z*
1	THF	Li	35[a]	0:100	75[a]	0:100
2	THF	K	0[b]			
3	THF	Na	57[a]	0:100		
4	DME	K	4[c]	0:100		
5	DME	Na	0[b]			

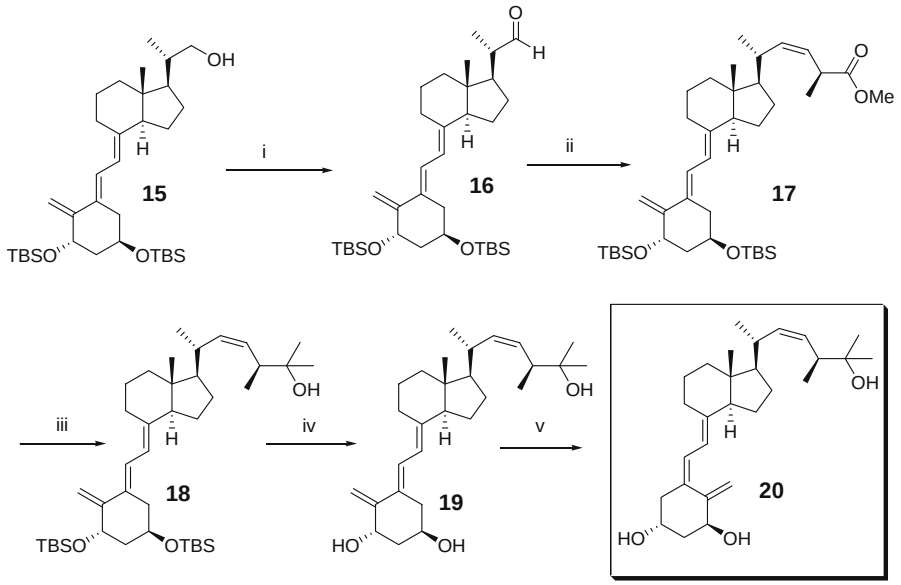
Conditions: [a] Aldehyde **4** (1 equiv), sulfone (1.45 equiv), base (1.36 equiv), −78 °C; [b] aldehyde **4** (1.5 equiv), sulfone (1 equiv), base (1.1 equiv), −55 °C; [c] aldehyde **4** (1 equiv), sulfone (1.45 equiv), base (1.36 equiv), −55 °C.



Scheme 2.



Scheme 3. Reagents and conditions: (i) (a) TESCl, imid, CH_2Cl_2, 0 °C (80%); (b) TBAF, THF (99%); (ii) TPAP, NMO, CH_2Cl_2 (93%); (iii) **3a**, LiHMDS, THF, −78 °C (75%); (iv) (a) MeLi, Et_2O, −78 °C (79%); (b) TBAF, THF (99%); (v) (a) TPAP, NMO, CH_2Cl_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, CH_2Cl_2, molecular sieves (95%); (ii) **3a**, LiHMDS, THF, −78 °C (65%); (iii) MeLi, Et_2O, −78 °C (85%); (iv) TBAF, THF (93%); (v) anthracene, Et_3N, *hv*, CH_2Cl_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}H NMR ($CDCl_3$, δ): 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}C NMR ($CDCl_3$, δ): 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_2, C-1), 53.8 (CH, C-24), 46.4 (CH_2), 43.2 (CH, C-20), 40.9 (CH_2), 35.8 (CH_2), 32.5 (CH_2), 29.6(CH_2), 28.1 (CH_2), 27.8 (CH_3, C-26 and 27), 24.0 (CH_2), 22.6 (CH_2), 21.5 (CH_3, C-28), 16.5 (CH_3, C-21), 12.5 (CH_3, C-18); MS (FAB$^+$) [m/z, (%)]: 412.32 ([M$^+$], 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$^+$): calcd for $C_{28}H_{44}O_2$ 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}H NMR ($CDCl_3$, δ): 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_3-21 or 28), 0.94 (3H, d, J = 6.8 Hz, CH_3-21 or 28), 0.57 (3H, s, H-18); ^{13}C NMR ($CDCl_3$, δ): 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_2-19), 72.7 (C-25), 70.8 (CH-1), 66.9 (CH-3), 56.7 (CH-14), 56.4 (CH-17), 45.3 (CH_2), 45.9 (C-13), 42.8 (CH-24), 40.4 (CH_2), 35.0 (CH-20), 29.1 (CH_2), 27.7 (CH_2), 27.0 (CH_3-26 or 27), 26.7 (CH_3-26 or 27), 23.6 (CH_2), 22.3 (CH_2), 21.3 (CH_3-28), 16.4 (CH_3-18), 12.4 (CH_3-21); MS (EI$^+$) [m/z, (%)]: 429.28 [(M+1)$^+$, (6)], 428.27 [M$^+$, (5)], 427.27 [(M−1)$^+$, (3)], 411.27 (16), 277.09 (10), 269.14 (4), 230.20 (3), 199.15 (3); HRMS (EI$^+$): calcd for $C_{28}H_{44}O_3$ 429.3369, found 429.3363.