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Synthesis of 22-oxaspiro[4.5]decane CD-ring modified analogs of 1α,25-dihydroxyvitamin D_3

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ABSTRACT

In search of analogs of 1α,25-dihydroxyvitamin D_3 featuring a dissociation of calcemic and other activities, a series of stereoisomeric 19-nor-22-oxa derivatives, characterized by a spiro[4.5]decane cyclic system instead of the classical CD-ring system, have been synthesized in an enantioselective way.

The biological action of vitamin D_3 (**1**, cholecalciferol) originates from the dihydroxylated metabolite 1α,25-dihydroxyvitamin D_3 (**2**, calcitriol). Next to its classical role in the regulation of calcium homeostasis, these actions also involve immunomodulation, cell differentiation, and antiproliferation.[1] The search for analogs with potential therapeutic applications was initiated by the discovery that in the 22-oxa derivative **3** (OCT) the calcemic and antiproliferative-prodifferentiating activities were separated (Fig. 1).[2] Next to the 22-oxa modification a few other variations are relevant to the present work. In this context KH-1060 (**4**) is exemplary.[3] This analog, which is still among the most active analogs discovered so far, features, next to the 22-oxa modification, also epimerization at C20, chain elongation, and 25-diethyl instead of dimethyl substitution. The deletion of C19, which is involved in the reversible [1,7]-sigmatropic shift responsible for the well-known vitamin-previtamin equilibration (Fig. 1) is usually accompanied by a reduction in calcemic activity.[4] Whereas the above modifications are located in the flexible parts of the molecule, our laboratories have been essentially focusing on structural changes in the central CD-ring system.[5,6]

In this context we wish to report here on the synthesis and biological activity of side chain modified 19-nor-22-oxaspiro[4.5]decane CF-ring analogs **5–8** wherein the spiro-ring system can be considered as the formal result of the deletion of C15 and C16, and of the connection between C18 and C21.[7,8] First we will describe analogs **5** featuring the classical vitamin D side chain in four stereoisomeric series **a**, **b**, **c**, and **d**. Next we will report, within the stereoisomeric series **a** and **b**, on the development of analogs such as **6**, **7,** and **8**, in which the side chain has been modified aiming at an increase of biological activity.

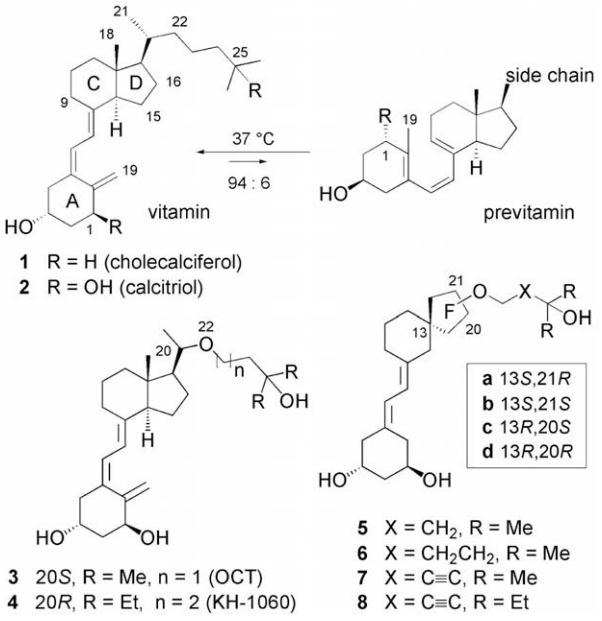

Figure 1. Structures of the natural vitamin D derivatives **1** and **2**, of the 22-oxa analogs **3** and **4**, of the reported spiro[4.5]decane analogs **5–8**, and of the vitamin–previtamin equilibrium.

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Central in the synthesis of the analogs in the four series **a**, **b**, **c**, and **d** stands the preparation of the four enantiopure stereoisomeric alcohols **10a–d** (Fig. 2), which are correctly functionalized for the introduction of the flexible parts of the molecule: the side chain via Williamson ether alkylation and the seco-B, A-ring moiety via Wittig–Horner appendage (vide infra).[9] Since the four alcohols will be obtained upon reduction of the corresponding enantiomeric ketones (+)-**9** and (−)-**9**, an efficient synthetic strategy requires the generation of the stereogenic C13 quaternary center in **9** to proceed via a reliable and preferably enantiospecific route.

The chosen synthetic route is illustrated for the synthesis of (+)-**9** in Scheme 1. It essentially follows work previously described by Yao and Wang,[10] which involves the construction of the chiral spirocenter via two well-established procedures: (i) an asymmetric conjugate addition on 2-cyclohexenone, and (ii) a Rh(II)-catalyzed carbene insertion reaction with full retention of absolute configuration.[11] Also in our hands did Shibasaki's enantioselective version of the Michael addition involving the enolate of dimethyl malonate with (*S*)-AlLibis(binapthoxide) complex ((*S*)-ALB, from lithium aluminum hydride and (*S*)-BINOL) as heterobimetallic chiral catalyst lead to essentially enantiopure diester **11** in high yield (91%; ee >99%).[12] Acetal formation (to **12**), followed by Krapcho demethoxycarbonylation (to **13**) and saponification gave acid **14** in 82% combined yield.[13] Arndt-Eistert homologation of acid **14** was performed via thermal silver(I) benzoate (dioxane/water) induced Wolff rearrangement of diazoketone **15**,[14] prepared via reaction of the acid chloride with trimethylsilyl diazomethane.[15] The obtained acid **16** was further directly converted to diazoketone **17** (oxalyl chloride and trimethylsilyl diazomethane). The latter was then subjected to a stereospecific C–H insertion reaction involving the rhodium(II) octanoate dimer as the catalyst to yield ketone (+)-**9** in 50% yield with expected full retention of absolute configuration.[16] Obviously, the same sequence but involving (*R*)-ALB as the chiral catalyst led to the enantiomer (−)-**9**. The enantiopurity of (+)-**9** and (−)-**9** was determined as shown in Scheme 2. Acetalization of *rac*-**18** with (*R*,*R*)-2,3-butanediol gave the 1:1 diastereomeric mixture of acetals **19** and **20** which are nicely separated via chiral VPC.[17] Similar treatment of diketone (−)-**18,** obtained upon hydrolysis of (+)-**9,** led to bisacetal **19** with better than 99% de.

The final sequence to the analogs in the four stereoisomeric series proceeds via the alcohols **10** that are obtained upon reduction of the enantiomeric ketones **9** (Fig. 2). Reduction of (+)-**9** with sodium borohydride gave the epimeric alcohols **10a** and **10b** in 53% and 25% isolated yields, respectively. The same treatment of the enantiomer (−)-**9** gave **10c** and **10d** in 51% and 28% isolated yields, respectively.[18] The relative configuration of the alcohols in **10a** and **10b** (and in its enantiomeric pair **10c**/**10d**) follows from ^{1}H NMR measurements (vide infra).

The synthesis of the first series of analogs **5a–d** starting from the corresponding alcohols **10a–d** involves the attachment of the side chain (Scheme 3) and the appendage of the A-ring (Scheme 4). Both sequences are described for the compounds in **a** series. After alkylation of the alkoxide derived from **10a** with 3-methyl-2-butenyl bromide and tetrabutylammonium iodide as catalysts (to **21a** in 95% yield), subsequent mercury(II) assisted water addition (to alcohol **22a** in 90% yield) and acid hydrolysis gave alcohol **23a** (82% yield), which was protected as triethylsilyl ether **24a** (86% yield).[9] The same uneventful sequence led, starting from **10b**, **10c**, and **10d** to the corresponding cyclohexanones **24b**, **24c**, and **24d,** respectively (not shown).

The appendage of the 19-nor A-ring to ketone **24a** was achieved using the reliable Wittig–Horner procedure involving the known phosphine oxide **31**.[19] After fluoride-induced silyl ether deprotection a 3:1 mixture of dienes (*E*)-**5a** and (*Z*)-**5a** is obtained (87% yield) which is separated by HPLC affording pure (*E*)-**5a** in 65% iso-

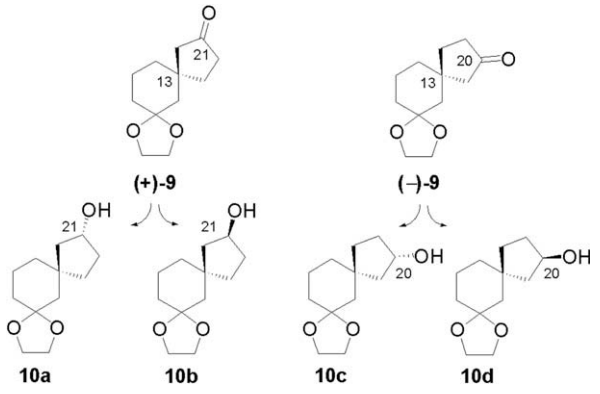
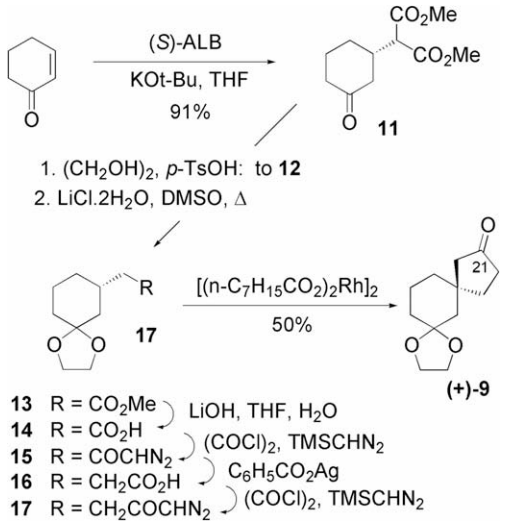
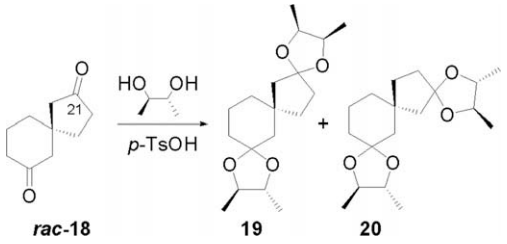


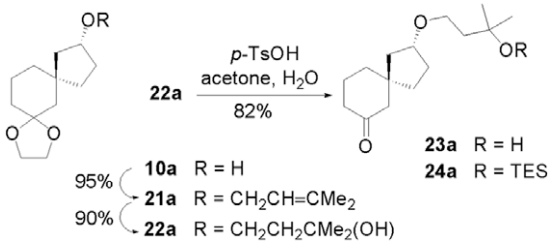
Figure 2. General strategy for obtention of the stereoisomeric series **a**, **b**, **c**, and **d**.



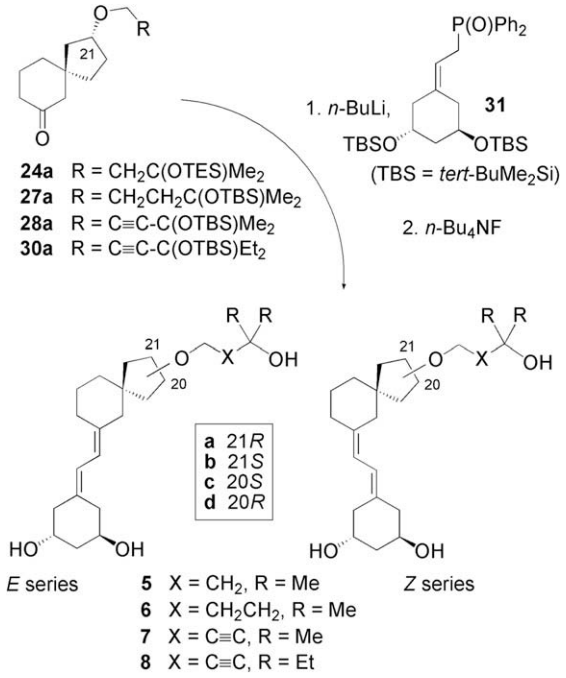
Scheme 1. Synthesis of (+)-**9**.



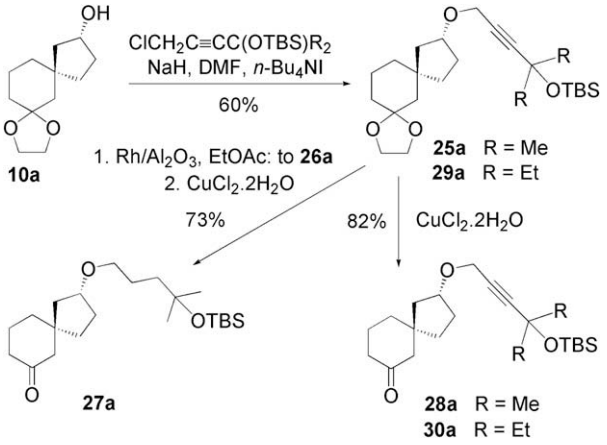
Scheme 2. Determination of the enantiomeric purity of **9**.



Scheme 3. Synthesis of spiroketones **24**.



Scheme 4. Synthesis of analogs **5a–d**, **6a** and **6b**, **7a** and **7b**, and **8a** and **8b**.



Scheme 5. Synthesis of spiroketones **27**, **28**, and **30**.

lated yield. The identification of the major isomer as the (*E*)-**5a** derivative rests on ^{1}H NMR COSY and 2D NOESY measurements (Fig. 3). In the same way cyclohexanones **24b**, **24c**, and **24d** led to mixtures of (*E*)- and (*Z*)-derivatives affording after HPLC purification analogs **5b** (56%), **5c** (59%) and **5d** (68%), respectively.

The biological evaluation of the analogs includes the determination of the binding affinity for the porcine intestinal VDR, and the antiproliferative activity in vitro on breast cancer MCF-7 cells.[20] The analogs **5c** and **5d** did not show any relevant biological activity. On the other hand the analogs **5a** and **5b** displayed a modest activity in the inhibition of the proliferation of MCF-7 cells when compared with the activity of calcitriol (10% of the calcitriol activity). On the basis of this observation the further search for active analogs was restricted to derivatives in the **a** and **b** stereoisomeric series.

The synthesis of the analogs **6a**, **7a**, and **8a** proceeded via ketones **27a**, **28a**, and **30a**, respectively (Scheme 5). In the case of **27a** the synthesis involves alkylation of **10a** to **25a** (60% yield), followed by hydrogenation (to **26a**) and acetal deprotection to yield **27a** (73%). Ketone **28a** was directly obtained via copper(II) chloride-induced hydrolysis of **25a** (82%).[21] In the case of **30a** the alkylation was performed with the corresponding ethyl-substituted propargylic chloride (to **29a**) followed by hydrolysis. In the same way **10b** was converted to **27b**, **28b**, and **30b** (not shown). It is important to note here that the detailed analysis of ^{1}H NMR data obtained for ketones **27a** and **27b** allows for their stereochemical assignment, and hence also for the structural determination of the intermediate alcohols **10a** (and enantiomer **10c**) and **10b** (and enantiomer **10d**). The relevant NOE measurements are shown in Figure 3.

The further conversion of ketones **27a** and **27b**, **28a** and **28b**, **30a** and **30b** into the corresponding analogs **6a** and **6b**, **7a** and **7b**, **8a** and **8b** proceeds in the same way as was described for the conversion of **24a** into (*E*)-**5a** (Scheme 4). The separation of the propargylic (*E*)- and (*Z*)-dienes **7** and **8** however proved more difficult so that the (*E*)-analogs remained contaminated with varying amounts of the (*Z*)-isomer: **7a** (20%), **7b** (9%), **8a** (4%), **8b** (<1%).

As was the case for analogs **5a–d**, the six new analogs did not show any relevant affinity for the VDR; the best result was obtained for **6b** with 3% of the calcitriol affinity. The activity in the inhibition of the MCF-7 cells on the other hand increased with increasing chain length and was markedly higher in the **a** series than in the **b** series: 2%/0.9%, 10%/0%, and 80%/10% of the activity of calcitriol were measured for **6a/6b**, **7a/7b**, and **8a/8b**, respectively. These preliminary results are in line with the observation that there exists a relationship between the position of the 25-hydroxy group as determined by the conformation of the side chain and the prodifferentiating/antiproliferative activity of an analog.[22] The latter aspect and other biological results will be covered in a full account.

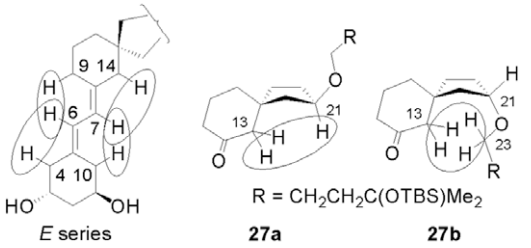


Figure 3. ^{1}H NMR NOESY measurements of (*E*)-dienes **5–8** and of spirocyclic ketones **27a** and **27b**.

Acknowledgments

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18. Relevant spectroscopic data for **10a**: $[\alpha]_D$ 1.59 (*c* 0.95; $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): 1.42–1.63 (12H, m), 1.65–1.69 (1H, m), 1.85–1.94 (1H, m), 1.97 (1H, dd, *J* = 6.9, 13.9 Hz), 3.90 (4H, s), 4.33 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 21.17 (CH_2), 34.71 (CH_2), 35.12 (CH_2), 37.31 (CH_2), 38.70 (CH_2), 43.15 (C), 46.12 (CH), 48.56 (CH_2), 64.41 (CH_2), 64.44 (CH_2), 74.20 (CH), 109.42 (C). Relevant spectroscopic data for **10b**: $[\alpha]_D$ −8.8 (*c* 1; $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): 1.28 (2H, m), 1.50 (1H, m), 1.54–1.61 (6H, m), 1.66 (2H, q, *J* = 13.6 Hz), 1.67 (1H, m), 1.76 (1H, dt, *J* = 8.2, 12.9 Hz), 1.84 (1H, dd, *J* = 6.6, 13.9 Hz), 1.87–1.93 (1H, m), 3.89–3.94 (4H, m), 4.32 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 20.91 (CH_2), 34.40 (CH_2), 35.04 (CH_2), 37.04 (CH_2), 37.45 (CH_2), 42.91 (C), 46.39 (CH), 48.43 (CH_2), 64.09 (CH_2), 73.72 (CH), 109.40 (C).
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