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D- and L-Serine, useful synthons for the synthesis of 24-hydroxyvitamin D_3 metabolites. A formal synthesis of 1α,24*R*,25-$(OH)_3$-D_3, 24*R*,25-$(OH)_2$-D_3 and 24*S*,25-$(OH)_2$-D_3

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Abstract—D- and L-Serine have been used for the enantioselective synthesis of tosylates **7a** and **7b**, useful building blocks for the synthesis of triols **5a** and **5b** which have already been obtained via a diastereoselective synthesis and used for the synthesis of **2a**, **2b** and **2c**. We have thus performed a formal synthesis of 24*S*,25-$(OH)_2$-D_3, 24*R*,25-$(OH)_2$-D_3 and 1α,24*R*,25-$(OH)_3$-D_3.

1α,25-Dihydroxyvitamin D_3 (**1a**, calcitriol) (Fig. 1) is the hormonally active form of vitamin D_3 (**1b**). Besides regulating calcium homeostasis, it is also involved in other cellular processes, including cell differentiation, immune system regulation and gene transcription.[1] The latter function, mediated by the nuclear vitamin D receptor (found in more than thirty different tissues and cancer cell lines), raises the possibility of developing 1α,25-$(OH)_2$-D_3 analogues for specific therapeutic applications.

1α,25-$(OH)_2$-D_3 (**1a**, calcitriol) and 24*R*,25-$(OH)_2$-D_3 (**2a**, secalciferol) are the major active metabolites of vitamin D_3 (**1b**). However, the biological activity of vitamin D has generally been attributed to calcitriol leaving secalciferol's functions relatively unexplored. In the last 25 years, a great deal of effort has been devoted to the elucidation of the biological function of secalciferol, and as a consequence more than 350 papers have been published about the biological activity of this metabolite.[2] Most of the available syntheses of secalciferol use the lengthy and less efficient steroidal biomimetic route,[3] and consequently the price of secalciferol is rather high (450 €/μg). Recently, Sarandeses and co-workers described a stereoselective convergent synthesis of

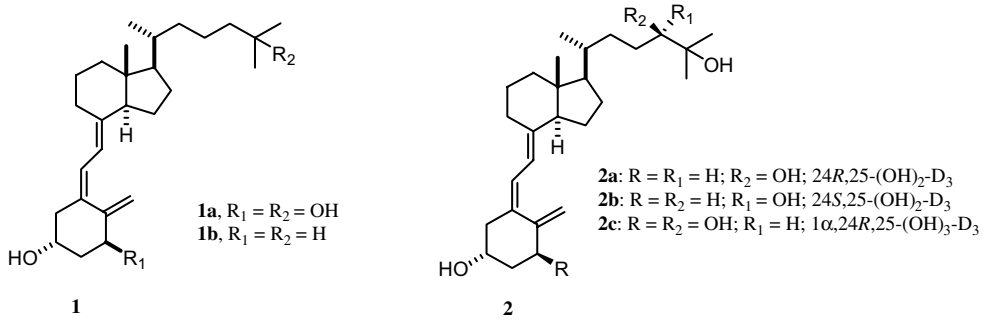

Figure 1.

Keywords: Vitamin D; Calcitriol; Secalciferol; Aminoacid; Enantioselective synthesis.
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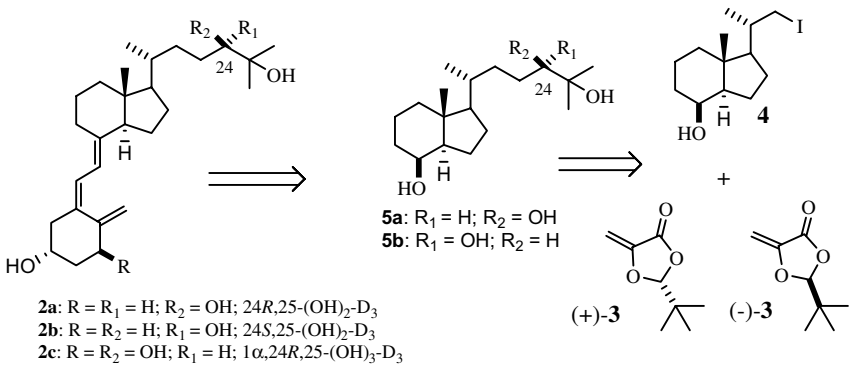
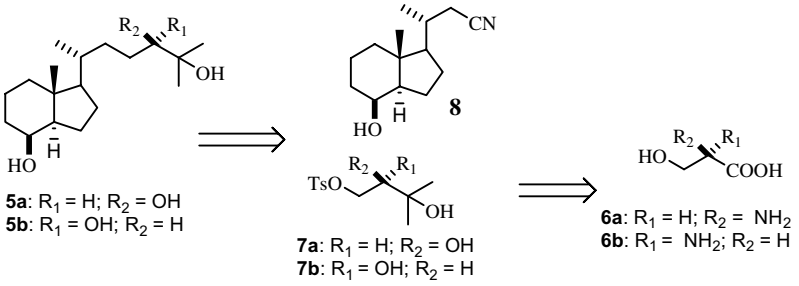
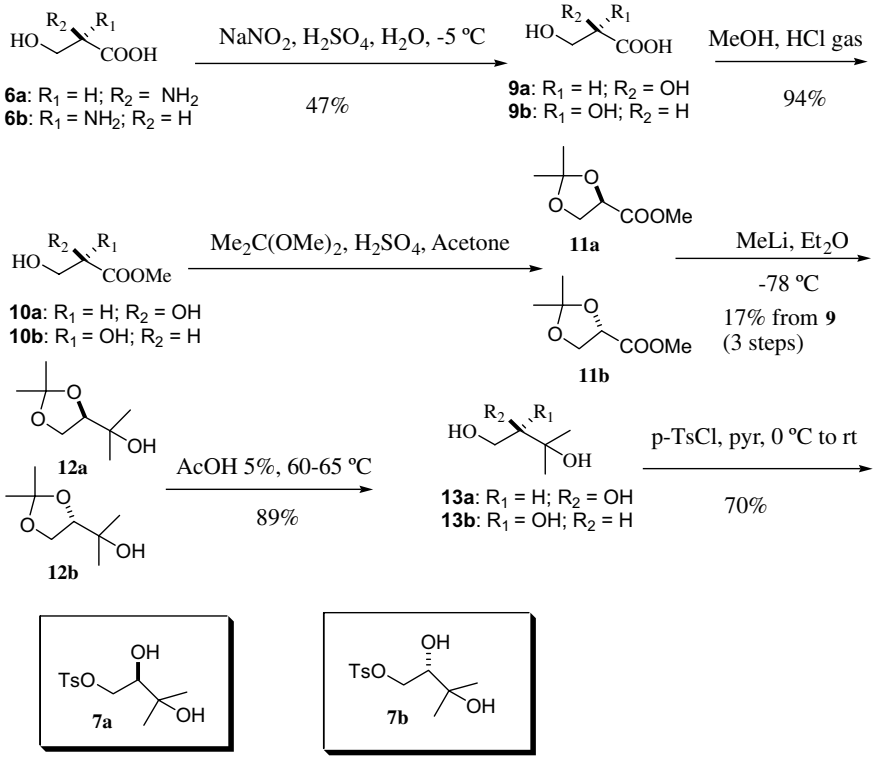
24-substituted metabolites and analogues of vitamin D in which the stereogenic centre at C-24 was generated through ultrasonically induced conjugate addition of an iodide to a dioxolanone[4] (Scheme 1).



Scheme 1.



Scheme 2. Retrosynthetic analysis for **5a** and **5b**.



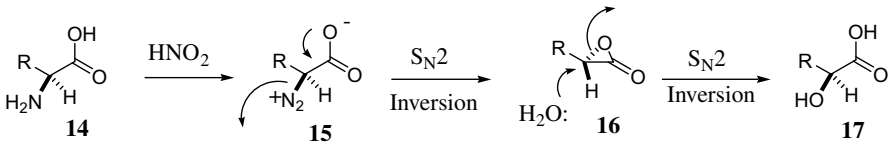
Scheme 3. Synthesis of tosylates **7a** and **7b**.

This approach clearly improves the so far available syntheses of secalciferol, but since it is a diastereoselective approach (**5a** and **5b** are obtained as a mixture of diastereoisomers albeit with a high de), this means that an enantioselective, flexible and convergent synthesis of secalciferol is still in need. In Scheme 2 is depicted the enantioselective synthesis of **5a** and **5b** from commercially available amino acids D- and L-serine **6a** and **6b** and nitrile **8**.[5]

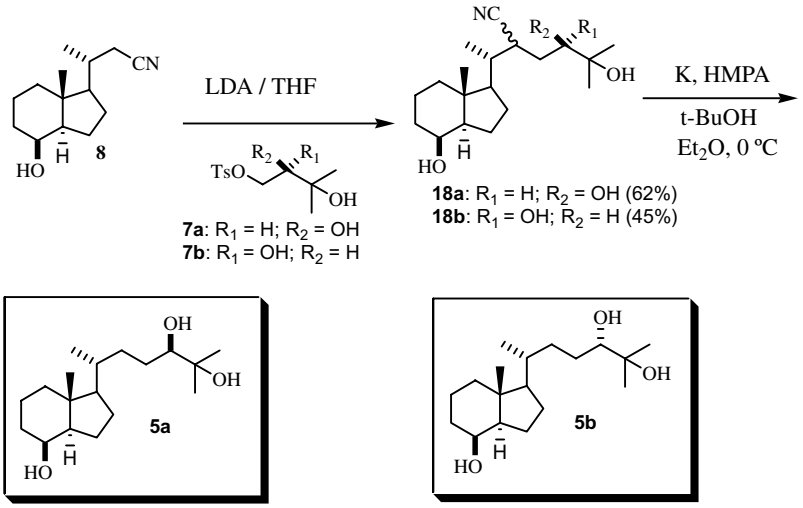
Tosylates **7a** and **7b** were obtained as depicted in Scheme 3. Nitrous desamination of **6a** and **6b** gave acids **9a** and **9b** which were esterified using methanol and HCl gas to provide ester diols **10a** and **10b**, which were protected as acetonides **11a** and **11b**. Reaction of **11a** and **11b** with methyllithium afforded alcohols **12a** and **12b**, which on reaction with acetic acid gave triols **13a** and **13b**. Selective tosylation of **13a** and **13b** afforded the desired tosylates **7a** and **7b** (the yields obtained for both enantiomers were similar).

It is worth mentioning that the first step of this reaction sequence occurs with retention of configuration as depicted in the following mechanism (Scheme 4).[5]

With tosylates **7a** and **7b** in hand, the stage was set for their coupling with nitrile **8** using our previously described methodology.[6] Nitrile **8** was deprotonated with 2 equiv of LDA in THF at −78 °C and reacted with tosylates **7a** and **7b** to afford a diastereoisomeric mixture



Scheme 4. Reaction mechanism of α-amino acids with HNO_2.



Scheme 5. Synthesis of triols **5a** and **5b** from nitrile **8**.

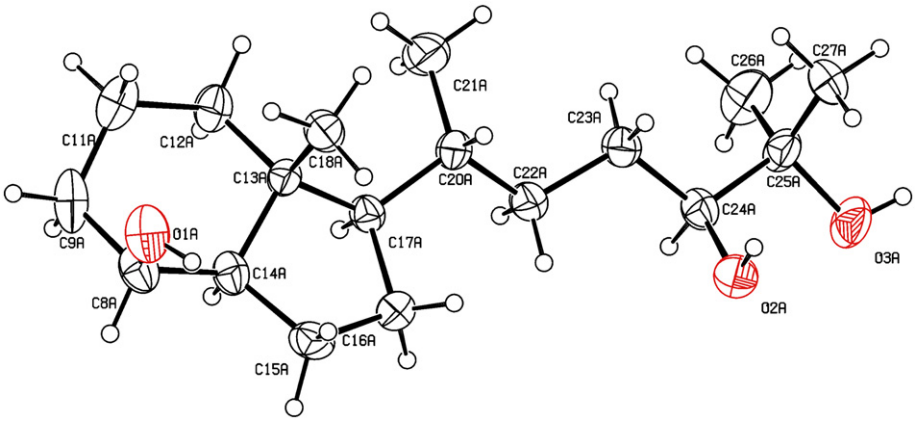


Figure 2. X-ray structure of **5b**.

of nitriles **18**, which upon treatment with potassium metal in portions provided triols **5a** (39%) and **5b** (33%)[7] (Scheme 5).

Triols **5a** and **5b** have been previously synthesized by Sarandeses and co-workers and were used for the convergent synthesis of **2a**, **2b** and **2c** via a Wittig–Horner coupling with the corresponding ring A phosphine oxide.[4] We have thus performed a formal synthesis of 24*S*,25-$(OH)_2$-D_3, 24*R*,25-$(OH)_2$-D_3 and 1α,24*R*,25-$(OH)_3$-D_3.

Compounds **5a** and **5b** have been synthesized through an enantioselective route starting from a chiral amino acid, hence their structure is unambiguous. Nevertheless, recrystallization of triol **5b** in hexane and ethyl acetate afforded crystals which were subjected to X-ray crystallographic analysis,[8] thus confirming its structure to be that shown in Figure 2.

In conclusion, we have performed a formal asymmetric synthesis of secalciferol and 24-substituted metabolites and analogues of vitamin D. Tosylates **7a** and **7b** are useful building blocks easily obtained from commercially available amino acids. Further investigations on the synthesis of novel vitamin D thia-analogues using these synthons will be reported in due course.[9]

Acknowledgements

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7. Compound **5a**: ^{1}H NMR ($CDCl_3$, δ): 4.06 (1H, br s, H-8), 3.32 (1H, m, H-24), 2.01 (2H, m), 1.88 (1H, m), 1.79 (2H, m), 1.2 (3H, s, H-26 or 27), 1.15 (3H, s, H-26 or 27), 0.92 (3H, s, H-18), 0.89 (3H, d, $J = 6.47$ Hz, H-21); ^{13}C NMR ($CDCl_3$, δ): 78.74 (CH-24), 73.18 (C-25), 69.39 (CH-8), 56.61 (CH-17), 52.56 (CH-14), 41.86 (C-13), 40.37 (CH_2), 35.10 (CH-20), 33.55 (CH_2), 32.65 (CH_2), 28.06 (CH_2), 27.21 (CH_2), 26.57 (CH_3-26 or 27), 23.22 (CH_3-26 or 27), 22.49 (CH_2), 18.39 (CH_3-21), 17.41 (CH_2), 13.54 (CH_3-18); HRMS (FAB): calcd for $C_{18}H_{34}O_3Na$: 321.2400; found: 321.2407. Compound **5b**: ^{1}H NMR ($CDCl_3$, δ): 4.05 (1H, br s, H-8), 3.27 (1H, d, $J = 9.29$ Hz, H-24), 1.98 (1H, d, $J = 13.22$ Hz, H-14), 1.19 (3H, s, H-26 or 27), 1.14 (3H, s, H-26 or 27), 1.89 (6H, m, H-18 and 21); ^{13}C NMR ($CDCl_3$, δ): 79.96 (CH-24), 73.66 (C-25), 69.77 (CH-8), 56.94 (CH-17), 52.97 (CH-14), 42.25 (C-13), 40.78 (CH_2), 35.88 (CH-20), 33.94 (CH_2), 33.46 (CH_2), 28.74 (CH_2), 27.53 (CH_2), 26.89 (CH_3-26 or 27), 23.57 (CH_3-26 or 27), 22.90 (CH_2), 17.82 (CH_2), 14.57 (CH_3-21), 13.93 (CH_3-18); HRMS (FAB): calcd for $C_{18}H_{34}O_3Na$: 321.2400; found: 321.2410.
8. X-ray crystal structure analysis of **5b**: Bruker Smart CCD diffractometer, Mo-K_α-radiation ($\lambda = 0.71073$ Å), T 293(2) K. Crystal size: $0.26 \times 0.24 \times 0.22$ mm^3, colourless irregular prism, space group $C2$, monoclinic, $a = 13.401(2)$, $b = 25.538(4)$, $c = 12.2778(19)$ Å, $\beta = 117.714(3)°$, $V = 3720.0(10)$ Å^3, $Z = 8$, $\rho_{cal} = 1.082$ g/cm^3, θ range = 1.59–28.08°, 10,228 reflections collected, 6938 independent ($R_{int} = 0.0673$), 402 parameters, final R indices [$I > 2\sigma$], $R = 0.0486$, $wR = 0.0940$, GOF = 0.735. Structure solution: direct methods (SHELXS97), refinement on F^2 (SHELXL97). H atoms were calculated. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Centre No. CCDC 240720. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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