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Tetrahedron Letters 45 (2004) 4619–4621
Tetrahedron Letters

Vitamin D and click chemistry. Part 1: A stereoselective route to vitamin D analogues with triazole rings in their side chains

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Received 22 March 2004; revised 16 April 2004; accepted 21 April 2004

Abstract—Efficient preparation of vitamin D CD ring system synthons with triazole rings in their side chains is based on the formation of the triazole ring from a [3+2]-cycloaddition of a vitamin D side chain terminal azide with a terminal acetylene.

1α,25-Dihydroxy vitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3[1] (**2**, cholecalciferol), exerts control over important physiological processes, including calcium and phosphorus metabolism, cellular differentiation and immune reactions.[2] However, the clinical utility of this hormone for treatment of cancers and skin disorders is limited by its hypercalcaemic effects. There is accordingly much interest in the design and synthesis of analogues of **1** with more selective (or even different) biological effects.[2]

Most of the analogues of **1** synthesized so far show modifications at the side chain but only a limited number of these analogues are in use as drugs.[2f] It is well known that azasteroids show noteworthy pharmacological activity,[3,4] however very few aza-analogues of vitamin D have been reported.[3–5] As part of our research programme on the synthesis of vitamin D analogues with heterocyclic side chains we previously reported the synthesis of the side chain of analogue **3** (Fig. 1) containing a pyrazole ring.[5c] We now report our preliminary results on the synthesis of vitamin D analogues with a triazole ring in their side chain based on the use of click chemistry[6] (Scheme 1).

Selective tosylation of the primary alcohol of diol **5** gave tosylate **7** in 93% yield, and protection of the secondary alcohol of **7** (99%), followed by azide displacement of the C-22 primary tosylate afforded a 99% yield of azide **8**,[7] which underwent a [3+2]-cycloaddition with terminal acetylene **9**[8] to afford triazole **10**[7] in 85% yield. Removal of the silyl protecting groups of **10** by reaction

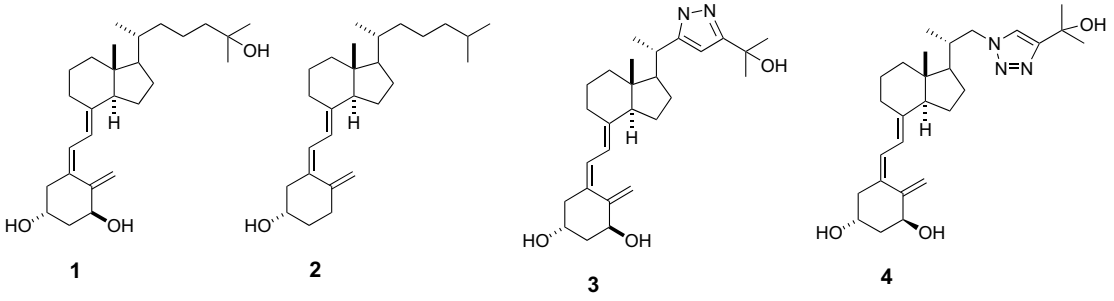

Figure 1.

Keywords: Vitamin D; Analogues; Wittig–Horner; Triazole; Side chain; Antiproliferative.
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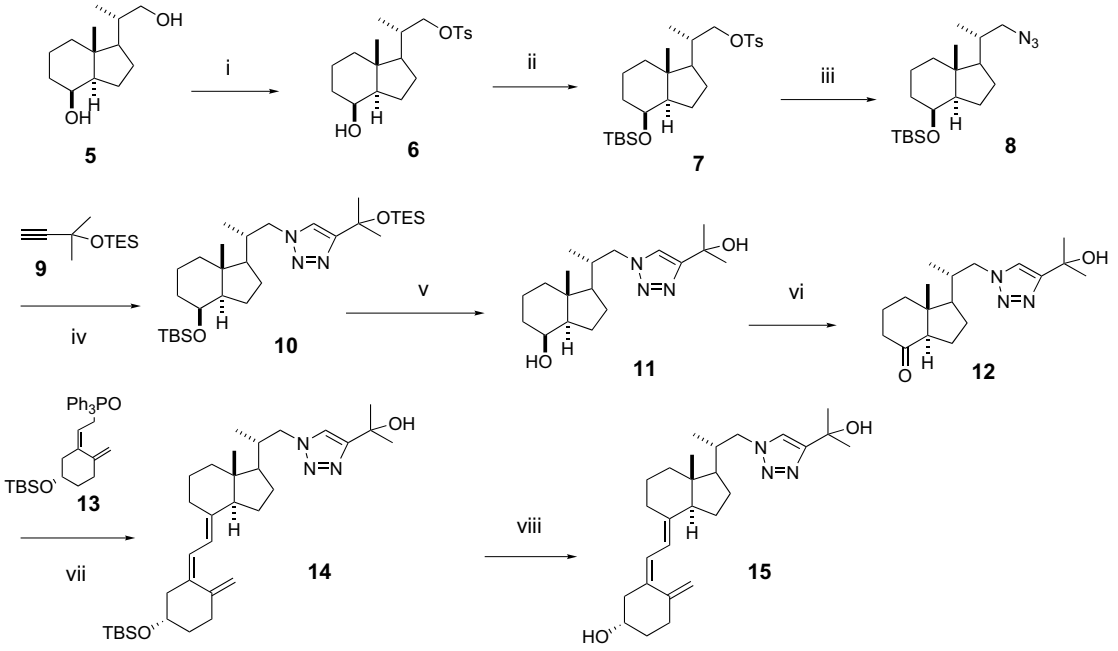
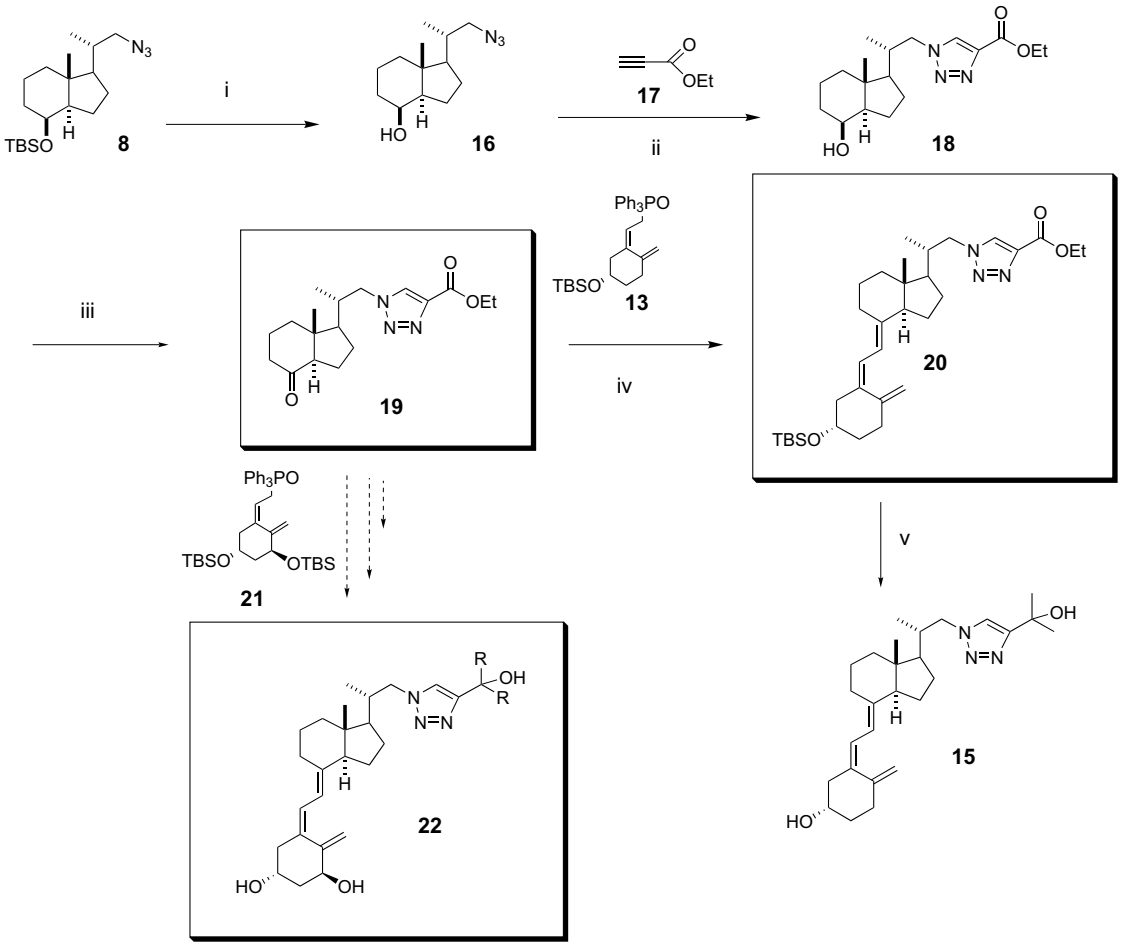
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.04.117



Scheme 1. Reagents and conditions: (i) *p*-TsCl, py (93%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C (99%); (iii) NaN_3, DMF, rt (99%); (iv) **9**, $CuSO_4{\cdot}3H_2O$, sodium ascorbate, H_2O/^{t}BuOH 2:1 (85%); (v) HF, MeCN (86%); (vi) PDC, CH_2Cl_2, rt (50%); (vii) **13**; *n*-BuLi, THF, −78 °C (50%); (viii) *n*-Bu_4NF, THF, rt (83%).



Scheme 2. Reagents and conditions: (i) HF, MeCN, rt (98%); (ii) **16**, $CuSO_4{\cdot}3H_2O$, sodium ascorbate, H_2O/^{t}BuOH 2:1 (99%); (iii) TPAP, NMO, CH_2Cl_2, rt (80%); (iv) **13**; *n*-BuLi, THF, −78 °C (75%); (v) (a) MeLi, Et_2O, −20 °C; (b) *n*-Bu_4NF, THF, rt (49%, two steps).

with HF in acetonitrile at room temperature, gave diol **11**.[7] Oxidation of **11** with pyridinium dichromate afforded ketone **12**,[7] so setting the stage for the Wittig–Horner reaction with phosphine oxide **13**[9] leading to the desired analogue **15**.[7]

Evaluation of the in vitro antiproliferative activity of analogue **15** was done in murine keratinocytes using Johns Hopkins's standard protocol.[10] However no antiproliferative activity was found for **15**. We then designed a more versatile route that would allow not only the synthesis of analogues **4** and **15** but also a wide range of analogues of **4** such as compounds **22** (Scheme 2).

[3+2]-Cycloaddition of azide **16**[7] with ethylpropiolate **17** afforded nearly quantitatively triazole **18**.[7] Oxidation of alcohol **18** with TPAP gave key ketone **19**[7] in 80% yield. Wittig–Horner reaction of **19** with phosphine oxide **13** generated the labile triene unit, affording key intermediate **20**,[7] which leads to **15** upon reaction with MeLi followed by desilylation. The synthesis of analogues **22** is currently under way in our laboratory with a view to their biological evaluation.

Acknowledgements

This work was supported by grants from the Xunta de Galicia (PGIDT01PXI30105PR) and the Vicerectorate for Research of the University of Vigo. We also thank Solvay Pharmaceuticals (Weesp, The Netherlands) for the gift of starting materials; the NMR service of the CACTI, University of Vigo, for NMR studies and Johns Hopkins Prof. Gary Posner, Thomas Kensler and Mr. Patrick Dolan for the in vitro antiproliferative assays.

References and notes

1. Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrinol. Rev.* **1995**, *16*, 200–257.
2. For general reviews of vitamin D chemistry and biology, see: *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; (a) Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop: Riverside, CA, 1997; (b) Feldman, D.; Glorieux, F. H.; Pike, J. W. *Vitamin D*; Academic: San Diego, 1997; (c) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98–114; (d) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398; (e) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952; (f) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889–3895.
3. Suh, B.-C.; Jeon, H. B.; Posner, G. H.; Silverman, S. M. See following paper, *Tetrahedron Lett.* **2004**, *45*, doi:10.1016/j.tetlet.2004.04.118
4. Oves, D.; Ferrero, M.; Fernández, S.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 1154–1157, and references cited therein.
5. (a) Fall, Y.; Puente, M.; Gómez, G.; Bolasimno, T.; Suarez, P. L.; Gándara, Z. *Abstracts of the 12th Workshop on Vitamin D*; Maastricht: The Netherlands, July 6–7, 2003; (b) Gómez, G.; Suarez, P. L.; Sáa, C.; Fall, Y.; Puente, M. *Abstracts of the 12th Workshop on Vitamin D*; Maastricht: The Netherlands, July 6–7, 2003 (c) Fall, Y.; Barreiro, C.; Fernández, C.; Mouriño, A. *Tetrahedron Lett.* **2002**, *43*, 1433–1436; (d) Sestelo, J. P.; de Uña, O.; Mouriño, A.; Sarandeses, L. A. *Synlett* **2002**, *5*, 719–722; (e) Fernández-Gacio, A.; Mouriño, A. *Eur. J. Org. Chem.* **2002**, 2529–2534.
6. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (c) Tornϕe, C. W.; Christensen, M.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
7. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR, analytical, and/or high resolution mass spectral data.
8. Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6344–6352.
9. (a) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264–1269; (b) Mascareñas, J. L.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, 1269–1272.
10. Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280–3287.