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Vitamin D: a concise synthesis of the C_{19} hydroxylated enyne A-ring, an interesting precursor for the preparation of C_{19} substituted vitamin D analogues

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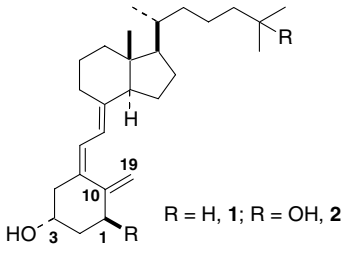
Abstract—A new C_{19} hydroxylated enyne **15**, as potential A-ring building block of vitamin D analogues, was synthesized in enantiomerically pure form in nine steps from (−)-(*S*)-limonene. This short synthesis involved ozonolyzis of 1,2-limonene oxide followed by a Criegee rearrangement, epoxide *trans* diaxial ring opening by lithium acetylide, elimination, epoxidation and *syn* β-elimination of the resulting homopropargylic oxirane.

Over the last decades, chemical and biochemical researches on vitamin D **1** have steadily increased and became of significant interest with the discovery of 1α,25-dihydroxy vitamin D_3 or calcitriol **2**, the hormonally active metabolite of vitamin D. Compound **2** is well known as a strong calcium and phosphorus regulator, but it also plays an important role in the regulation of malignant cell proliferation, implied in cancers and other hyperproliferation diseases, cellular differentiation and immunology.[1] Unfortunately, doses required in treatments cause hypercalcaemia side effects that limit its application as a valuable therapeutical agent. Owing to these properties, preparation of vitamin D analogues has attracted the interest of numerous synthetic groups. Derivatives with modified side chains, A rings and CD bicyclic systems variously substituted have gained attention as potential new drugs, due to their higher efficacy and lower toxicity.[2] To date, few modifications have been reported on the trienic unit except, for example, the replacement of the C_{10}–C_{19} methylene by a 10,10-dimethyl group,[3] the synthesis of 19-*nor*-1α,25-dihydroxy vitamin D_3[4] and the presence of alkyl substituents in C_{19} position.[5] Otherwise, π-electron-donating substituents such as alkoxy groups directly branched on the triene moiety should influence the[1,7] sigmatropic process (a crucial step required in the transformation of **4** to **3**) and then, the biological activity of the compound should be modified.



In order to synthesize vitamin D and its analogues, several strategies have been elaborated and reported in the literature.[2] Among these, Mouriño proposed an interesting convergent approach based on the construction of a dienyne system **4** via a Sonogashira-type coupling between the vinyl triflate of the CD-ring Windaus–Grundmann ketone **5** with the A-ring enyne type **6**.[6] A similar synthetic plan was chosen for the preparation of C_{19} substituted vitamin D analogues as depicted in the following retrosynthetic format (Scheme 1).

Keywords: Vitamin D; Limonene; Criegee rearrangement; Epoxide ring opening.

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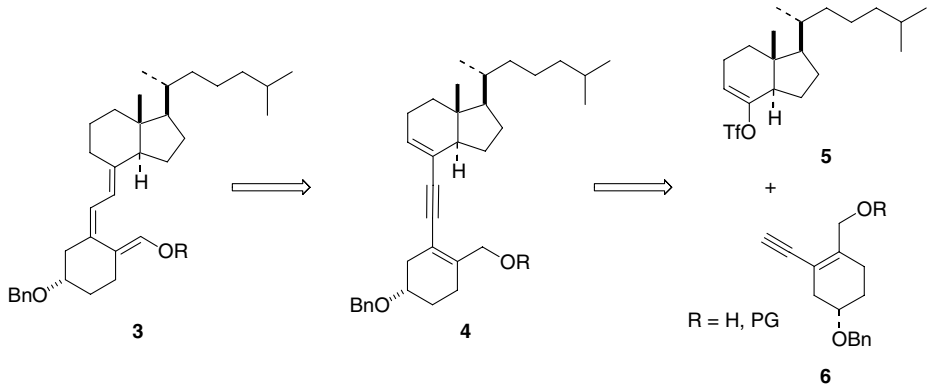
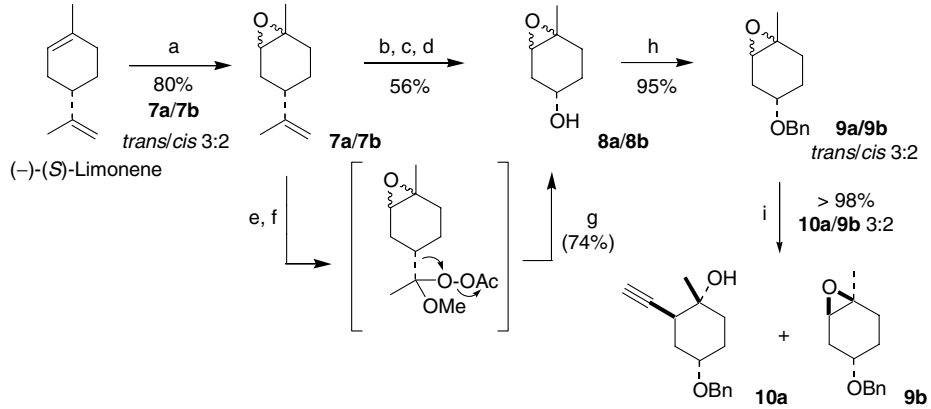


Scheme 1.

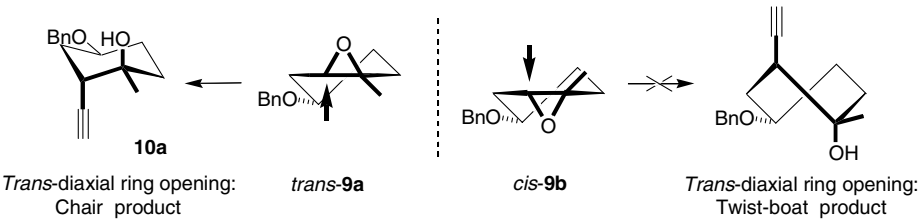
In the present work, we report the synthesis of the C_{19} hydroxylated enyne A-ring enantiomerically enriched in only nine steps starting from (−)-(*S*)-limonene (puriss.) or the commercially available *cis* and *trans* mixture of 1,2-limonene oxide **7**.[7] Conversion of **7a** and **7b** to secondary alcohols **8a** and **8b** was easily achieved in three steps and 56% overall yield via sequential ozonolyzis of the isopropylidene moiety followed by a Baeyer–Villiger rearrangement and saponification of the resulting acetate. However, the same transformation can be performed in better yields (>74%) via ozonolyzis followed by Criegee rearrangement as a 'one pot' process.[8] Then, the generated secondary alcohol **8** was protected with a benzyl group under classical conditions, leading to **9** (Scheme 2). A mixture of *trans* and *cis* epoxides **9a/b**[9] treated with an excess of lithium acetylide—ethylenediamine complex in DMSO at room temperature during 3 days gave the *trans* diaxial homopropagylic alcohol **10a**[10] in 58% yield, which results from the selective ring opening of *trans* epoxide as depicted in Scheme 2.[11] The *cis* isomer remained almost completely unchanged whatever the conditions used.[12] A kinetic separation, where one of both diastereoisomers is more reactive than the other one, was operating (Scheme 3).

Dehydration of tertiary alcohol **10a** promoted by action of $POCl_3$ in pyridine at 0 °C delivered the required *exo* methylene adduct **11** as well as the expected *endo* olefin **12** in a 7:3 ratio and in quantitative yield. A range of reaction conditions (*p*-TSA, Burges's reagent, $BF_3{\cdot}Et_2O$, $CuSO_4$, PBr_3/pyridine, Ac_2O/pyridine) were tested to improve the selectivity in favour of one of both elimination products but without success. Then, the crude mixture was oxidized quantitatively by *m*-CPBA/CH_2Cl_2 into epoxides **13** and **14** as a single diastereoisomer (Scheme 4). The regioisomers can easily be separated by flash chromatography.

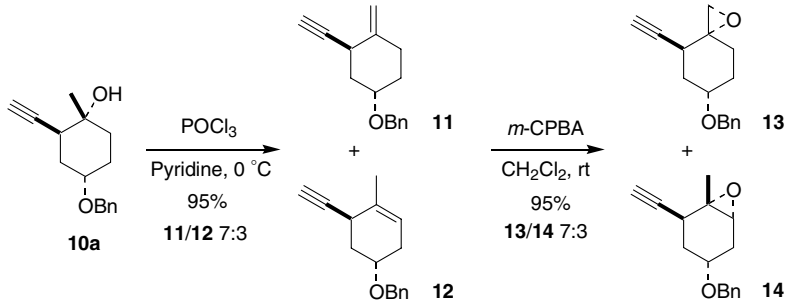
According to Crandall's procedure on simple cyclic oxiranes, treatment of each homopropargylic epoxides **13** and **14** with lithium diethyl amide liberates the primary allylic alcohol **15** and the secondary allylic alcohol **16** in 42% and 48% yields, respectively. Lithium amide promotes the β-elimination of **13** and **14**, which occurs via a *syn* pathway.[13] Compound **15**[14] and related protected derivatives are ready to be engaged in palladium(0) catalyzed-Sonogashira coupling reactions with CD-ring fragments for the preparation of C_{19} substituted vitamin D derivatives. Compound **16** as well as the ketone **17**, easily obtained by oxidation of **16** with



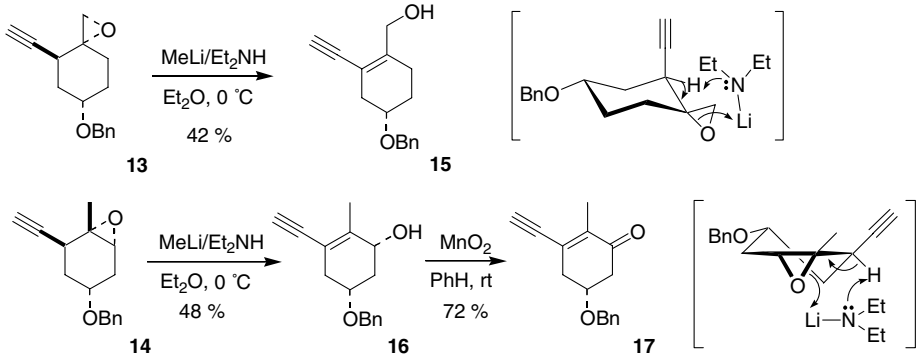
Scheme 2. Reagents and conditions: (a) *m*-CPBA/CH_2Cl_2, rt, **7a/7b** (80%, *trans*/*cis* 3:2); (b) O_3, CH_2Cl_2/MeOH (10:1), −78 °C then Me_2S (89%); (c) *m*-CPBA/CH_2Cl_2, rt, 3 days, (80%); (d) K_2CO_3, MeOH/H_2O (1:1), rt, **8a/8b** (79%) and (56% over three steps); (e) O_3, CH_2Cl_2/MeOH (10:1), −78 to 15 °C; (f) Ac_2O (7 equiv)/Et_3N (7 equiv)/DMAP (0.15 equiv), −25 to −8 °C then quenched by MeOH; (g) NaOAc (0.2 equiv)/MeOH, 37 °C (74% over three steps in a one pot process); (h) NaH/TBAI/$PhCH_2Br$/THF (95%); (i) lithium acetylide—EDA/DMSO, 3 days, **10a/9b** (>98%, **10a/9b** 3:2).



Scheme 3.



Scheme 4.



Scheme 5.

MnO_2, can also be useful building blocks for the synthesis of vitamin D_3 analogues (Scheme 5).

In conclusion, we have developed a short and practical approach to the preparation of the enantiomerically enriched alcohols **15** (7.5% yield), **16** (3.5% yield) and the ketone **17** (2.6%) from the natural substrate (−)-(*S*)-limonene. Further investigations extended to the synthesis of vitamin D analogues using these new building blocks and studies on the influence of C_{19} alkoxide groups on the[1,7] hydrogen sigmatropic shift, that follows the cross-coupling step between the A-ring enyne and the enol triflate of the CD-ring Windaus–Grundmann ketone, are being pursued in our laboratory.

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