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Novel Synthesis of 2-Substituted 19-Norvitamin D A-Ring Phosphine Oxide from D-Glucose as a Building Block

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Abstract—19-Norvitamin D A-ring phosphine oxide **5** was synthesized by a new sequence mode starting from D-glucose as a chiral template. Transformation of the pyranoside ring into the A-ring carbocycle was achieved by the Pd-catalyzed Ferrier rearrangement. The phosphine oxide **5** was obtained in an 18% overall yield by this novel cost-effective method.

Active vitamin D_3, 1α,25-dihydroxyvitamin D_3 **1** elicits its biological functions such as calcium and phosphorous homeostasis, cell differentiation, and immunoregulation by binding to the vitamin D receptor (VDR) and regulating the transcription of target genes.[1] Until recently, attention has been focused mostly on the side-chain derivatives of vitamin D, and we have developed a structure–function theory for vitamin D focusing on the side chain.[2] Recently, however, interest in vitamin D drug development has shifted to the A-ring.[3] 1α,25-Dihydroxy-19-norvitamin D_3 **2**, which lacks the 10(19)-exomethylene group of **1**, has reduced VDR affinity (30% of **1**) and shows a non-calcemic activity profile.[4,5] Interestingly, introduction of a C(2)-substituent to 19-norvitamin D analogues restores the VDR affinity as well as the calcemic activity.[6,7] Thus, 2-substituted 19-norvitamin D analogues open a new horizon in the field of synthetic vitamin D drugs.

The 19-norvitamin D skeleton is constructed using the standard convergent method based on coupling of the A-ring phosphine oxide with the C/D-ring 25-hydroxy Grundmann's ketone. Although at least three methods for synthesis of the 19-nor-A-ring phosphine oxide have been reported,[5,8,9] for the synthesis of 2-substituted 19-norvitamin D analogues (Fig. 1), the method starting from expensive (−)-quinic acid is both convenient and versatile.[5] We have envisioned a new method for synthesizing the A-ring phosphine oxide **5**, a key intermediate for the 2-substituted 19-norvitamin D analogue. Here we report the synthesis of **5** starting from low-cost D-glucose as a chiral building block and its application to novel 2-substituted 19-norvitamin D analogue synthesis.

Our retrosynthetic analysis of the A-ring synthon is outlined in Figure 2: phosphine oxide **5** can be derived from the cyclohexanone derivative **6**, which is obtained from **7**. The key step of the synthesis, conversion of the pyranoside ring to a carbocyclic system, can be achieved by Ferrier rearrangement of the hex-5-enopyranoside **8**, which is readily available from the 2-deoxypyranoside derivative **9**. Ultimately, we envisioned D-glucose to be a suitable chiral template for the 2-substituted 19-nor-A-ring synthon **5**.

D-Glucose was easily transformed to an anomeric mixture of 2-deoxypyranoside **10** (ca. α/β = 10:1)[10] by a 4-step, one-column procedure with a 92% overall yield. Alkaline hydrolysis of **11**, followed by benzylideneacetalization afforded the acetal **11** (89%). After protection of a hydroxyl group at C(3) as a benzyl ether, the 4,6-*O*-benzylidene acetal ring was cleaved by $LiAlH_4$ in the presence of $AlCl_3$ to give the dibenzyl ether **12** (76%). Iodination of the alcohol **12** gave the iodide, which upon treatment with AgF (or DBU), afforded the hex-5-enopyranoside **13** (78%). Among various methods used

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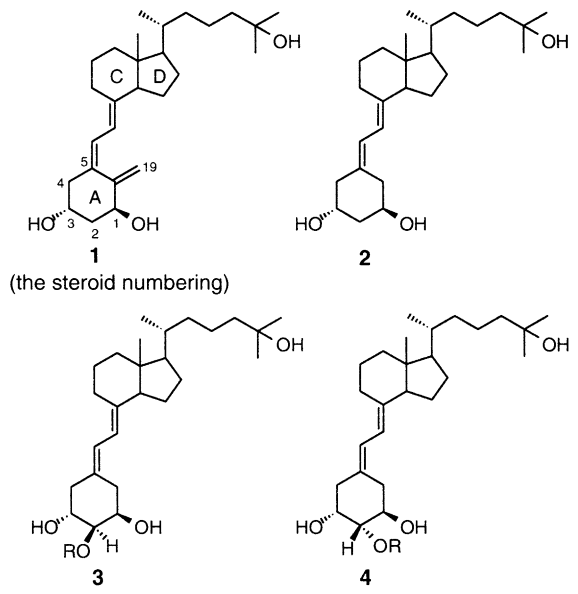

Figure 1. Structures of the active vitamin D_3 and its 19-norvitamin D analogue.

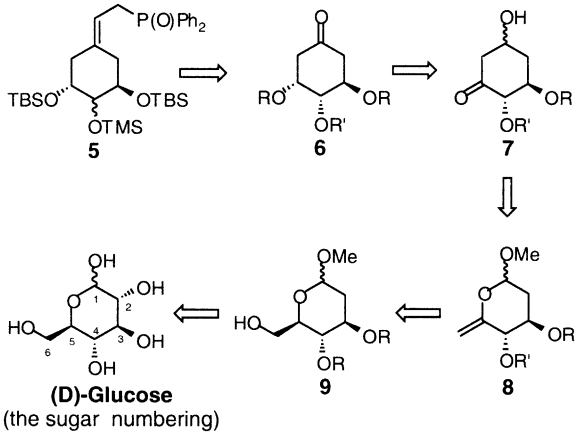

Figure 2. Retrosynthetic analysis of the A-ring phosphine oxide.

for the rearrangement of pyranosides into carbocyclic compounds, we investigated the Pd (II)-mediated Ferrier reaction.[11] Under mild and neutral conditions (catalytic amount of $PdCl_2$ in an aqueous dioxane, 60 °C), **13** was converted to the hydroxy ketone derivative, which was silylated to yield the *t*-butyldimethylsilyl ether **14** as a separable diastereoisomeric mixture (ca. 1α-isomer/1β-isomer = 6:1, 89%). The reduction of the major 1α-isomer of **14** with L-Selectride® proceeded stereoselectively with an excellent yield (95%) to give the 5α-hydroxy isomer **15** as a sole product. A similar result was obtained using the 1β-isomer of **14** to give the corresponding 5α-hydroxy compound. The stereochemistry at C(1) has little effect on the stereoselectivity of the reduction of the 5-ketone **14**, probably because the equatorially oriented 4α-benzyloxy group hinders reduction from the α side. Protection of the hydroxyl group and subsequent desilylation afforded the tri-*O*-benzyl ether **16** (89%). Swern oxidation of **16**, followed by Pd/C-catalyzed hydrogenolysis of the benzyl ether proceeded quantitatively to give the 3,4,5-triol, which was regioselectively silylated with bulky *t*-butyldimethylsilyl chloride to give the cyclohexanone derivative **17** (72%) as a single product. Peterson olefination of **17** and transformation to the final phosphine oxide **5** were accomplished by a method analogous to that developed by DeLuca and co-workers.[4] After protection of the hydroxyl group of **17** with TMS-imidazole, reaction with methyl (trimethylsilyl)acetate was carried out to give an allylic ester quantitatively, which on reduction with (*iso*-Bu)$_2$AlH afforded the corresponding alcohol **18**. This allylic alcohol was converted to the A-ring phosphine oxide **5** via allylic tosylate and the diphenylphosphine derivative with a 78% yield. The overall yield of **5** from glucose was about 18% and better than that via the (−)-quinic acid route (about 13%

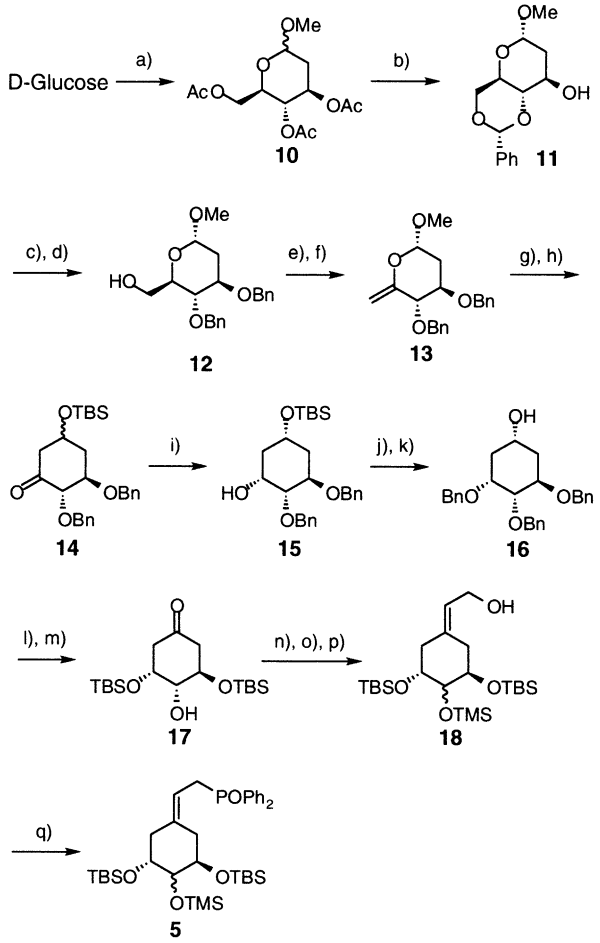

Figure 3. Synthesis of the A-ring phosphine oxide from D-glucose: (a) (1) Ac_2O, $HClO_4$, then HBr; (2) Zn-aq AcOH; (3) MeOH, pTsOH (92%); (b) (i) NaOMe, MeOH; (ii) $PhCH(OMe)_2$, pTsOH (89%); (c) BnBr, DMF (90%); (d) $LiAlH_4$, $AlCl_3$, Et_2O (84%); (e) I_2, PPh_3, THF (82%); (f) AgF, Py. (95%); (g) $PdCl_2$, dioxane, H_2O (92%); (h) *t*-BuSi(Me)$_2$Cl, DMF (97%); (i) L-Selectride, THF (95%); (j) BnBr, DMF (94%); (k) Bu_4NF, THF (95%); (l) DMSO, $(COCl)_2$, CH_2Cl_2 (98%); (m) (1) H_2/Pd/C, EtOH, (2) *t*-BuSi(Me)$_2$Cl, DMF (73%); (n) TMS-imidazole, CH_2Cl_2 (99%); (o) TMS–CH_2CO_2Me, BuLi, THF (99%); (p) (*iso*-Bu)$_2$AlH, Tol (98%); (q) (1) TsCl, BuLi, THF, then Ph_2PH; (2) 10% H_2O_2, CH_2Cl_2 (78%).

overall yield). It should be noted that compounds **11** and **14** serve as useful intermediates for preparing other modified A-ring derivatives, expanding the method for synthesis of diverse 19-norvitamin D analogue: for example, deoxygenation of the C(3)-hydroxyl group of **11** can afford the A-ring having 1,2- or 2,3-vicinal hydroxyl groups, and the A-ring synthon with 1,3,4- or 1,3,10-trihydroxyl groups can be synthesized directly from the Ferrier-ketone **14** (Figs. 3 and 4).

We synthesized six 2-substituted 19-norvitamin D analogues **3a**,**b**,**c** and **4a**,**b**,**c** using the phosphine oxide **5**.[15] We obtained 1α,2α,25- and 1α,2β,25-trihydroxy-19-norvitamin D **3a** and **4a**,[6] by reaction with 25-hydroxy Grundmann's ketone **19**.[12] 2-Hydroxyethoxy- (**3b**, **4b**) and 2-diethylcarbamoylmethoxy-19-norvitamin D analogues (**3c**, **4c**) were obtained from 2-hydroxy derivatives **20** and **21** by the Williamson ether synthesis.

The binding affinity of **3** and **4** for the bovine thymus VDR was evaluated. It should be noted that the 2β-hydroxyethoxy analogue **4b** has equivalent affinity with the natural ligand **1**, while the 2α-isomer **3b** and the carbamoyl derivative **3c** were 10-fold and 2000-fold less potent than **1**, respectively. It has been reported that among the 2-substituted vitamin D analogues, 2α-isomers have higher VDR affinity than the corresponding 2β-isomers.[3,7,13] In the present case of 2-hydroxyethoxy-19-norvitamin D derivatives **3b** and **4b**, the situation is reversed. The natural ligand **1** is harbored in the VDR adopting the β-conformation at the A-ring, where the 1α-hydroxyl group takes an equatorial conformation and the 10(19)-exocyclic methylene group is oriented towards the β-face.[14] In a preliminary docking study of compounds **3b** and **4b**, we assume that both can be accommodated in the ligand binding pocket with the β-form, Arg274 and Asp144 playing a key role in anchoring the ligands at the C(2) substituent. However, more detailed studies such as site directed mutation analyses are necessary to identify the key interactions responsible for their potency differences. These studies are under investigation and will be reported elsewhere.

In conclusion, we have accomplished a new and easy method for efficient synthesis of the 2-substituted 19-norvitamin D A-ring building block starting from D-glucose. We synthesized six 2-substituted 19-norvitamin D derivatives using this A-ring synthon and their VDR affinity was evaluated. We are continuing the synthesis of a variety of 2-substituted 19-norvitamin D analogues using this methodology and a full account will be published in due course.

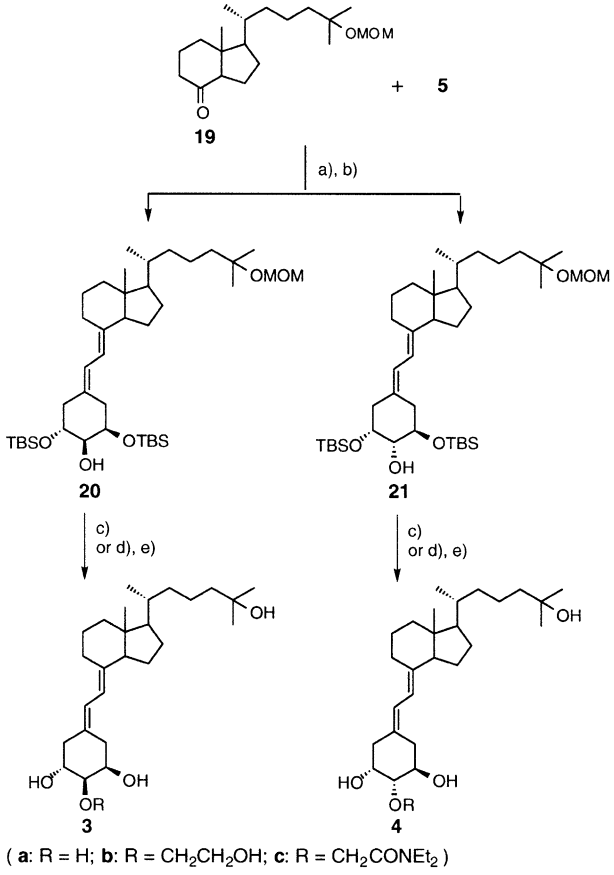

Figure 4. Synthesis of 2-substituted 19-norvitamin D analogues: (a) PhLi, THF (51%); (b) aq AcOH, THF (82%); (c) $BrCH_2CH_2OTBS$, NaH, DMF, THF (41% for **3b**, 88% for **4b**); (d) $BrCH_2CONEt_2$, NaH, DMF, THF (67% for **3c**, 67% for **4c**); (e) (−)-camphorsulfonic acid, MeOH (42% for **3b**, 51% for **4b**, 84% for **3c**, 67% for **4c**).

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15. Satisfactory spectral characterization of all intermediates was obtained. Spectral data of **3a**, **4a**, **18** and **5** were in accordance with those reported in literature[6]). Data for **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.55 (3H, s, 18-H), 0.93 (3H, d, J = 6.4 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 3.37 (1H, dd, J = 7.8, 3.0 Hz, 2-H), 3.71–3.83 (4H, m, OCH_2CH_2O), 3.96, 4.14 (each 1H, m, 3, 1-H), 5.84, 6.34 (each 1H, J = 11.2 Hz, 7, 6-H). UV λ_{max} (MeOH): 242, 251, 261 nm. MS m/z (%): 464 (M^+, 61), 446 (100), 428 (63). HR-EI–MS m/z: 464.3505 (calcd for $C_{28}H_{48}O_5$: 464.3502). **4b**: δ: 0.54 (3H, s, 18-H), 0.94 (3H, d, J = 6.4 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 3.32 (1H, dd, J = 8.7, 2.9 Hz, 2-H), 3.65–3.89 (4H, m, OCH_2CH_2O), 3.84, 4.17 (each 1H, m, 3, 1-H), 5.84, 6.29 (each 1H, J = 11.2 Hz, 7, 6-H). MS m/z (%): 464 (M^+, 63), 446 (100), 428 (58). **3c**: δ: 0.55 (3H, s, 18-H), 0.93 (3H, d, J = 6.4 Hz, 21-H), 1.14, 1.19 (each 3H, t, J = 7.1 Hz), 1.22 (6H, s, 26, 27-H), 3.19, 3.41 (each 1H, q, J = 7.1 Hz), 3.32 (1H, dd, J = 7.5, 1.9 Hz, 2-H), 4.01 (3H, m, 3, 1-H, OH), 4.30, 4.39 (each 1H, d, J = 15.8 Hz), 5.85, 6.33 (each 1H, J = 11.2 Hz, 7, 6-H). UV λ_{max} (EtOH): 243, 251, 261 nm. MS m/z (%): no M^+, 497 (14), 479 (12), 383 (32), 365 (100). **4c**: δ: 0.54 (3H, s, 18-H), 0.93 (3H, d, J = 6.4 Hz, 21-H), 1.15, 1.19 (each 3H, t, J = 7.1 Hz), 1.22 (6H, s, 26, 27-H), 3.27 (1H, dd, J = 8.7, 2.8 Hz, 2-H), 3.83, 4.05 (each H, m, 3, 1-H), 4.32, 4.36 (each 1H, d, J = 15.9 Hz), 5.87, 6.29 (each 1H, J = 11.2 Hz, 7, 6-H). MS m/z (%): no M^+, 497 (12), 479 (12), 383 (8), 365 (100).