The Modified Julia Olefination in Vitamin D_2 Synthesis

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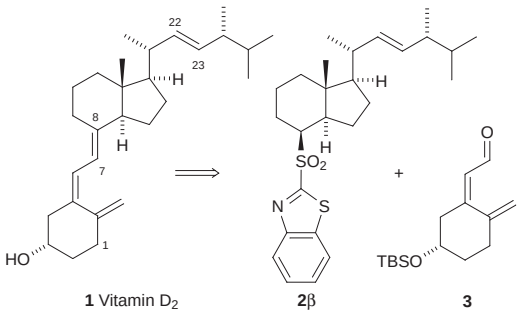
Abstract: A partial synthesis of vitamin D_2 employing fragments derived from a new improved degradation procedure is described. The 7,8-double bond of the vitamin D triene system was synthesised via the modified Julia olefination. The new procedure is more efficient than the classical Julia olefination.

Key words: vitamin D, alkene synthesis, sulfone, benzothiazole, one-pot Julia olefination

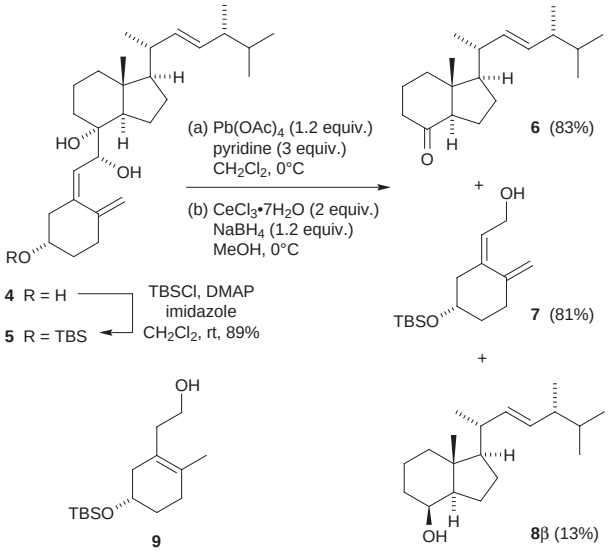
The synthesis of vitamin D and its metabolites continues to attract intense interest owing to their potential for the treatment of rickets, renal osteodystrophy, osteoporosis, psoriasis, leukemia, breast and prostate cancer, AIDS, and Alzheimer's disease. [1] Construction of the conjugated triene system has been a major stimulus to the development of new connective olefin syntheses. A conspicuous example is the Julia olefination which was first developed as an alternative to the Horner–Wittig reaction to construct the 7,8-double bond in a synthesis of vitamin D_4 (the 22,23-dihydro analogue of vitamin D_2) in 1979. [2] The classical Julia olefination has since entered the repertoire as one of the standard fragment linkage reactions in complex natural product synthesis despite its length (3/4 steps) and the need for sodium amalgam in the final stage. [3] We now report the construction of the 7,8-double bond of vitamin D_2 (**1**) using the recently reported one-pot modified Julia olefination[4–6] via union of the benzothiazolyl sulfone **2β** and the aldehyde **3** (Scheme 1).



1 Vitamin D_2 **2β** **3**

Scheme 1

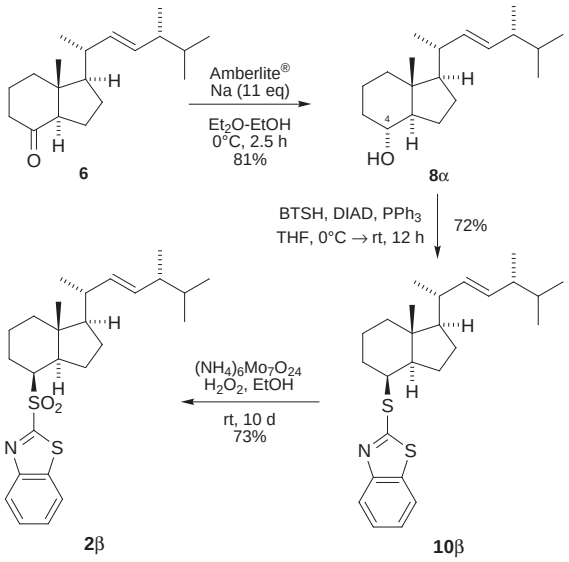
The requisite fragments for our study were prepared by a modification of a procedure of Toh and Okamura.[7] Thus, the known vitamin D_2 triol **4**[8] (Scheme 2) was converted to the mono-TBS ether **5** and the vicinal diol cleaved with lead tetraacetate. The resultant mixture of carbonyl compounds was reduced with sodium borohydride in the presence of cerium trichloride according to the procedure of Luche[9] to give A-ring dienol **7** (81%) and the Windaus–Grundmann C19 ketone **6** (83%)[10] together with 13% of the corresponding CD-ring β-hexahydrindanol **8β**. In the original Okamura procedure, the diol cleavage step is followed by reduction of the mixture of carbonyl compounds with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) to give **8β** as the only CD-ring component and A-ring dienol **7** contaminated with varying amounts of the alcohol **9**. In our modification, the absence of contamination by **9** and the formation of ketone **6** rather than alcohol **8β** significantly increased the efficiency of the synthesis (vide infra).



Scheme 2

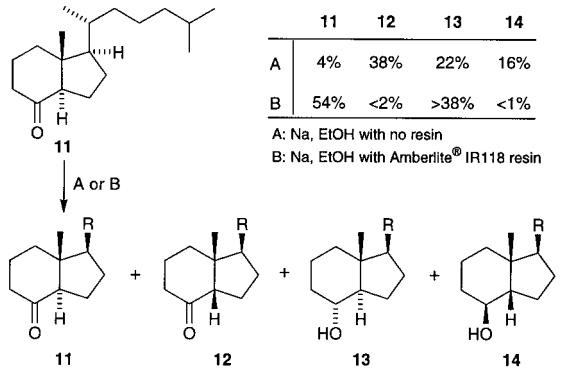
The next step of the synthesis required substitution of the hydroxy function at C4 of the hexahydroindanol by a 2-sulfanylbenzothiazole unit. Attempts to accomplish this task by a Mitsunobu reaction on the axial alcohol **8β** gave mainly recovered starting alcohol together with some elimination products. We therefore required a synthesis of the equatorial alcohol **8α** for which the ketone was the most convenient starting material. However, attempts to prepare **8α** by Bouveault-Blanc reduction of ketone **6** (Scheme 3) were complicated by competing base-cataly-

sed epimerisation of the *trans*-hydrindanone and subsequent reduction of the *cis*-hydrindanone. However, the epimerisation reaction could be suppressed by conducting the reduction in the presence of dried Amberlite IR118 acidic exchange resin to give pure **8α** in 81% yield. Mitsunobu reaction of **8α** with 2-sulfanylbenzothiazole now occurred in good yield to afford the corresponding β-thioether **10β.** Synthesis of the vitamin D_2 CD-ring sulfone **2β** was completed by an extremely sluggish Mo(VI)-catalysed oxidation.



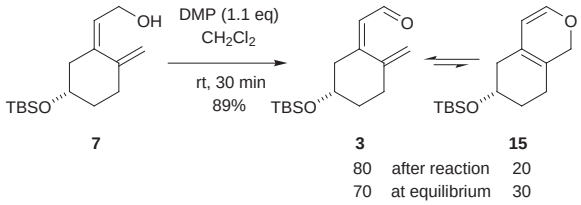
Scheme 3

In order to quantify the extent of the epimerisation problem and its suppression by the ion exchange resin, we conducted a similar reduction on Grundmann's ketone **11** (the CD fragment of vitamin D_3) and the product distribution of the alcohols ascertained by gas chromatography and of the ketones by ^{13}C NMR spectroscopy (using the C18 methyl resonance) before complete consumption of ketone **11**. The results are summarised in Scheme 4.



Scheme 4

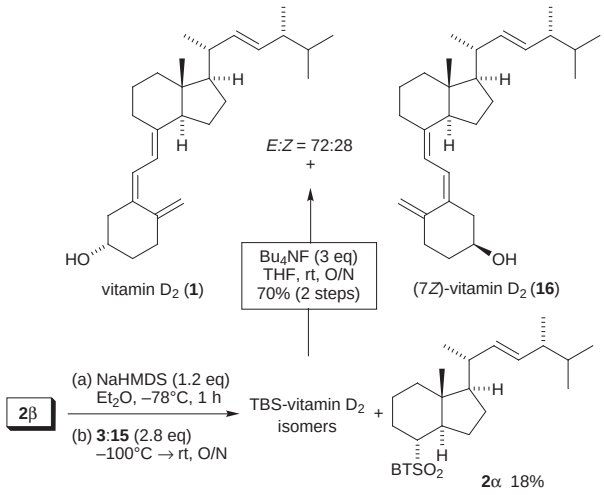
Dess-Martin oxidation of the pure A-ring dienol **7** (Scheme 5) led to the rapid formation of the dienal **3** which exists in equilibrium with its cyclic tautomer **15**. Shortly after isolation, the ratio of **3** to **15** was approximately 8:2 according to ^1H NMR spectroscopy of the mixture and at equilibrium the final ratio is 7:3. Complete separation of these ring-chain tautomers is impossible owing to rapid interconversion and pointless since the pyran acts as a latent aldehyde equivalent in the Julia olefination.



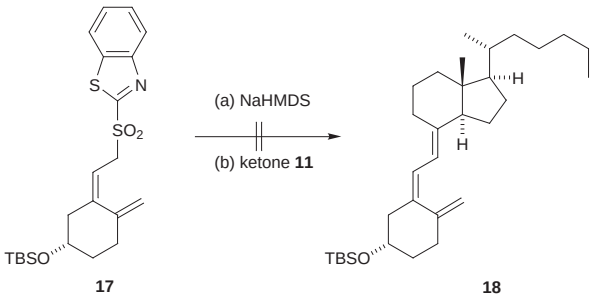
Scheme 5

The synthesis of vitamin D_2 was completed (Scheme 6) by metallation of the sulfone **2β** (1 equiv.) with NaHMDS (1.2 equiv.) at –78 °C followed by addition of the equilibrium mixture of aldehyde **3** and its ring tautomer **15** (4:1, 2.8 equiv.) at –100 °C. On gradual warming, the modified Julia olefination went to completion to give a mixture of vitamin D_2 TBS ether and its 7*Z* isomer (7*E*:7*Z* = 72:28, ca 70%) along with 16% recovered aldehyde and 18% of the sulfone **2α**. The chromatographically purified mixture of isomeric vitamin D_2 TBS ethers was deprotected with TBAF in quantitative yield and the isomers separated by careful chromatograpy to give crystalline vitamin D_2 (**1**) and its rather unstable 7*Z* isomer **16**. A separate experiment established the configurational instability of the β-sulfone **2β**: treatment of **2β** with NaHMDS (6 equiv.) in Et_2O at –78 °C for 1.5 h followed by quenching at low temperature with MeOH gave epimeric sulfones **2α** and **2β** in 92% yield with **2α** predominating (α:β = 85:15). Attempts to improve the efficiency of the coupling by inverting the role of the two fragments were abandoned when a related study directed towards the synthesis of vitamin D_3 (Scheme 7) failed to yield any triene product.

In conclusion, the modified Julia olefination presented here is more convenient and higher yielding than the classical reaction for the linkage of A-ring and CD-ring vitamin D fragments first applied to vitamin D_4. Furthermore, a repetition of the synthesis of vitamin D_4 with the benefit of modern separation and analytical techniques[11] has revealed that the modified Julia olefination also offers slightly better stereoselectivity. In any case, stereoselectivity is less important than linkage efficiency since (7*Z*)-vitamin D trienes can be photoisomerised into the natural (7*E*) isomers.[12] Finally, our synthesis of vitamin D_2 has uncovered for the first time some stereochemical limitations to the modified Julia olefination which were not ap-



Scheme 6



Scheme 7

parent from earlier successful syntheses of dienes[13] and trienes.[14]

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of N_2. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2 was freshly distilled from CaH_2. Preparative chromatographic separations were performed on Macherey-Nagel silica gel 60 (230–400 mesh) and reactions were followed by TLC analysis using Macherey-Nagel silica gel 60 plates with fluorescent indicator (254 nm) and visualised with UV or phosphomolybdic acid. All commercially available reagents were purchased from Aldrich and were used as supplied.

Mps were recorded using open capillary tubes on a Griffin melting point apparatus and are uncorrected. Specific optical rotations ($[\alpha]_D$) were measured at ambient temperature (24±3 °C) from $CHCl_3$ solutions using a 5 mL cell with 1 dm path length. IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer using a thin film supported between NaCl plates or KBr discs where stated. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, w = weak or br = broad. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified or on a Bruker AM360. All spectra were obtained in $CDCl_3$ solution in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of $CHCl_3$ ($\delta_H = 7.27$ or $\delta_C = 77.2$). Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. Numbers in parentheses following the chemical shift in the ^{13}C NMR spectra refer to the number of attached hydrogens as revealed by DEPT experiments employing secondary pulses at 90° and 135°. Low (LRMS) and high (HRMS) resolution mass spectra were run on a Jeol JMS700 spectrometer. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%).

(3β,5*Z*,7*R*,8α,22*E*)-3-(*tert*-Butyldimethylsilyloxy)-9,10-secoergosta-5,10(19),22-triene-7,8-diol (5)

To a stirred suspension of triol **4** (5.0 g, 11.6 mmol),[7,8] imidazole (2.4 g, 35.3 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) in anhyd CH_2Cl_2 (50 mL) at r.t. under N_2 was added dropwise over 30 min *tert*-butylchlorodimethylsilane (1.83 g, 12.2 mmol) in anhyd CH_2Cl_2 (50 mL) and the resultant mixture stirred overnight. After this time the organic phase was washed successively with H_2O (2 × 50 mL), brine (50 mL) and then dried ($MgSO_4$) and concentrated in vacuo. The crude residue was then further purified via column chromatography (eluting with 20% Et_2O in hexanes) to yield the monosilylated product **5** (5.60 g, 10.3 mmol, 89%) as a white powder: mp 128–129 °C (hexanes); $[\alpha]_D = +76.6$ (*c* = 0.50, $CHCl_3$).

IR (KBr): ν = 3421 (br), 2956 (s), 2860 (s), 1461 (m), 1371 (m), 1254 (m), 1096 (s), 1005 (m), 870 (m), 837 (m), 775 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.52 (1H, dm, *J* = 9.8 Hz), 5.21 (1H, dd, *J* = 15.2, 7.1 Hz), 5.14 (1H, dd, *J* = 15.2, 7.4 Hz), 4.98 (1H, br s), 4.92 (1H, d, *J* = 9.8 Hz), 4.88 (1H, br s), 3.72 (1H, tt, *J* = 9.7, 4.2 Hz), 2.48–2.37 (2H, m), 2.19 (1H, ddd, *J* = 11.9, 10.0, 1.7 Hz), 2.05–1.90 (3H, m), 1.89–1.40 (10H, m), 1.30–1.08 (5H, m), 0.98 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 0.86–0.80 (9H, m), 0.07 (3H, s), 0.06 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 145.9 (0), 141.8 (0), 135.6 (1), 132.2 (1), 124.8 (1), 111.1 (2), 75.0 (0), 71.4 (1), 70.9 (1), 59.8 (1), 57.5 (1), 47.2 (2), 44.2 (0), 43.0 (1), 40.2 (1), 40.2 (2), 37.6 (2), 36.8 (2), 33.5 (2), 33.3 (1), 27.9 (2), 26.0 (3C, 3), 22.0 (2), 20.8 (3), 20.6 (2), 20.2 (3), 19.8 (3), 18.3 (0), 17.9 (3), 13.2 (3), –4.4 (3), –4.5 (3) ppm.

LRMS (CI mode, NH_3): *m*/*z* = 562 (15%), 527 (30), 509 (72), 377 (13), 294 (100), 267 (57), 249 (51).

Anal. Calcd. for $C_{34}H_{60}O_3Si$ (M = 544): C, 74.94; H, 11.10. Found C, 74.99; H, 10.9.

Oxidative Cleavage of Diol 5

To a stirred solution of the diol **5** (3.0 g, 5.5 mmol) and pyridine (1.34 mL, 1.31 g, 16.6 mmol) in anhyd CH_2Cl_2 (25 mL) at 0 °C under N_2 was added portionwise $Pb(OAc)_4$ (2.93 g, 6.6 mmol) and the resultant suspension stirred vigorously for 10 min. The mixture was then filtered through a Celite pad and the residue washed well (3 × 5 mL CH_2Cl_2). The filtrate and combined washings were then concentrated in vacuo and subsequently dissolved in a solution of cerium(III) chloride heptahydrate (4.11 g, 11.0 mmol) in MeOH (30 mL). The mixture was then cooled to 0 °C, treated with $NaBH_4$ (0.26 g, 6.8 mmol) and stirred for 15 min. H_2O (30 mL) and Et_2O (30 mL) were then added and the layers shaken well and then separated. The aqueous phase was then further extracted (3 × 10 mL Et_2O) and the combined organic extracts washed with brine (15 mL), dried ($MgSO_4$) and then concentrated in vacuo. The crude residue was then further purified via column chromatography (eluting with 10–15% Et_2O in hexanes) to yield in order of elution: the Windaus-Grundmann C19 ketone (**6**, 1.26 g, 4.6 mmol, 83%),[15] the corresponding over-reduced β-alcohol product **8β** (0.20 g, 0.72

mmol, 13%)[16] and the A-ring dienol **7** (1.20 g, 4.5 mmol, 81%)[7] all as clear oils.

[1*R*-[1α,(1*R,2*E*,4*R**),3aβ,7aα]]-Octahydro-7a-methyl-1-(1,4,5-trimethylhex-2-enyl)-1*H*-inden-4-one (6)**
$[\alpha]_D$ = –19.1 (*c* = 1.00, $CHCl_3$).

IR (film): ν = 2958 (s), 1716 (s), 1460 (m), 1372 (m), 972 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.25 (1H, dd, *J* = 15.3, 7.2 Hz), 5.17 (1H, dd, *J* = 15.3, 7.9 Hz), 2.46 (1H, ddm, *J* = 11.0, 7.7 Hz), 2.33–2.17 (2H, m), 2.11–1.42 (12H, m), 1.35–1.30 (1H, m), 1.05 (3H, d, *J* = 6.7 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.6 Hz), 0.83 (3H, d, *J* = 6.7 Hz), 0.66 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.3 (0), 135.1 (1), 132.7 (1), 62.3 (1), 56.8 (1), 50.0 (0), 43.0 (1), 41.2 (2), 40.1 (1), 39.1 (2), 33.2 (1), 27.9 (2), 24.3 (2), 21.2 (3), 20.1 (3), 19.8 (3), 19.3 (2), 17.8 (3), 12.9 (3) ppm.

LRMS (EI+mode): *m*/*z* = 276 (100%), 261 (6), 233 (32), 215 (41), 192 (13), 178 (34), 151 (55), 133 (49), 109 (44).

(*S*,*Z*)-[5-(*tert*-Butyldimethylsilyloxy)-2-methylenecyclohexylidene]ethanol (7)
$[\alpha]_D$ = +44.0 (*c* = 0.43, $CHCl_3$).

IR (film): ν = 3340 (m, br), 2986 (s), 1254 (m), 1094 (s), 1006 (m), 836 (m), 774 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.45 (1H, tm, *J* = 7.0 Hz), 4.97 (1H, br s), 4.63 (1H, br s), 4.27 (1H, dd, *J* = 12.5, 7.3 Hz), 4.19 (1H, ddd, *J* = 12.4, 6.2, 1.8 Hz), 3.85 (1H, tt, *J* = 8.6, 4.0 Hz), 2.45–2.35 (2H, m), 2.25–2.17 (1H, m), 2.13–2.03 (1H, m), 1.92–1.84 (1H, m), 1.65–1.54 (1H, m), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 145.1 (0), 140.7 (0), 125.1 (1), 112.1 (2), 70.3 (1), 60.0 (2), 46.2 (2), 36.2 (2), 32.5 (2), 26.0 (3), 18.3 (0), –4.5 (3), –4.5 (3).

LRMS (CI mode, NH_3): *m*/*z* = 286 (100%), 268 (37), 251 (16), 119 (16).

[1*R*-[1α,(1*R,2*E*,4*R**),3aβ,4β,7aα]]-Octahydro-7a-methyl-1-(1,4,5-trimethylhex-2-enyl)-1*H*-inden-4-ol (8α)**
To a stirred suspension of the Windaus-Grundmann C19 ketone **6** (1.0 g, 3.62 mmol), dried Amberlite® IR118 acidic ion-exchange resin (5.8 g, commercially supplied grade (Aldrich) dried at 0.1 mmHg, 50 °C, 5 h) and anhyd EtOH (9 mL) in Et_2O (36 mL) at 0 °C under N_2 was added portionwise sodium metal (1.38 g, 60 mmol, ca 20 portions) over 2.5 h. After this time H_2O (15 mL) was added and the biphasic mixture filtered to remove the resin beads. The resin beads were then washed well (3 × 10 mL Et_2O) into the filtrate and the layers separated. The aqueous phase was then extracted (2 × 10 mL Et_2O) and the combined organic extracts washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was further purified via column chromatography (eluting with 25% Et_2O in hexanes) to yield the vitamin D_2 CD-ring α-alcohol **8α** (812 mg, 2.92 mmol, 81%) as a crystalline solid: mp 81–83 °C (hexanes); $[\alpha]_D$ = –24.4 (*c* = 0.95, $CHCl_3$).

IR (KBr): ν = 3325 (br s), 2958 (s), 1459 (s), 1368 (m), 1093 (m), 1068 (m), 1031 (m), 1007 (m), 970 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.22 (1H, dd, *J* = 15.2, 7.1 Hz), 5.16 (1H, dd, *J* = 15.3, 7.6 Hz), 3.58 (1H, ddd, *J* = 10.4, 10.4, 4.3 Hz), 2.07–1.94 (2H, m), 1.90–1.05 (14H, m), 1.01 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 6.7 Hz), 0.82 (3H, d, *J* = 6.7 Hz), 0.69 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 135.8 (1), 132.1 (1), 71.3 (1), 57.5 (1), 56.6 (1), 44.8 (0), 43.0 (1), 40.0 (1), 39.3 (2), 36.1 (2), 33.3 (1), 28.4 (2), 23.6 (2), 22.0 (2), 21.1 (3), 20.1 (3), 19.8 (3), 17.8 (3), 12.4 (3).

LRMS (EI+mode): *m*/*z* = 278 (22%), 260 (8), 217 (36), 180 (29), 151 (20), 135 (100), 109 (31), 93 (35).

Anal. Calcd. for $C_{19}H_{34}O$ (M = 278): C, 81.95; H, 12.31. Found C, 81.82; H, 12.22.

[1*R*-[1α,(1*R,2*E*,4*R**),3aβ,4α,7aα]]-4-[(Benzothiazol-2-yl)sulfanyl]octahydro-7a-methyl-1-(1,4,5-trimethylhex-2-enyl)-1*H*-indene (10β)**
To a stirred solution of the α-alcohol **8α** (512 mg, 1.84 mmol), 2-sulfanylbenzothiazole (Aldrich, 460 mg, 2.75 mmol) and PPh_3 (814 mg, 3.0 mmol) in anhyd THF (10 mL) under N_2 at 0 °C was added dropwise diisopropyl azodicarboxylate (555 mg, 2.75 mmol) in anhyd THF (3 mL). After 1 h the reaction was allowed to warm to r.t. and stirred for a further 24 h. The solvent was then removed in vacuo and the crude residue further purified via column chromatography (eluting with 10% Et_2O in hexanes) to yield **10β** (562 mg, 1.32 mmol, 72%) as a colourless solid: mp 68–70 °C (hexanes); $[\alpha]_D$ = +36.1 (*c* = 0.40, $CHCl_3$).

IR (film): ν = 2954 (s), 1456 (s), 1428 (m), 992 (s), 754 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.85 (1H, dm, *J* = 8.1 Hz), 7.74 (1H, dm, *J* = 7.9 Hz), 7.34 (1H, ddd, *J* = 8.5, 7.3, 1.3 Hz), 7.30–7.25 (1H, m), 5.24 (1H, dd, *J* = 15.3, 7.2 Hz), 5.16 (1H, dd, *J* = 15.3, 8.0 Hz), 4.56 (1H, br s), 2.20 (1H, dm, *J* = 10.5 Hz), 2.05–1.95 (2H, m), 1.93–1.12 (12H, m), 1.02 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.91 (3H, s), 0.85 (3H, d, *J* = 6.7 Hz), 0.84 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.7 (0), 153.4 (0), 135.6 (1), 135.2 (0), 132.3 (1), 126.1 (1), 124.2 (1), 121.5 (1), 121.0 (1), 56.5 (1), 52.5 (1), 48.5 (1), 43.0 (1), 42.8 (0), 40.2 (2), 40.2 (1), 33.5 (2), 33.3 (1), 27.8 (2), 24.5 (2), 21.0 (3), 20.1 (3), 19.8 (3), 18.7 (2), 17.8 (3), 13.8 (3).

LRMS (EI+mode): *m*/*z* = 427 (45%), 394 (66), 384 (25), 260 (11), 168 (58), 125 (40).

Anal. Calcd. for $C_{26}H_{37}NS_2$ (M = 427): C, 73.01; H, 8.72; N, 3.27. Found C, 72.97; H, 8.73; N, 3.26.

[1*R*-[1α,(1*R,2*E*,4*R**),3aβ,4α,7aα]]-4-[(Benzothiazol-2-yl)sulfonyl]octahydro-7a-methyl-1-(1,4,5-trimethylhex-2-enyl)-1*H*-indene (2β)**
A stirred solution of the thioether **10β** (523 mg, 1.22 mmol) in EtOH (15 mL) at 0 °C was treated with ammonium heptamolybdate tetrahydrate (150 mg, 0.12 mmol) in 30% H_2O_2 (680 mg, 6.0 mmol) and the resultant suspension allowed to warm to r.t. over 1 h. After subsequent stirring at rt for 2 d, TLC analysis indicated the complete consumption of the sulfide and showed the formation of two diastereomeric sulfoxides. Further Mo catalyst (150 mg, 0.12 mmol) in 30% H_2O_2 (680 mg, 6.0 mmol) was added and the mixture stirred at r.t. for a further 6 d. Due to sluggishness of the oxidation of the sulfoxides to the sulfone, a further two portions of Mo/H_2O_2 (as before) were added over the next 2 d during which time the reaction was continously sonicated. After this protracted reaction time the mixture was diluted with Et_2O (50 mL) and H_2O (30 mL) and the layers shaken and then separated. The aqueous layer was then extracted (4 × 15 mL Et_2O) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and then concentrated in vacuo. The residue was then further purified via column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfone **2β** (410 mg, 0.89 mmol, 73%) as fine white needles: mp 135–137 °C (EtOH); $[\alpha]_D$ = –10.4 (*c* = 0.52, $CHCl_3$).

IR (KBr): ν = 2953 (s), 1470 (m), 1321 (s), 1302 (s), 1151 (m), 1128 (s), 762 (s), 730 (m), 671 (m), 601 (m), 527 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.20 (1H, dm, *J* = 8.1 Hz), 8.01 (1H, dm, *J* = 7.8 Hz), 7.63 (1H, tm, *J* = 7.2 Hz), 7.58 (1H, tm, *J* = 7.2 Hz), 5.26 (1H, dd, *J* = 15.3, 7.4 Hz), 5.16 (1H, dd, *J* = 15.3, 8.3 Hz), 4.26 (1H, br t, *J* = 5.4 Hz), 2.34 (1H, qd, *J* = 12.7, 6.0 Hz),

2.24–2.00 (4H, m), 1.96–1.62 (4H, m), 1.60–1.43 (4H, m), 1.38–1.26 (1H, m), 1.20–1.14 (1H, m), 1.14 (3H, s), 1.04 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.5 Hz), 0.83 (3H, d, *J* = 6.6 Hz).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.5 (0), 152.9 (0), 137.0 (0), 135.3 (1), 132.5 (1), 127.9 (1), 127.7 (1), 125.5 (1), 122.5 (1), 61.2 (1), 56.1 (1), 52.1 (1), 43.0 (1), 41.3 (0), 40.5 (1), 40.2 (2), 33.2 (1), 27.5 (2), 27.1 (2), 23.9 (2), 21.1 (3), 20.2 (3), 19.8 (3), 18.5 (2), 17.8 (3), 13.1 (3).

LRMS (EI+mode): *m*/*z* = 459 (3%), 416 (11), 395 (35), 352 (30), 334 (30), 261 (57), 200 (58), 136 (100).

HRMS (EI+mode): Found $M^{+\bullet}$, 459.2269. $C_{26}H_{37}NO_2S_2$ requires 459.2266.

Anal. Calcd. for $C_{26}H_{37}NO_2S_2$ (M = 459): C, 67.93; H, 8.11; N, 3.05. Found C, 67.98; H, 8.12; N, 3.05.

(*S*,*Z*)-[5-(*tert*-Butyldimethylsilyloxy)-2-methylenecyclohexylidene]acetaldehyde (3)

To a stirred solution of the A-ring dienol **7** (175 mg, 0.65 mmol) in anhyd CH_2Cl_2 (2 mL) at r.t. under N_2 was added Dess-Martin periodinane[17] (305 mg, 0.72 mmol). The resultant mixture was then stirred for 30 min and subsequently diluted with Et_2O (10 mL), poured into sat. $Na_2S_2O_3$–$NaHCO_3$ (15 mL) and stirred vigorously for a further 10 min. The layers were then separated and the aqueous phase extracted (2 × 5 mL Et_2O). The combined organic extracts were then washed with sat. $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was then filtered through a short (4 cm) silica pad (eluting with 7% Et_2O in hexanes) to yield a pure mixture of the aldehyde **3**[18] and its tautomeric pyran **15** (154 mg, **3**:**15** = 4:1, 0.58 mmol, 89%) as a clear oil. A dynamic equilibrium exists between the two isomers: $CHCl_3$ solutions of the separated components both exhibit **3**:**15** = 7:3 after 36 h at r.t.

(*S*,*Z*)-[5-(*tert*-Butyldimethylsilyloxy)-2-methylenecyclohexylidene]acetaldehyde (3)

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.81 (1H, d, *J* = 8.0 Hz), 5.89 (1H, dm, *J* = 8.0 Hz), 5.21 (1H, m), 5.00 (1H, m), 4.06 (1H, tt, *J* = 6.8, 3.4 Hz), 2.60–2.54 (2H, m), 2.42 (1H, dd, *J* = 13.3, 6.9 Hz), 2.25 (1H, ddd, *J* = 12.4, 7.7, 4.6 Hz), 1.95–1.86 (1H, m), 1.80–1.70 (1H, m), 0.87 (9H, s), 0.07 (6H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 192.8 (0), 163.2 (0), 144.0 (0), 128.5 (1), 116.8 (2), 69.5 (1), 46.3 (2), 35.4 (2), 31.5 (2), 25.9 (3C, 3), 18.2 (0), –4.5 (3), –4.6 (3).

***(S)*-3,4-Dehydro-6-(*tert*-butyldimethylsilyloxy)-5,6,7,8-tetrahydroisochroman (15)**

^{1}H NMR (360 MHz, $CDCl_3$): (selected) δ = 6.36 (1H, d, *J* = 5.5 Hz), 5.02 (1H, d, *J* = 5.7 Hz), 4.43 (2H, m), 3.91 (1H, dddd, *J* = 11.2, 8.1, 5.1, 3.4 Hz) +other signals.

^{13}C NMR (MHz, $CDCl_3$): δ = 143.2 (1), 123.0 (0), 119.4 (0), 105.9 (1), 68.3 (2), 68.1 (1), 36.8 (2), 31.6 (2), 26.1 (3C, 3), 25.3 (2), 18.4 (0), –4.5 (3), –4.6 (3).

Vitamin D_2 (1)

To a stirred solution of the β-sulfone **2β** (50 mg, 0.11 mmol) in anhyd Et_2O (4 ml) at –78 °C under N_2 was added dropwise a solution of sodium hexamethyldisilazide (65 µl, 2.0 M in THF, 0.13 mmol) and the resultant yellow solution stirred for 1 h. After this time the mixture was cooled to –100 °C and a solution of the freshly prepared aldehyde–pyran mixture (**3**:**15** ~ 4:1, 80 mg, 0.31 mmol) in anhyd Et_2O (2 mL) added dropwise. The reaction was then allowed to warm steadily to r.t. over the next 1.5 h and then stirred overnight. After this time the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2 × 5 mL Et_2O) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and then concentrated in vacuo to yield 111 mg of a crude oil. The residue was then further purified via column chromatography (eluting with 1–10% Et_2O in hexanes) to yield 57 mg of non-polar material (containing vitamin D_2 TBS ethers and pyran **15**), recovered aldehyde **3** (13 mg, 0.05 mmol, 16%) and epimeric α-sulfone **2*α*** (9 mg, 0.02 mmol, 18%). A solution of the non-polar material in anhyd THF (2 mL) at r.t. under N_2 was then treated with tetrabutylammonium fluoride trihydrate (135 mg, 0.43 mmol) and stirred overnight. After this time the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2 × 5 mL Et_2O) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and then concentrated in vacuo. The residue was then further purified via column chromatography (eluting with 20% Et_2O in hexanes) to yield a pure mixture of natural vitamin D_2 (**1**) and (7*Z*)-vitamin D_2 (**16**) as a clear oil (30 mg, 0.076 mmol, 70% (2 steps), **1**:**16** = 72:28). The vitamin D_2 isomers can be separated by careful chromatography (eluting with 10–15% Et_2O in hexanes); the previously unreported unnatural isomer **27** shows only limited stability in $CDCl_3$.

[1*R*-[1*α*,(1*R,2*E*,4*R**),3aβ,4β,7a*α*]]-4-(Benzothiazol-2-yl)thiooctahydro-7a-methyl-1-(1,4,5-trimethylhex-2-enyl)-1*H*-indene (2*α*)**

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.24 (1H, dm, *J* = 7.7 Hz), 8.02 (1H, dm, *J* = 7.1 Hz), 7.65 (1H, td, *J* = 7.2, 1.4 Hz), 7.60 (1H, td, *J* = 1.3 Hz), 5.21 (1H, dd, *J* = 15.2, 7.1 Hz), 5.14 (1H, dd, *J* = 15.2, 7.7 Hz), 3.67 (1H, td, *J* = 11.7, 3.4 Hz), 2.07–1.89 (3H, m), 1.84 (1H, sextet, *J* = 6.7 Hz), 1.76–1.65 (3H, m), 1.62–1.52 (3H, m), 1.50–1.13 (5H, m), 1.01 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.83 (3H, d, *J* = 6.5 Hz), 0.81 (3H, d, *J* = 6.5 Hz), 0.75 (3H, s).

Vitamin D_2 (1)

Mp 109–110 °C (MeOH–H_2O). (lit. [19] 118 °C). NMR data is in complete agreement with that previously reported.[20,21]

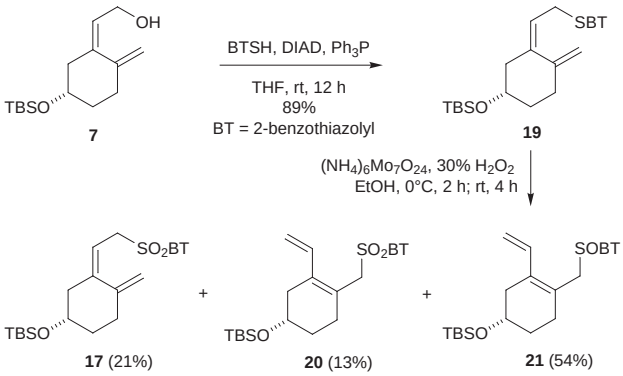
(7*Z*)-Vitamin D_2 (16)

The stereochemistry of **16** was assigned by analogy with other reported (7*Z*)-vitamin D congeners.[12,22]

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.36 (1H, d, *J* = 11.6 Hz), 6.23 (1H, d, *J* = 11.6 Hz), 5.28–5.15 (2H, m), 5.09 (1H, m), 4.85 (1H, m), 3.82 (1H, tt, *J* = 9.1, 4.1 Hz), 2.52 (1H, dd, *J* = 12.3, 3.2 Hz), 2.38 (1H, dt, *J* = 13.9, 5.0 Hz), 2.30–1.20 (20H, m), 1.03 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.5 Hz), 0.85 (3H, d, *J* = 6.4 Hz), 0.83 (3H, d, *J* = 6.1 Hz), 0.66 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 144.4 (0), 141.7 (0), 136.0 (0), 135.8 (1), 132.2 (1), 123.5 (1), 121.8 (1), 113.3 (2), 70.2 (1), 56.3 (1), 55.1 (1), 46.7 (0), 46.6 (2), 43.0 (1), 40.8 (2), 40.5 (1), 39.1 (2), 35.9 (2), 33.3 (1), 32.7 (2), 28.5 (2), 26.5 (2), 24.3 (2), 21.6 (3), 20.2 (3), 19.8 (3), 17.8 (3), 13.1 (3).

Scheme 8 depicts the synthesis of sulfone **17**.



Scheme 8

(*Z*,*S*)-2-[2-[5-(*tert*-Butyldimethylsilyloxy)-2-methylenecyclohexylidene]ethylsulfanyl]benzothiazole (19)

To a stirred solution of the A-ring dienol **7** (540 mg, 2.0 mmol), PPh_3 (630 mg, 2.4 mmol) and 2-sulfanylbenzothiazole (550 mg, 3.3 mmol) in anhyd THF (10 mL) at r.t. under N_2 was added dropwise neat diisopropyl azodicarboxylate (0.48 g, 2.4 mmol). The resultant solution was stirred for 12 h and then concentrated in vacuo. The crude residue was further purified via column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfide **19** (747 mg, 1.79 mmol, 89%) as a clear oil: $[\alpha]_D$ = +36.9 (*c* = 1.04, $CHCl_3$).

IR (film): ν = 2934 (s), 2855 (s), 1460 (s), 1428 (s), 1252 (m), 1092 (s), 997 (s), 902 (m), 869 (m), 836 (s), 774 (s), 755 (s), 726 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.88 (1H, dm, *J* = 8.2 Hz), 7.76 (1H, dm, *J* = 8.0 Hz), 7.42 (1H, ddd, *J* = 8.4, 7.3, 1.2 Hz), 7.30 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz), 5.51 (1H, tm, *J* = 7.8 Hz), 5.06 (1H, br s), 4.87 (1H, br s), 4.19 (1H, dd, *J* = 12.8, 7.9 Hz), 4.11 (1H, ddd, *J* = 12.8, 7.6, 1.1 Hz), 3.83 (1H, tt, *J* = 8.2, 3.7 Hz), 2.50–2.38 (2H, m), 2.22 (1H, dd, *J* = 12.9, 8.1 Hz), 2.11 (1H, dddm, *J* = 14.4, 8.4, 4.4 Hz), 1.90–1.82 (1H, m), 1.62 (1H, dddd, *J* = 12.9, 9.8, 8.2, 4.6 Hz), 0.87 (9H, s), 0.04 (6H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 167.1 (0), 153.5 (0), 145.1 (0), 142.9 (0), 135.5 (0), 126.2 (1), 124.3 (1), 121.7 (1), 121.1 (1), 119.0 (1), 112.1 (2), 70.1 (1), 46.3 (2), 36.2 (2), 32.6 (2), 32.5 (2), 26.0 (3C, 3), 18.3 (0), –4.5 (3), –4.5 (3).

LRMS (EI+mode): *m*/*z* = 417 (37%), 370 (25), 285 (17), 252 (17), 224 (26), 193 (17), 149 (18), 119 (100), 91 (52), 73 (64).

HRMS (EI+mode): Found $M^{+\bullet}$, 417.1619. $C_{22}H_{31}NOS_2Si$ requires 417.1616.

Oxidation of Thioether 19

A stirred solution of the thioether **19** (200 mg, 0.48 mmol) in EtOH (5 mL) at 0 °C was treated with ammonium heptamolybdate tetrahydrate (150 mg, 0.12 mmol) in 30% H_2O_2 (230 mg, 2.0 mmol). The resulting yellow suspension was allowed to stir for 2 h at 0 °C and then for a further 4 h at r.t. The mixture was then diluted with H_2O (10 mL) and extracted (4 × 10 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residue was then further purified via column chromatography (eluting with 10–25% Et_2O in hexanes) to yield in order of elution: the sulfone **17** (44 mg, 0.10 mmol, 21%), the isomeric sulfone **20** (28 mg, 0.06 mmol, 13%) and its parent sulfoxides **21** (113 mg, 0.26 mmol, 54%, dr = 1:1) all as clear oils.

(*Z*,*S*)-2-[2-[5-(*tert*-Butyldimethylsilyloxy)-2-methylenecyclohexylidene]ethylsulfanyl]benzothiazole (17)

$[\alpha]_D$ = +9.2 (*c* = 0.48, $CHCl_3$).

IR (film): ν = 2930 (s), 2856 (s), 1472 (m), 1332 (s), 1252 (m), 1149 (s), 1091 (s), 868 (m), 837 (m), 763 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.23 (1H, dm, *J* = 7.6 Hz), 8.02 (1H, dm, *J* = 7.6 Hz), 7.65 (1H, ddd, *J* = 7.2, 7.2, 1.4 Hz), 7.60 (1H, ddd, *J* = 7.3, 7.3, 1.3 Hz), 5.35 (1H, t, *J* = 7.6 Hz), 4.99 (1H, br s), 4.83 (1H, m), 4.57 (1H, dd, *J* = 14.2, 8.9 Hz), 4.28 (1H, ddd, *J* = 13.0, 6.2, 1.2 Hz), 3.55 (1H, tt, *J* = 8.8, 3.8 Hz), 2.42 (1H, dd, *J* = 12.9, 3.9 Hz), 2.25 (1H, dt, *J* = 12.1, 4.4 Hz), 2.23–2.16 (1H, m), 1.77–1.67 (2H, m), 1.55–1.46 (1H, m), 0.84 (9H, s), 0.00 (3H, s), –0.01 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.0 (0), 152.9 (0), 149.0 (0), 144.5 (0), 137.0 (0), 128.2 (1), 127.8 (1), 125.6 (1), 122.5 (1), 112.8 (2), 108.9 (1), 70.3 (1), 55.4 (2), 46.8 (2), 36.1 (2), 32.3 (2), 26.0 (3C, 3), 18.3 (0), –4.6 (3), –4.6 (3).

LRMS (CI mode, *iso*butane): *m*/*z* = 450 (100%), 136 (26).

HRMS (CI mode): Found $(M+H)^+$, 450.1595. $C_{22}H_{32}NO_3S_2Si$ requires 450.1593.

(*S*,*Z*)-4-[(Benzothiazol-2-yl)sulfonyl]methyl-1-[(1,1-dimethylethyl)dimethylsilyl]oxy-3-vinylcyclohex-3-ene (20)

IR (film): ν = 2929 (s), 2856 (s), 1472 (s), 1334 (s), 1252 (s), 1152 (s), 1097 (s), 1006 (m), 882 (m), 837 (s), 763 (s), 729 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.23 (1H, dm, *J* = 7.9 Hz), 7.99 (1H, dm, *J* = 8.4 Hz), 7.64 (1H, ddd, *J* = 8.2, 7.2, 1.4 Hz), 7.59 (1H, ddd, *J* = 8.1, 7.2, 1.3 Hz), 6.50 (1H, dd, *J* = 17.1, 10.9 Hz), 5.01 (1H, d, *J* = 16.4 Hz), 4.79 (1H, d, *J* = 11.1 Hz), 4.42 (1H, d, *J* = 14.2 Hz), 4.33 (1H, d, *J* = 14.0 Hz), 3.97–3.90 (1H, m), 2.59–2.34 (3H, m), 2.07 (1H, ddm, *J* = 17.2, 7.0 Hz), 1.84–1.75 (1H, m), 1.68–1.58 (1H, m), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 165.4 (0), 153.0 (0), 137.7 (0), 136.7 (0), 133.1 (1), 128.1 (1), 127.8 (1), 125.6 (1), 122.3 (1), 121.9 (0), 114.8 (2), 67.1 (1), 58.8 (2), 35.3 (2), 31.5 (2), 30.1 (2), 26.0 (3C, 3), 18.3 (0), –4.4 (3), –4.5 (3).

LRMS (CI mode, isobutane): *m*/*z* = 450 (100%), 136 (16).

(*S*,*Z*)-4-[(Benzothiazol-2-yl)sulfinyl]methyl-1-[(1,1-dimethylethyl)dimethylsilyl]oxy-3-vinylcyclohex-3-ene (21)

IR (film): ν = 2928 (s), 2856 (s), 1472 (m), 1252 (s), 1007 (s), 1004 (m), 881 (m), 836 (s), 774 (m), 760 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, isomeric mixture - * denotes a resolved signal arising from a single isomer): δ = 8.06 (1H, dm, *J* = 8.2 Hz), 7.99 (1H, dm, *J* = 8.1 Hz), 7.56 (1H, ddd, *J* = 8.4, 7.3, 1.3 Hz), 7.51–7.45 (1H, m), 6.65 (1H, dd, *J* = 17.1, 11.0 Hz), 5.15 (1H, d, *J* = 17.1 Hz), 4.96 (1H, d, *J* = 11.0 Hz), 4.17 (1H*, d, *J* = 13.1 Hz), 4.09 (1H*, d, *J* = 13.0 Hz), 4.03 (1H*, d, *J* = 13.1 Hz), 3.96 (1H*, d, *J* = 12.8 Hz), 3.99–3.90 (1H, m), 2.52–2.20 (3H, m), 2.19–2.08 (1H, m), 1.85–1.74 (1H, m), 1.68–1.56 (1H, m), 0.89 (9H*, s), 0.88 (9H*, s), 0.07 (3H, s), 0.07 (3H, s).

^{13}C NMR (90 MHz, $CDCl_3$, isomeric mixture - † denotes signals common to both isomers): δ = 177.6† (0), 153.9† (0), 136.1 (0), 136.0 (0), 135.4 (0), 135.4 (0), 133.4 (1), 133.3 (1), 127.0† (1), 126.3† (1), 124.5 (0), 124.3 (0), 124.1 (1), 124.0 (1), 122.4 (1), 122.4 (1), 114.4 (2), 114.3 (2), 67.4 (1), 67.2 (1), 61.9 (2), 61.8 (2), 35.1† (2), 31.6 (2), 31.4 (2), 31.0 (2), 30.6 (2), 26.0† (3C, 3), 18.3† (0), –4.5† (3), –4.5† (3).

LRMS (CI mode, *iso*butane): *m*/*z* = 434 (100%), 251 (20), 184 (20), 119 (39).

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