Pergamon

Tetrahedron Letters 41 (2000) 775–779

TETRAHEDRON LETTERS

Synthesis of two 6-*s*-*cis* locked stereoisomeric analogues of the steroid hormone 1α,25-dihydroxyvitamin D_3: 1α,25-dihydroxy-19-*nor*-previtamin D_3 and 1β,25-dihydroxy-19-*nor*-previtamin D_3

Mónica Díaz, Miguel Ferrero, Susana Fernández and Vicente Gotor *

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, 33071- Oviedo, Spain

Received 22 October 1999; accepted 17 November 1999

Abstract

An efficient synthesis of A-ring precursors **8** and **9** from inexpensive commercially available (−)-quinic acid has been developed. A-Ring synthon **8** has been obtained through a short sequence (eight steps) in high overall yield (30%). One key step in the synthesis of A-ring precursor **9** is the selective deprotection of a silyl ether in an α,β-unsaturated ester **12**. However, of note is the excellent yield of the Mitsunobu process on derivative **15**, which takes place with the total inversion of configuration, giving ester **16**. Coupling of A-ring synthons **8** and **9** with the appropriate CD-rings/side chain fragment **7**, provides access to 6-*s*-*cis* locked analogues of the steroid hormone 1α,25-$(OH)_2$-D_3: 1α,25-$(OH)_2$-19-*nor*-pre-D_3 (**3**) and novel 1β,25-$(OH)_2$-19-*nor*-pre-D_3 (**4**). © 2000 Elsevier Science Ltd. All rights reserved.

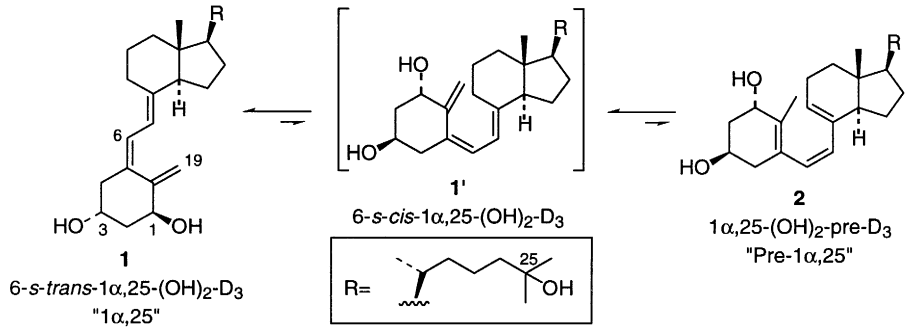
Keywords: previtamin D_3 analogues; quinic acid.

1. Introduction

It is well established that 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3] (**1**, Scheme 1), in addition to its classical role in calcium homeostasis, affects the human immune system, inhibits cell proliferation, and promotes cellular differentiation,[1] via genomic mechanisms[2] by interaction with a nuclear/cytosol vitamin D receptor (n-VDR) to regulate gene transcription. However, not all actions of 1α,25-$(OH)_2$-D_3 are mediated by genome activation. There is clear evidence that this secosteroid can also generate biological responses via non-genomic pathways[3] by interaction with a membrane vitamin D receptor (m-VDR), which generates rapid biological responses believed to be independent of direct interaction with the genome.

* Corresponding author. E-mail: vgs@sauron.quimica.uniovi.es (V. Gotor)

PII: S0040-4039(99)02152-8

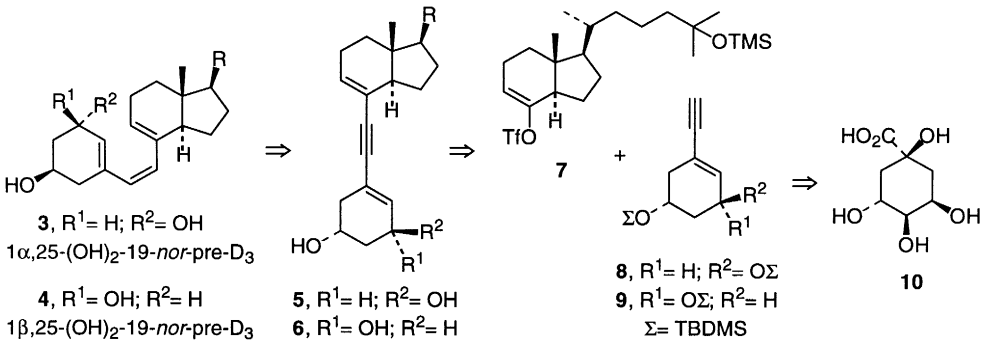


Scheme 1.

The array of biological responses include both non-genomic and genomic effects, and there is considerable promise for the efficacy of 1α,25 analogues as chemotherapeutic agents in a variety of human disease states.[4]

1α,25-$(OH)_2$-D_3 exists as two conformationally equilibrating forms (6-*s*-*trans* **1** and a minor form 6-*s*-*cis* **1′**), which exist in slow chemical equilibrium (5–10%) with 1α,25-dihydroxyprevitamin D_3 [1α,25-$(OH)_2$-pre-D_3] (**2**). It was found that whereas 1α,25 (**1**) is significantly more active than pre-1α,25 (**2**) (in a penta-deuterated form)[5] in assays reflecting genomic responses, the latter was equally as active as 1α,25 in assays for measuring non-genomic effects.[6] It was proposed that 6-*s*-*cis*-1α,25 (**1′**) is the active conformer for eliciting non-genomic effects, with pre-1α,25 (**2**) simply behaving as an excellent analogue of this conformer.[7] There is a significant influence from stereochemistry in mediating these non-genomic responses.[8] Different analogues can induce different shapes of protein folding resulting in different conformations of the protein–analogue complex, each leading to different biological responses. It became of interest to prepare locked analogues of the 6-*s*-*cis* conformer of 1α,25 incapable of isomerizing to the 6-*s*-*trans* conformation of 1α,25, which is thermodynamically more stable.

Given the importance of A-ring stereochemistry for binding the ligand to the hormone receptor, we decided (in our framework on vitamin D_3 A-ring analogues[9]) to synthesize stable previtamin analogues **3** and **4** (Scheme 2), which are unable to undergo rearrangement to the respective vitamin D form by virtue of the absence of the C-19 methyl group.

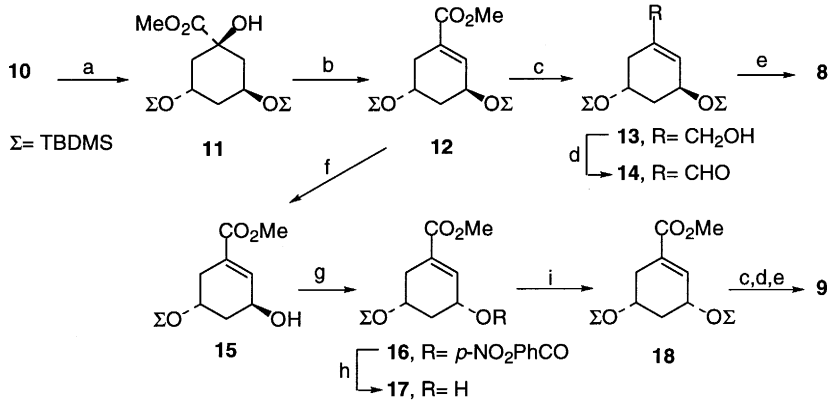


Scheme 2.

2. Results and discussion

These analogues (**3** and **4**, Scheme 2) were synthesised by a convergent route[10] from the protected A-ring synthons **8** or **9** and the known CD-triflate **7**,[5,10b,11] as shown in the retro-synthetic route in Scheme 2.

The preparation of the A-ring precursors started with the synthesis of compound **11**[12] from (−)-quinic acid (**10**). Dehydration of the hydroxy ester **11** with $POCl_3$ afforded **12** (Scheme 3). Transformation of the ester into the aldehyde was best carried out through a two-step sequence: reduction of the ester to alcohol with DIBAL-H gave rise to alcohol **13**, and then oxidation of the latter with pyridinium chlorochromate yielded aldehyde **14**. Formation of enyne **8** was accomplished by reaction with trimethylsilyldiazomethane in good yield. We obtained A-ring synthon **8** through a short sequence (eight steps) in high overall yield (30%) and using an inexpensive, commercially available starting material.[13]

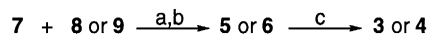


Scheme 3. **a**: Ref. 14 (57%, four steps). **b**: $POCl_3$, Py (80%). **c**: DIBAL-H, toluene (96%). **d**: PCC, CH_2Cl_2 (98%). **e**: $TMSCHN_2$, ^nBuLi, THF (70%). **f**: 1 equiv. TBAF, THF (84%). **g**: PPh_3, DIAD, *p*-NO_2PhCO_2H, THF (98%). **h**: MeONa, MeOH (83%). **i**: TBDMSCl, imidazole, CH_2Cl_2 (95%)

The key step to prepare A-ring precursor **9** was the selective deprotection of compound **12**. The process was performed by dropwise addition of only 1 equivalent of TBAF at 0°C. Under these conditions, selective desilylation of the C-3 hydroxyl group was achieved with 84% yield of mono-deprotected alcohol **15**, after purification by flash chromatography. Traces of starting material **12** and the corresponding diol were isolated. A slight excess of TBAF decreased the yield of **15** due to the total deprotection of both silyl protecting groups. The next step was the inversion of secondary alcohol **15**, for which we used Mitsunobu's method.[14] The reaction took place with total inversion, giving **16** in almost quantitative yield (98%). After methanolysis of the *p*-nitrobenzoic ester **16**, compound **17** was obtained in high isolated yield (83%). This was performed using MeONa in MeOH followed by neutralization with ammonium chloride; if an acid is used undesired silyl deprotection is produced simultaneously. It is noteworthy that the Mitsunobu reaction on the diol from the di-deprotection of compound **12**, although only C-3 inversion took place selectively, gave a poor yield of inverted derivative and we isolated appreciable amounts of starting material. Hence the importance of this selective deprotection, of which just a few examples are reported in the literature is apparent.[15] The previously described reaction sequence from **12** to **8** was followed to obtain compound **9** from **18**.

A-Ring synthons **8** or **9** were coupled with 25-OTMS protected triflate **7** using $Pd(PPh_3)_2(OAc)_2$-CuI catalyst and Et_2NH in DMF (Scheme 4). The resulting silyloxy dienynes were deprotected with TBAF

to afford the trihydroxydienynes **5** or **6**. Careful catalytic hydrogenation of triols **5** or **6** in MeOH, in the presence of Lindlar catalyst and quinoline poison, generated previtamins **3** or **4**.[16]



Scheme 4. **a**: $Pd(PPh_3)_2(OAc)_2$-CuI, Et_2NH, DMF. **b**: TBAF, THF (85%, two steps). **c**: Lindlar, quinoline, H_2, MeOH (70%)

In summary, we have developed an efficient synthesis of A-ring precursors **8** and **9** from inexpensive (−)-quinic acid. Key features of these approaches are the selective deprotection of a silyl ether derivative and the excellent yield of the Mitsunobu reaction, which takes place with total inversion of configuration. Coupling of these synthons with the appropriate CD-rings/side chain fragment provides access to the important 6-*s-cis* locked analogues **3** and **4**. Synthesis of other possible previtamin stereoisomers is now in progress in our laboratory.

Acknowledgements

Financial support from Comisión Interministerial de Ciencia y Tecnología (Spain; Project BIO98-0770) and Fundación Príncipe de Asturias (Dr. Severo Ochoa Award to M.F.) is gratefully acknowledged. We also thank the Ministerio de Educación y Cultura (Spain) for postdoctoral fellowships (S.F. and M.F.) and Solvay-Duphar (Wesp, Holland) for the generous gift of vitamin D_3 which was used for preparation of Grundmann's ketone.

References

1. (a) *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology, and Clinical Applications*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994. (b) Uskokovic, M. R. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1783–1896.
2. (a) Lowe, K. E.; Maiyar, A. C.; Norman, A. W. *Crit. Rev. Eukar. Gene Exp*. **1992**, 2, 65. (b) Pike, J. W. *Annu. Rev. Nutr.* **1991**, *11*, 189–216. (c) *Vitamin D: Gene Regulation, Structure–Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991. (d) Norman, A. W. *Vitamin D: The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979.
3. (a) Norman, A. W.; Nemere, I.; Zhou, L. X.; Bishop, J. E.; Lowe, K. E.; Maiyar, A. C.; Collins, E. D.; Taoka, T.; Sergeev, I.; Farach-Carson, M. C. *J. Steroid Biochem. Molec. Biol*. **1992**, *41*, 231–240. (b) Deboland, A. R.; Nemere, I.; Norman, A. W. *Biochem. Biophys. Res. Commun*. **1990**, *166*, 217–222.
4. (a) Ettinger, R. A.; DeLuca, H. F. *Adv. Drug. Res*. **1996**, *28*, 269–312. (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrine Rev*. **1995**, *16*, 200–257.
5. Curtin, M. L.; Okamura, W. H. *J. Am. Chem. Soc*. **1991**, *113*, 6958–6966.
6. Norman, A. W.; Okamura, W. H.; Farach-Carson, M. C.; Allewaert, K.; Branisteanu, D.; Nemere, I.; Muralidharan, K. R.; Bouillon, R. *J. Biol. Chem*. **1993**, *268*, 13811–13819.
7. Okamura, W. H.; Midland, M. M.; Norman, A. W.; Hammond, M. W.; Dormanen, M. C.; Nemere, I. *Ann. New York Acad. Sci*. **1995**, *761*, 344–348.
8. (a) Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I.; Norman, A. W. *J. Steroid Biochem. Molec. Biol*. **1995**, *53*, 603–613. (b) Dormanen, M. C.; Bishop, J. E.; Hammond, M. W.; Okamura, W. H.; Nemere, I.; Norman, A. W. *Biochem. Biophys. Res. Commun*. **1994**, *201*, 394–401.
9. (a) Gotor-Fernández, V.; Ferrero, M.; Fernández, S.; Gotor, V. *J. Org. Chem*. **1999**, *64*, 7504–7510. (b) Ferrero, M.; Fernández, S.; Gotor, V. *J. Org. Chem*. **1997**, *62*, 4358–4363. (c) Fernández, S.; Díaz, M.; Ferrero, M.; Gotor, V. *Tetrahedron Lett*. **1997**, *38*, 5225–5228. (d) Fernández, S.; Ferrero, M.; Gotor, V.; Okamura, W. H. *J. Org. Chem*. **1995**, *60*, 6057–6061.
10. (a) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485–3498. (b) Barrack, S. A.; Gibbs, R. A.; Okamura, W. H. *J. Org. Chem*. **1988**, *53*, 1790–1796.
11. Maynard, D. F.; Trankle, W. G.; Norman, A. W.; Okamura, W. H. *J. Med. Chem*. **1994**, *37*, 2387–2393.

12. This compound was previously described by: Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett*. **1991**, *32*, 7663–7666.
13. Compound **8** was previously synthesized from shikimic acid by: Sarandeses, L. A.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *Tetrahedron Lett*. **1992**, *33*, 5445–5448.
14. (a) Hughes, D. L. *Org. Prep. Proc. Int*. **1996**, *28*, 127–164. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28.
15. (a) Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2055–2058. (b) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett*. **1995**, *36*, 5761–5764.
16. All products were characterized by ^{1}H, ^{13}C NMR, IR, optical rotation, MS, HRMS, and elemental analysis.