Tetrahedron Letters 54 (2013) 3514–3517

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of new calcitriol analogues with an oxolane moiety in their side chains

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ARTICLE INFO

Article history:
Received 15 March 2013
Revised 19 April 2013
Accepted 23 April 2013
Available online 1 May 2013

Dedicated to Dr. Simeon Arseniyadis on the occasion of his farewell to intensive research activities

Keywords:
Vitamin D
Calcitriol
Wittig–Horner
Side chain
Superagonist

ABSTRACT

Two new calcitriol analogues with an oxolane moiety in their side chains have been synthesized and their structures unambiguously confirmed by X-ray crystallographic analysis. These analogues could be potential candidates as superagonist ligands for the vitamin D nuclear receptor.

1α,25-Dihydroxyvitamin D_3 (**1a**, calcitriol) (Fig. 1) is the hormonally active form of vitamin D_3[1] (**1b**, cholecalciferol). It exerts control over important physiological processes, including calcium and phosphorus metabolism, cellular differentiation and immune reactions.[2] This has led to the speculation that **1a** could be a good candidate as a drug for treatment of cancers and skin disorders. However, its therapeutic utility is limited for effective doses leading to calcemic side effects. There is accordingly much interest in the design and synthesis of analogues of **1a** with more selective biological effects.[2]

As part of our research programme on the synthesis of vitamin D analogues with restricted side chain conformation,[3] we previously reported the synthesis of calcitriol analogues **2** and **3** with cyclic side chains (Fig. 1).[3a] Recently, Moras and co-workers[4] reported the design, synthesis and biological evaluation of two new calcitriol analogues **AMCR277A** and **AMCR277B** having an oxolane moiety in their side chains (Fig. 2).

Moras and co-workers concluded that AMCR277A was a VDR superagonist, whereas AMCR277B behaved like the natural ligand. These findings prompted us to release here our preliminary results

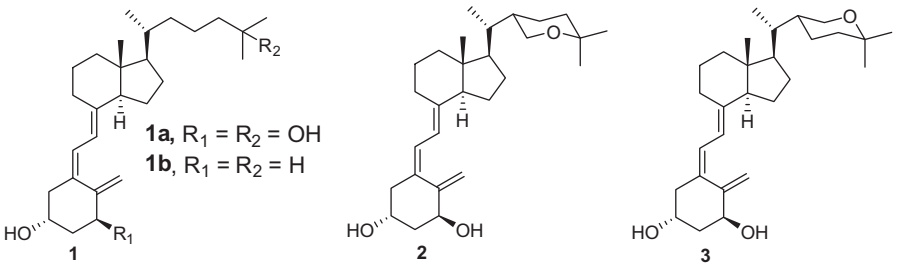

Figure 1. Calcitriol and its analogues with cyclic side chains.

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.04.098

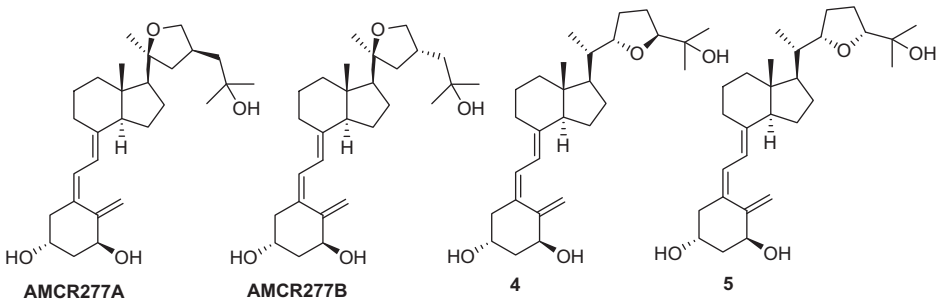
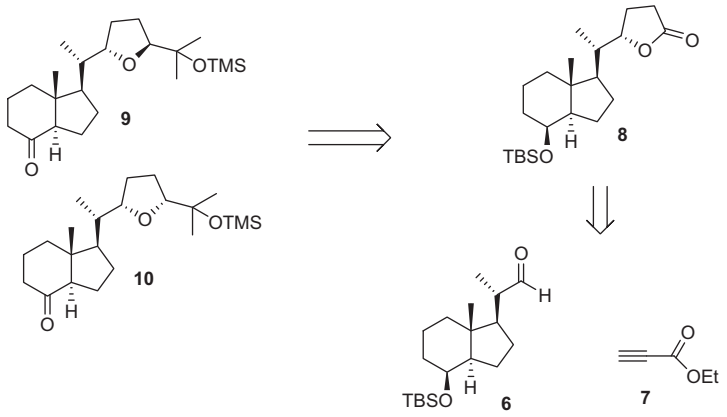
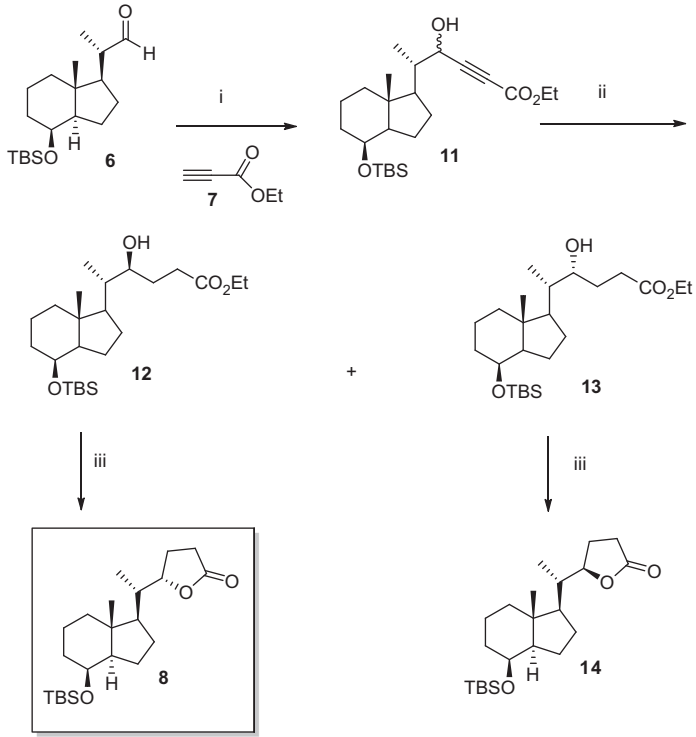


Figure 2. Calcitriol analogues with an oxolane moiety in their side chains.



Scheme 1. Retrosynthetic analysis for ketones **9** and **10**.



Scheme 2. Reagents and conditions: (i) **7**, LDA, THF, −78 °C (92%); (ii) H_2, Pd/C, MeOH, **12** (54%), **13** (42%); (iii) *p*TsOH, C_6H_6, rt, 16h, **8** (93%), **14** (90%).

on the synthesis of new calcitriol analogues **4** and **5** having an oxolane moiety in the side chain (Fig. 2).

We anticipated that the side chains of analogues **4** and **5** could be synthesized stereoselectively from aldehyde **6** and alkyne **7** via ketones **9** and **10** (Scheme 1).

Accordingly, lactone **8** was prepared as shown in Scheme 2.

Aldehyde **6**, easily prepared from Inhoffen-lythgoe diol using known procedure,[5] reacted with the lithium salt of alkyne **7** to afford an inseparable mixture of diastereoisomeric propargylic alcohols **11** in 92% yield.[6] Catalytic hydrogenation of **11** gave alcohols