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SYNTHESIS OF (C-11)-SUBSTITUTED ANALOGUES OF 1α,25-DIHYDROXYVITAMIN D_3

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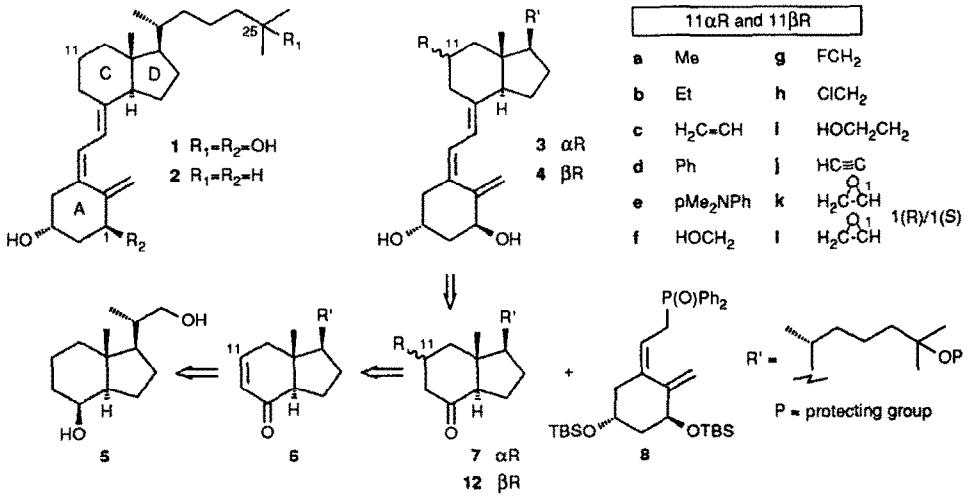
Abstract: The synthesis of a series of C-ring modified analogues of 1α,25-dihydroxyvitamin D_3, with various α- and β-oriented substituents on C-11, is described. It includes the construction of the 25-hydroxylated side-chain, the stereoselective introduction of the substituents at C-11 via conjugate organocuprate addition, and coupling with the A-ring.

1α,25-Dihydroxyvitamin D_3 (**1**, Scheme 1), the active metabolite of vitamin D_3 (**2**), has been shown to influence cell proliferation and differentiation[1], next to its normal role as calcium regulator[2]. Recently, there has been a growing interest in the development of structurally modified analogues of 1α,25-$(OH)_2$-D_3 with low calcemic effect but increased cell differentiating ability. In this respect mainly side-chain modifications have been investigated[3], which led to some interesting analogues (e.g. calcipotriol[4]). While some A-ring modified analogues are described[5], little has been done in the CD-ring fragment[6].

In the context of our work on CD-ring modified analogues of **1**, we wish to report on the synthesis of a series of C-11 substituted compounds **3** and **4**. Central in our planning stands the con-

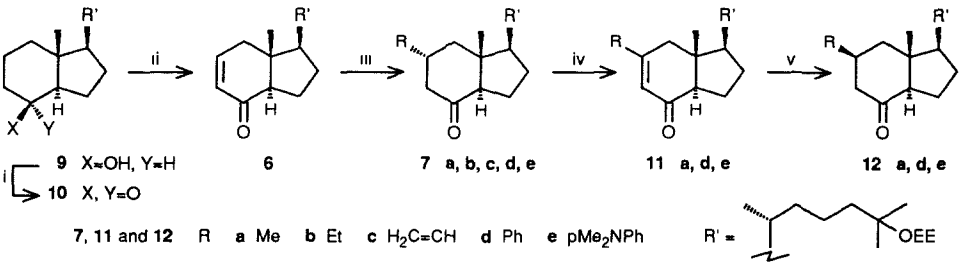


Scheme 1

jugate addition on the enone **6**, available from the Inhoffen-Lythgoe diol **5**[7]. The Lythgoe procedure[8] was used to couple the ketones **7** to the A-ring fragment **8**.

The CD-ring fragment **9** (Scheme 2) was synthesized from **5** via the method of Uskokovic[9]. An ethoxy ethyl protective group was chosen for the 25-hydroxyl function because of the extremely mild conditions necessary for the later deprotection in some of the fragile analogues. The commonly used oxidation method (PDC, PPTS, CH_2Cl_2, r.t.)[10] to convert the CD-ring alcohol **9** into the ketone **10** gave partial loss of the EE protecting group. This could be circumvented by ozone oxidation of **9** absorbed on silica, in $CFCl_3$ at -78°C. Conversion of ketone **10** into the key-enone **6** was accomplished by α-selenation and selenoxide elimination[11].

Conjugate addition to **6** of the appropriate lithium dialkylcuprates[12] in diethyl ether gave the 11α-substituted CD-ring ketones **7a** and **7b**, while lithium dialkylcyanocuprates[12] in THF or diethyl ether



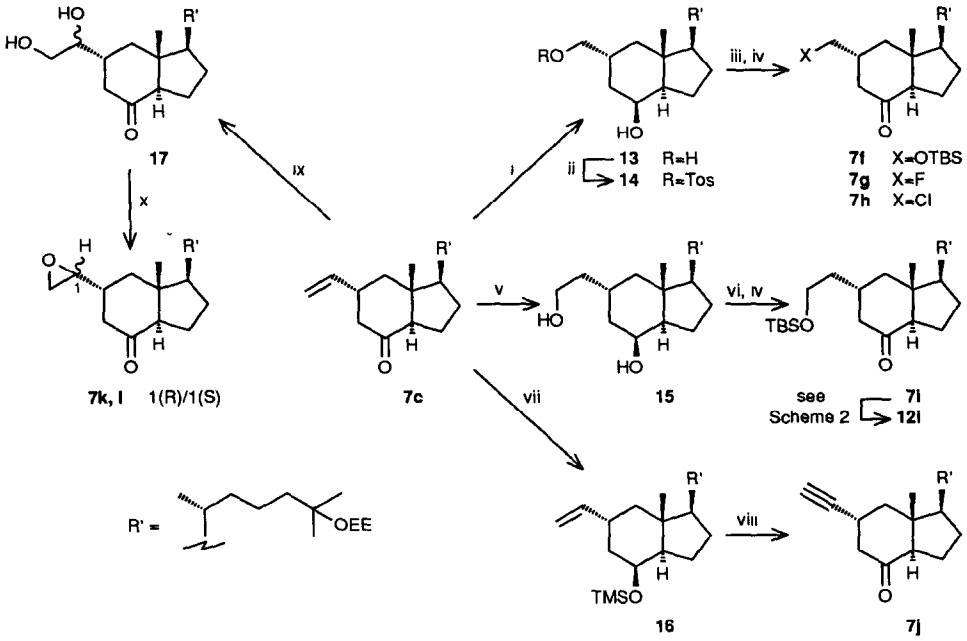
i. O_3, silica, $CFCl_3$, -78°C (70%); ii. (a) LDA, THF, -78°C; PhSeBr (1.2 equiv), -78°C (81%); (b) mCPBA (1.1 equiv), CH_2Cl_2, -15°C, 10 min (71%); iii. R_2CuLi (3 equiv, R=Me, Et), Et_2O, 0°C, 30 min; or $R_2CuCNLi$ (6 equiv, R=H_2C=CH, Ph, pMe_2NPh), THF or Et_2O, -78°C, 10 min, -40°C, 15 min (60-82%); iv. (a) LDA, THF, -78°C; PhSeBr (1.2 equiv), -78°C; (b) mCPBA (1.1 equiv), CH_2Cl_2, -15°C, 10 min (40-45%), v. H_2 (2.8 bar), Pd/C, EtOAc, Et_3N, r.t., 12h (45-80%).

Scheme 2

were used to obtain the compounds **7c**, **7d** and **7e**. The yields were in the range of 60-82%. As expected, the α-stereochemistry at C-11 was obtained because of steric hindrance of the β-side by the axially oriented 18-methyl substituent.

In order to obtain some analogues with the 11β-configuration, needed for evaluating the spatial requirements at C-11 for biological activity, **7a**, **d** and **e** were subjected to an α-selenation - selenoxide elimination sequence[13]. Catalytic hydrogenation of **11a**, **d** and **e** led exclusively to the 11β-epimers **12a**, **d** and **e**. The relative stereochemistry at C-11 was proven by comparative ^{1}H-NMR and nOe experiments carried out on **7a** and **12a**[14].

The ethenyl substituted **7c** (Scheme 3) allows the formation of a variety of functional groups needed for assessing the influence of electrostatic properties on the biological activity. Ozonisation of the double bond and reductive work-up gave diol **13**, which after selective silylation of the primary alcohol and oxidation led to the protected 11α-hydroxymethyl ketone **7f**. The 11α-fluoromethyl and 11α-chloromethyl ketones **7g** and **7h** were obtained via substitution of the intermediate tosylate **14** with the respective tetrabutylammonium halogenides[15] followed by oxidation. On the other hand, hydroboration of the double bond of **7c** using 9-BBN in THF with concomitant reduction of the C-8 car-



i. (a) O_3, MeOH, Pyr, -78°C; (b) $NaBH_4$, -78°C -> r.t., 30 min (50%); ii. TosCl (1.5 equiv), Pyr, 0°C, 14h (79%); iii. **13** -> **7f**: TBSCl (4.2 equiv), imidazole, DMF, r.t., 4h (84%); **14** -> **7g**, **h**: TBAX (3 equiv, X=F, Cl), THF, mol. sieves; r.t., 18h (64-70%); iv. O_3, silica, $CFCl_3$, -78°C (+70%); v. (a) 9-BBN (4 equiv), THF, r.t., 3h; (b) H_2O_2, NaOH, r.t., 12h (59%); vi TBSCl (4.2 equiv), imidazole, DMF, r.t., 4h (85%); vii. (a) $NaBH_4$, MeOH, 0°C (85%); (b) TSIM, THF, r.t. (91%); viii. (a) Pyr.HBr.Br_2, $CHCl_3$, Et_3N, 0°C (95%); (b) LICA, THF, -30°C (45%); (c) PPTS, CH_2Cl_2, r.t., 12h (95%); (d) PDC, PPTS, CH_2Cl_2, r.t. (90%); (e) TSIM, THF, r t. (81%); ix. OsO_4, NMMO, acetone, H_2O, r.t., 10h (60%); x. (a) TosCl (1.5 equiv), Et_3N, CH_2Cl_2, 0°C, 12h; (b) DBU (10 equiv), r.t., 3h (62%).

Scheme 3

bonyl function yielded the homologous diol **15**, which was transformed into the precursor **7l**. Further transformation into the 11β-epimer **12l** involved the same sequence as already depicted in Scheme 2. The 11α-ethynyl intermediate **7j** was obtained using a bromination - dehydrobromination sequence. For this purpose the C-8 carbonyl function was first reduced and the alcohol protected as a TMS ether to give **16**. After triple bond formation, treatment with PPTS in dichloromethane resulted in the removal of both the TMS and EE protecting groups. Subsequent to the oxidation step, the 25-hydroxyl group was reprotected as a TMS ether. Dihydroxylation of the double bond of **7c** afforded the diastereomers **17**; selective tosylation of the primary alcohol and DBU treatment led to the epoxides **7k** and **7l**, which could be separated by chromatography.

The ketones of the 11α-series **7** and of the 11β-series **12** were then coupled with the known A-ring phosphine oxide **8**[9] and afforded analogues **3** and **4** with protected hydroxyl functions. Whereas the yields of the couplings in the α-series varied from 70 to 90%, within the β-series only 15-30% of desired product is isolated next to recovered starting ketone, which is also in part isomerized at C-14. The lack of reactivity in the β-series is probably due to steric compression in the transition state in

which three β-oriented and 1,3-related substituents are involved. Finally, deprotection of **3** and **4** using Amberlyst-15® in methanol-THF or, in the case of the derivatives **3j**, **3k**, **3l** and **4e**, TBAF in THF gave the (C-11)-substituted 1α,25-$(OH)_2$-D_3 analogues **3** and **4**[16] in high yields.

It was found that the large or polar substituents sterically hinder the binding to the vitamin D receptor, whereas such analogs have an increased affinity to the serum vitamin D-binding protein. The *in vitro* effects of most analogs on HL-60 cell differentiation exceeded their effects on calcium metabolism *in vivo*. The full details of the biological studies are published elsewhere[17].

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13. This sequence is less efficient than the previous conversion of **10** into **6** for two reasons: (a) Due to steric hindrance, the introduction of the α-phenylseleno group into **7** leads to a 40-50% yield of two diastereomeric selenides next to starting material; at this stage chromatographic separation is not possible; (b) Only the β-oriented selenide can yield enone **11** via syn-elimination of the corresponding selenoxide. Hence only one of both diastereomers is useful. At this stage separation of enone **11** and ketone **7** is easily performed.
14. Interaction between H-11 and CH_3-18 in compound **7a** (α-stereochemistry), absent in compound **12a** (β-stereochemistry).
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