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Synthesis of Spiro[4.5]decane CF-Ring Analogues of 1α,25-Dihydroxyvitamin D_3

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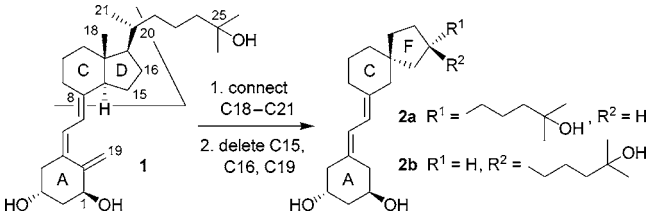
ABSTRACT



A novel series of analogues of calcitriol (1) is developed featuring a spirocyclic central core resulting from C18/C21-connection and C15/C16-deletion (2a, 2b). The synthesis of the key intermediate involves an Eschenmoser rearrangement of an enantiomerically pure bromo-substituted cyclohexenol.

1α,25-Dihydroxyvitamin D_3 (**1**, calcitriol), the hormonally active metabolite of vitamin D_3, has been shown to inhibit cellular proliferation and to induce cellular differentiation, next to its classical calciotropic activity.[1] Its therapeutic utility is, however, limited for effective doses leading to calcemic side effects. This has originated in a search for structural analogues of **1** that show a separation in calcemic and antiproliferative−prodifferentiating activities.[2,3]

One may distinguish three different parts in the structure of **1**: a central rigid CD-bicyclic entity to which are connected at C-20 and at C-8 two flexible portions, the side chain and the seco-B,A-ring system, respectively (Figure 1). For more than a decade our laboratories have focused on the development of nonsteroidal analogues possessing structural modifications in the central part of the molecule.[4] In the present work we report on the synthesis of spirocyclic CF-ring analogues **2a** and **2b** featuring a spiro[4.5]decane[5] to which are attached (i) the classical side chain in the two epimeric configurations at C-20[6] and (ii) the 19-nor modified seco-B,A-ring at C-8.[7] The two epimeric configurations at C-20 are relevant in that molecular modeling studies have shown the prodifferentiating activity to be dependent in certain cases on the preferred spatial orientation of the side

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(1) (a) Proceedings of the 12th Workshop on Vitamin D: Bouillon, R.; Norman, A. W.; Pasqualini, J. R., Eds. *J. Steroid Biochem. Mol. Biol*. **2004**, *89*−*90*, 1−633, and the previous 11 volumes in this series. (b) *Vitamin D*; Feldman, D., Glorieux, F. H., Eds.; Academic Press: San Diego, CA, 1997; 1285 pages.

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chain.[4b,8] Deletion of C-19 on the other hand prevents the [1,7]-sigmatropic hydrogen shift typical of the vitamin−

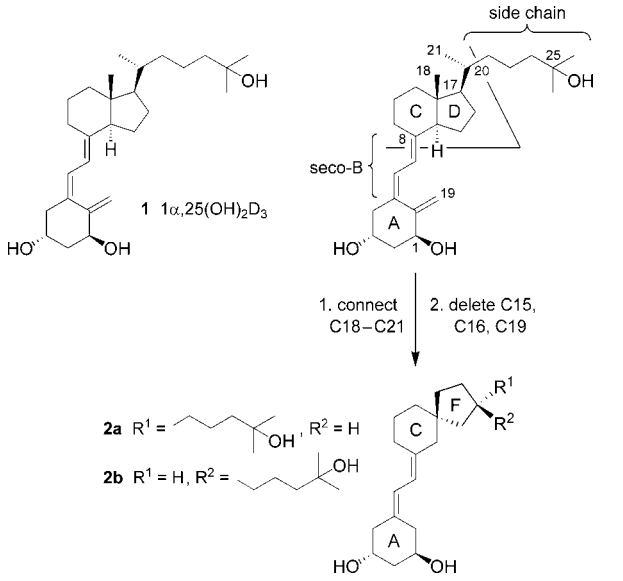

Figure 1. Spirocyclic CF-ring analogues **2a** and **2b**.

previtamin equilibrium, which in the absence of the natural *trans*-fused CD-ring system would favor the more substituted previtamin form (Figure 2).[9]

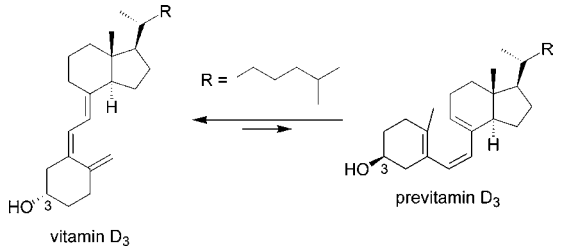

Figure 2. The vitamin−previtamin equilibrium.

The key intermediates involved in the synthesis of analogues **2a** and **2b** are shown in Figure 3. Analogues **2a** and **2b** are accessed from **3a** and **3b**, respectively. The hydroxymethyl group at C-20 allows for the introduction of the side chain,[3b] the carbonyl at C-8 for Wittig−Horner

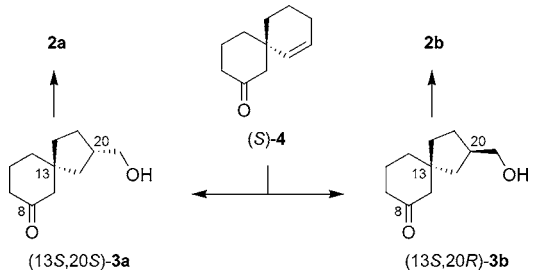

Figure 3. Key intermediates in the synthesis of **2a** and **2b**.

appendage of the seco-B,A-ring.[10] The two epimeric alcohols **3a** and **3b** are obtained from the enantiopure cyclohexene derivative (*S*)-**4**. It is noteworthy that (±)-**4** was used previously in the synthesis of 22-oxa-spiro[5.5]undecane CF-ring analogues.[5,11] We will further distinguish three stages in the synthesis: (i) the enantioselective synthesis of the spirocyclic enone (−)-**4** (Scheme 1); (ii) its conversion into epimers (+)-**16a** and (+)-**16b** (Scheme 2); and (iii) their eventual transformation into **2a** and **2b**, respectively (Scheme 4).

The major challenge in the synthesis of spirocyclic (−)-**4** resides in the asymmetric synthesis of the stereogenic quaternary spirocenter.[12,13] In this work this is realized via the Eschenmoser [3,3]-sigmatropic rearrangement of bromocyclohexenol (+)-**7** to amide (−)-**9**.[14] Subsequently, the spiro ring system was obtained via Dieckmann cyclization.[13] The required enantiopure allylic alcohol (+)-**7** was obtained through CBS (Corey−Bakshi−Shibata) reduction of the corresponding enone **6**.[15] Functional group manipulation of (−)-**9** led to diester (−)-**12**, which after Dieckmann cyclization and demethoxycarbonylation gave (−)-**4**. Although somewhat lengthy, 9 steps from the known bromocyclohexenone **5**,[16] the overall yield is satisfactory (44%) and the sequence is suitable for large-scale preparation.

The presence of the bromo substituent was crucial for the successful completion of the sequence: (i) by enhancing the

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(12) For examples of the enantioselective construction of quaternary stereogenic carbon centers, see: (a) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786−3789. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

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(14) For a sequential Claisen/ring-closing metathesis approach to spirocyclic cyclopentanes and cyclohexanes, see: Beaulieu, P.; Ogilvie, W. W. *Tetrahedron Lett.* **2003**, *44*, 8883−8885.

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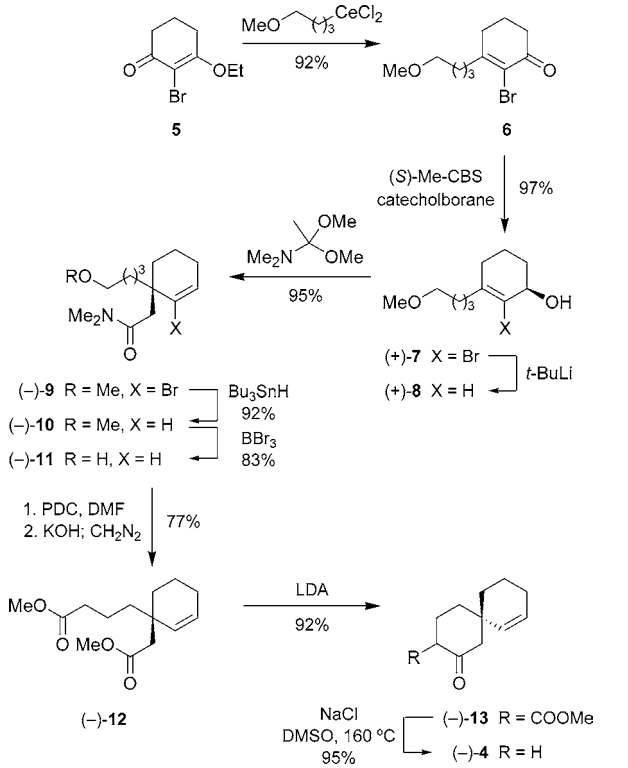
Scheme 1



prochiral nature of the carbonyl group in enone **6**, a very high enantiomeric excess (>98%) is achieved upon CBS reduction with (*S*)-methyloxazaborolidine as catalyst (0.2 equiv) and catecholborane as reducing agent (−95 °C, toluene; 97% yield);[17] (ii) by stabilizing the cyclohexenol moiety, both racemization and elimination upon [3,3]-sigmatropic rearrangement are prevented.[14,15a,18] Upon chromatographic purification of (+)-**8**, obtained by debromination of (+)-**7** (*t*-BuLi, −50 °C), some racemization was observed that was found to be induced by neighboring group participation of the ether oxygen of the methoxybutyl group. The latter participation is prevented by the presence of Br in (+)-**7**, probably for both steric and electronic reasons. Since elimination was observed upon acid-catalyzed ortho ester Claisen type rearrangement, the Eschenmoser variant with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene was applied instead (95% yield).[19] Under the neutral conditions of the process no racemization was observed.

The expected (*R*)-configuration of alcohol (+)-**7** following the well-established transition state model of the CBS reduction was further confirmed by ^{1}H NMR analysis of the diastereomeric MPA esters obtained from (*S*)-α-methoxyphenylacetic acid and the two enantiomeric alcohols (+)-**8** and (−)-**8**, which showed diagnostic chemical shift differences for the olefinic protons (Figure 4).[20]

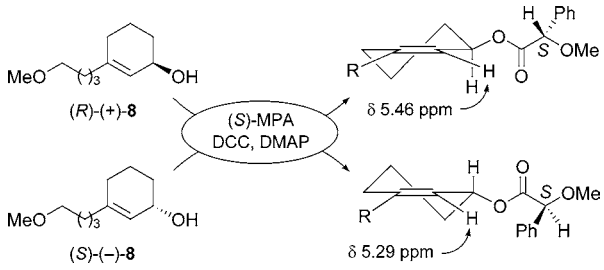
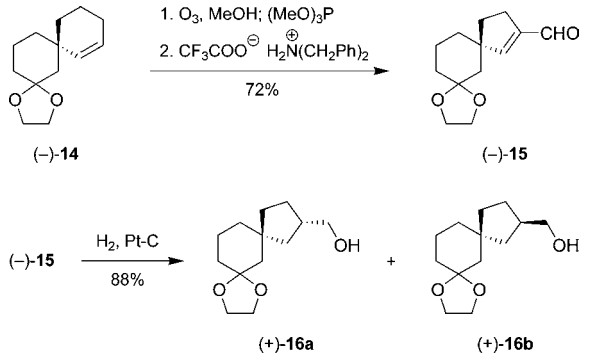


Figure 4. ^{1}H NMR stereochemical assignment of enantiomeric alcohols (+)-**8** and (−)-**8**.

The further conversion of spirocyclic enone (−)-**4** into the epimeric alcohols (+)-**16a** and (+)-**16b** is shown in Scheme 2. After acetal protection of (−)-**4** (95% yield), the cyclohexene ring in (−)-**14** is oxidatively cleaved (ozone, methanol; $(MeO)_3P$ workup) and the resulting dialdehyde is directly subjected to intramolecular aldol condensation (dibenzylammonium trifluoroacetate) yielding ring-closed unsaturated aldehyde (−)-**15** (72% yield). Upon catalytic hydrogenation of the latter a 1:1 mixture of the desired alcohols (+)-**16a** and (+)-**16b** (88% yield) is obtained, which can be separated by HPLC.

Scheme 2



Since the structural assignment of (+)-**16a** and (+)-**16b** was not successful by ^{1}H NMR, we devised a chemical sequence to assign unequivocally the epimeric structures (Scheme 3). Both epimers (+)-**3a** and (+)-**3b**, obtained after acid hydrolysis of (+)-**16a** and (+)-**16b**, respectively, were subjected to the following sequence: (i) Baeyer−Villiger oxidation, followed by transesterification of the resulting seven-membered lactones to yield a mixture of methyl esters **17** and **18** (ratio 8:2), which was separated by HPLC. Upon

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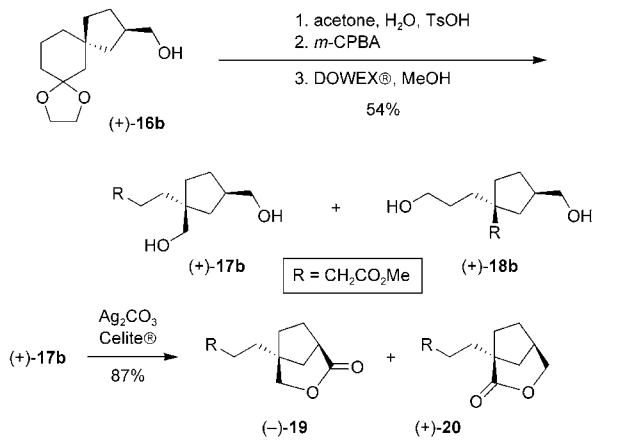
Scheme 3

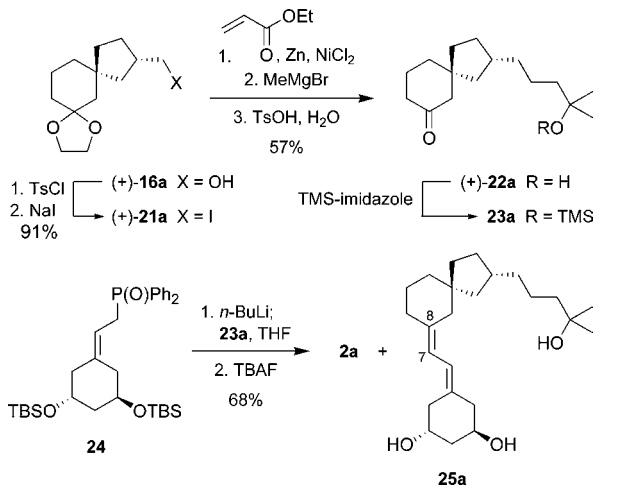


Fetizon oxidation of the major 1,5-diol (+)-**17b** obtained in the **b**-series a separable mixture (HPLC) of two γ-lactones (−)-**19** and (+)-**20** (87%; ratio 85:15) was formed.

The final conversion of spirocyclic alcohols (+)-**16a** and (+)-**16b** into analogues **2a** and **2b** follows the sequence that is shown for the **a**-series in Scheme 4. The introduction of the side chain is realized via Ni(0) catalyzed oxidative addition of iodide (+)-**21a** (obtained from (+)-**16a** in two steps) to ethyl acrylate,[21] an efficient method introduced by Mouriño in the vitamin D field.[22] Subsequently, Grignard reaction followed by acid hydrolysis leads to spirocyclic ketone (+)-**22a** (57% overall). The final Lythgoe coupling of the A-ring is performed by using the known phosphine oxide **24**[23] and trimethylsilyloxy protected **23a** (obtained from (+)-**22a** and trimethylsilylimidazole). After silyl ether deprotection a 3:1 mixture of desired **2a** and the corresponding (*Z*)-isomer **25a** is obtained (68% yield). Both isomers could be separated after repeated HPLC purification. The identification of the major isomer as (*E*)-derivative **2a** and the minor isomer as (*Z*)-derivative **25a** rests on ^{1}H NMR COSY and NOE measurements, which were performed on both isomers. A comparable result was obtained when the sequence was performed starting with epimeric alcohol (+)-**16b** (not shown), which eventually led to the isolation of the desired (*E*)-analogue **2b** and its (*Z*)-isomer **25b** (ratio 3:1, respectively; 85% yield).

Following the same strategy as described above another series of stereoisomeric analogues was obtained from (+)-(*R*)-**4** as key intermediate. Although the synthetic approach is not stereoselective (cf. hydrogenation of **15** and A-ring coupling), hence reducing the overall yield, it allows for the preparation of several analogues, the biological evaluation of which will be reported in a full account.[24]

Scheme 4



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Supporting Information Available: Experimental procedures and full characterization of all intermediates and 1α,25(OH)$_2$D$_3$ analogues **2a**, **2b**, **25a**, and **25b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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