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A Practical Synthesis of A-ring Precursors for 19-Nor-1α,25-dihydroxyvitamin D_3 Analogues.

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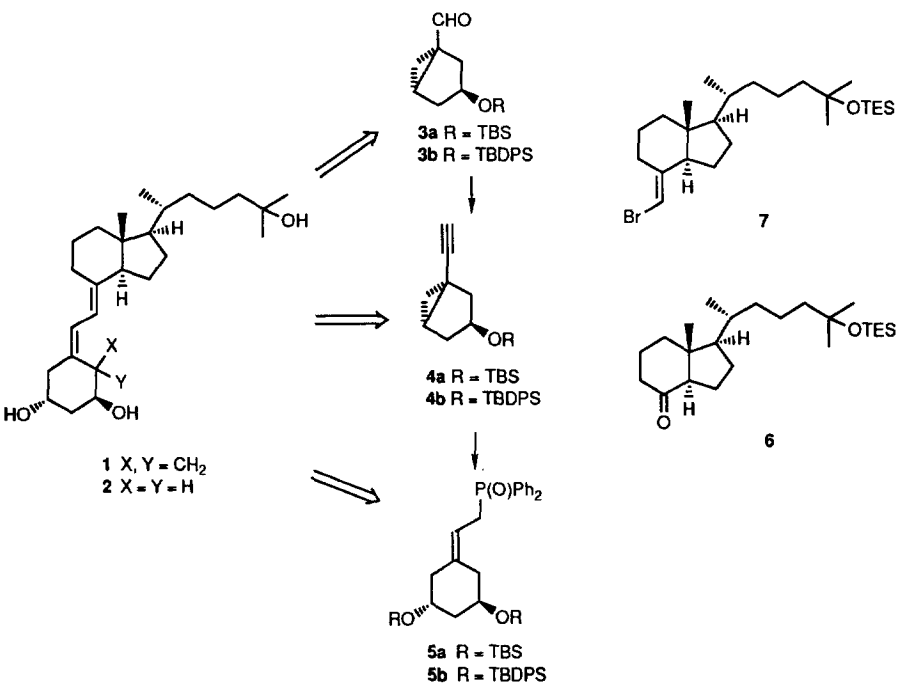
Abstract : A convergent, more practical route to the A-ring precursors **3** and **5** starting from enantiopure (2S,4S)-1,2:4,5-diepoxypentane (**11**) is described.

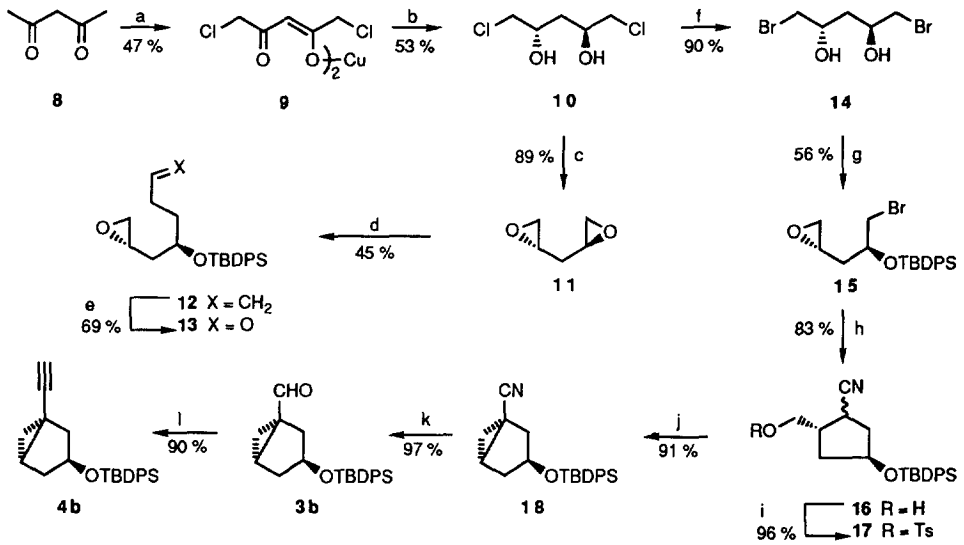
The importance of 1α,25-dihydroxyvitamin D_3 (calcitriol; **1**) the hormonally active metabolite of vitamin D_3, is presently well recognized.[1] Apart from its normal role as a calcium regulator other potential properties start to emerge, including regulation of cell proliferation and differentiation processes and immune modulation.[2]

During the last decade, there has been a growing interest in the development of analogues of 1α,25-$(OH)_2$-D_3 **1** with low calcemic effect but increased cell differentiating ability. Among the A-ring modifications, the 19-nor analogue **2** has been shown to induce interesting biological activities.[3,4]



Scheme 1

Recently we have described a novel synthesis of 19-nor vitamin D analogues[5] based on the known rearrangement of cyclopropylic alcohols into homoallylic alcohols subsequent to condensation of **4a** and **6**.[6,7,8] (scheme 1). The key 19-nor A-ring precursor **4a** was obtained from (-)-quinic acid and also *via* an alternative chemoenzymatic route starting from *cis*-1,3,5-cyclohexanetriol. These routes involve a rather linear approach; the first one, starting from (-)-quinic acid, suffered somewhat from low chemoselectivity and yield during the removal of the 1- and 4-hydroxy groups.



(a) $AlCl_3$, $ClCH_2COCl$, $PhNO_2$, CH_2Cl_2, 60°C, 4 h, $Cu(OAc)_2$; (b) (*i*) 10 % H_2SO_4, Et_2O; (*ii*) $[((R)BINAP)RuCl_2]_2Et_3N$, H_2, 1200 psi, 102°C; (c) KOH, Et_2O, r.t., 2 h; (d) (i) allyllithium, Et_2O, $BF_3.OEt_2$, -78°C, 1 h; (ii) TBDPSCl, DMAP, imid., DMF, r.t., 12 h; (e) OsO4, NaIO4, THF, H_2O, r.t., 1 h; (f) (*i*) KOH, ether; (*ii*) Li_2NiBr_4, THF, r.t., 5 h; (g) (*i*) TBDPSCl, imidazole, pyridine, -10°C; (*ii*) KOH; (h) $LiCH_2CN$ (10 eq.), THF, -78°C, 3 h; (i) TsCl, CH_2Cl_2, DMAP, Et_3N, 4°C, 12 h; (j) KHMDS, THF, -78°C, 3 h; (k) DIBAL-H, toluene, -78°C, 1 h; (l) $(MeO)_2P(O)CHN_2$, t-BuOK, THF, -78°C, r.t., 18 h.

Scheme 2

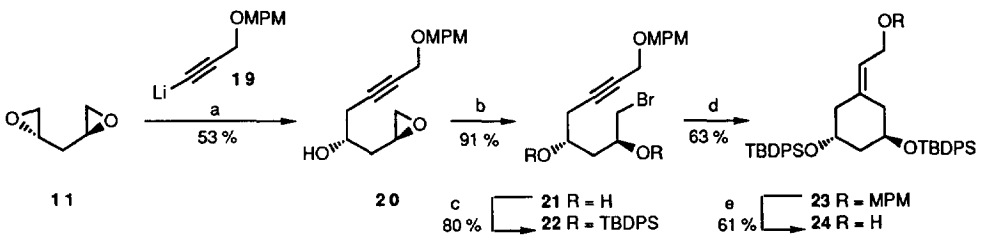
This encouraged us to investigate a more practical convergent synthesis of the intermediate **3b** (scheme 1). It seemed to us that (2*S*,4*S*)-1,2:4,5-diepoxypentane **11**, developed by Rychnovsky *et al.*,[9] could be an ideal chiral template for our purpose (scheme 2). This C2-symmetric diepoxide can be obtained in three steps from 2,4-pentanedione **8** with high optical purity (>97 % ee). The choice of **11** was furthermore stimulated by the recognition that it could also serve as starting point in a short alternative synthesis of phosphine oxide **5**, previously synthesized by DeLuca *et al.*[3b] from (-)-quinic acid. In analogy with Lythgoe's classical synthesis of **1**,[10] reaction derived from the anion of **5a** with **6** would lead to **2**.

Our strategy for the synthesis of the title compounds is based on the reported[9] selective opening of one epoxy function in **11** by the action of carbon nucleophiles. For our purpose a functionalized 2C unit has to be introduced. However we observed that **11** was unreactive towards the enolate anions of t-butyl acetate or acetonitrile under conditions for mono-reaction. On the other hand, reaction with allyllithium gave, after protection, the potential intermediate **12**. Double bond cleavage led to the unstable aldehyde **13**, for which no conditions could be found to effect ring closure. We therefore decided to investigate reactions on the bromo

epoxide **15** which is easily obtainable from **10**. The dichloride **10** was, *via in situ* formation of **11**, transformed in dibromide **14**. Selective mono-epoxide formation of **14** and hydroxy group protection next afforded **15**.

Gratifyingly, reaction of **15** with an excess of lithiated acetonitrile led in a one-pot reaction to the desired cyclopentane **16** (*trans-cis* 10:1) . Subsequent to faster reaction of the nucleophile with the bromide function, intramolecular exocyclic ring opening of the epoxide is now an efficient process. The remaining steps to the first target are straightforward and involve : (i) nucleophilic displacement of the tosylate, and (ii) reduction of the nitrile **18**. The aldehyde **3b**[11] was thereby obtained in 35 % overall yield in 6 steps from **10**.

We then turned our attention to the synthesis of the second target **5b** (scheme 3). Reaction of diepoxide **11** with the lithiated alkyne **19** allowed stepwise manipulation of both epoxides. Subsequent to mono-alkynylation to **20**, the other epoxide group was transformed into the protected bromo-alcohol **22**. Radical cyclization of **22** gave the desired cyclohexane **23**, which after deprotection of the allylic hydroxy function afforded **24** which can be transformed into the phosphine oxide **5b**, as described by DeLuca[3b] for **5a**.

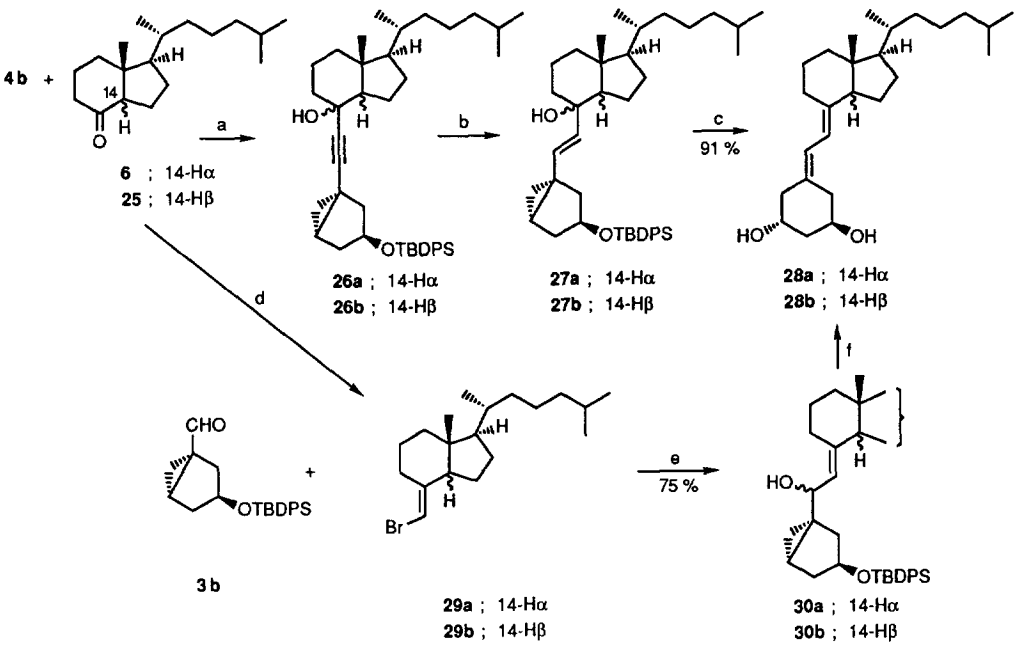


(a) $BF_3.OEt_2$, THF, -78°C, 2 h; (b) Li_2NiBr_4, THF, r.t., 2.5 h; (c) TBDPSCl, imidazole, CH_2Cl_2, DMAP, Et_2O, 12 h; (d) SmI_2 (0.1 M in THF), HMPA, THF, 0°C, 2 h; (e) DDQ, CH_2Cl_2/H_2O (18/1), r.t., 2.5 h.

Scheme 3

In our previous report,[5] 19-nor-1α,25-$(OH)_2$-D_3 **2** was obtained *via* coupling of the alkyne **4a** with bicyclic ketone **6** as described by Wilson *et al.*[7] for the synthesis of **1**, and illustrated in scheme 4 with the synthesis of 19-nor-1α-hydroxyvitamin D_3 **28a**. Because of our interest in 14-*epi* analogues we repeated the sequence starting from the C/D *cis* fused **25**. Previously reduction of **26a** was performed with $LiAlH_4$ in the presence of an excess NaOMe in order to avoid allene formation.[12] However, under these conditions **26b** gave substantial allene formation. We now found that Red-Al is very suitable for this reduction as no allene was formed. Solvolysis of **27b** and hydroxy group deprotection afforded only the *E*-isomer, 19-nor-14-epi-1α-hydroxyvitamin D_3 **28b**. It is remarkable that solvolysis performed on the corresponding free alcohol (deprotection of **27b**) led to a mixture of **28b** and the 7,8-*Z*-isomer in a 6:4 ratio. Apparently the bulky protective group seems to be crucial for orienting the 6,7 bond to the *E*-geometry in 14-*epi* analogues. This observation is contrast to the *trans* fused series where only the *E*-isomer is produced.

We also investigated an alternative route[7] involving coupling of aldehyde **3b** with vinylic lithium derivatives of respectively **29a** and **29b** respectively . The formation of **29a** (*E*/*Z* 30:1) has been previously described by Trost *et al.*[13] Under identical reaction conditions the 14-epimer **25** gave **29b** together with to the *Z*-isomer in 3.5:1 ratio. We found that under more dilute conditions and using the bulkier potassium counterion a ratio of 4o:1 in favour of **29b** was obtained (72 %). In **30a,b** the 7,8-*E*-geometry is preserved and in both cases solvolysis led exclusively to the desired *E* geometry, in the product demonstrating that the allylic nature of the hydroxy group is of no influence on the concerted process of cyclopropyl ring opening.



(a) n-BuLi, THF, -50°C → r.t., 1 h; 98 % for **26a**, 80 % for **26b**; (b) $(MeOCH_2CH_2O)_2AlH_2Na$, Et_2O, r.t., 12 h; 90 % for **27a**, 81 % for **27b**; (c) (*i*) PTSA (0.3 eq), dioxane:H_2O 1:1, 63°C, 6 h; (*ii*) TBAF, THF, r.t.; 90 % for **28a**, 65 % for **28b**; (d) for **6** : $Ph_3P^+CH_2BrBr^-$, NaHMDS, THF, -60°C → r.t., 1 h (60 % yield); for **25** : $Ph_3P^+CH_2BrBr^-$, KHMDS, THF, -78°C → r.t., 3 h (72 % yield); (e) t-BuLi, THF, -78°C, 2 h (75 %); (f) as for (c); 72 % for **28a**, 81 % for **28b**.

Scheme 4

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11. In this synthesis the TBDPS protective group was choosen instead of TBS (ref. 5) because we have observed that **3a** and **4a** are rather volatile during oil pump drying.
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14. Selected analytical data : **3b** : $[\alpha]_D^{20}$ -90 (c 1.00, $CHCl_3$), **4b** : $[\alpha]_D^{20}$ -86.3 (c 1.60, $CHCl_3$), ^1H NMR : compare ref. 5.

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