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[3,3]-Sigmatropic rearrangements: short, stereocontrolled syntheses of functionalized vitamin D_3 side-chain units

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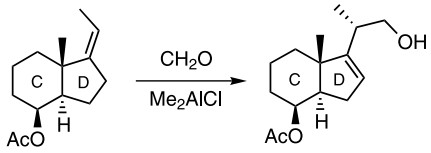
Abstract—Enantiomerically pure C,D-ring allylic alcohol **4** stereospecifically undergoes five types of [3,3]-sigmatropic rearrangements to give C-23 functionalized 16-ene vitamin D_3 side-chain units with natural C-20(*S*) stereochemistry. © 2002 Elsevier Science Ltd. All rights reserved.

The natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) and some synthetic analogs are currently being evaluated as drug candidates for cancer chemoprevention[1] and chemotherapy,[2] as well as for treatment of other human diseases such as osteoporosis and skin and immunological disorders.[3,4] Synthesis of rationally designed analogs[5] of calcitriol (**1**) often requires attaching a C,D-ring unit to an A-ring unit via a Horner–Wadsworth–Emmons (HWE) coupling to form the conjugated triene system (Fig. 1).[6]

Pioneering research at Hoffmann–La Roche Inc. established that the presence of a double bond between carbon atoms 16 and 17 often produces analogs having especially desirable pharmacological characteristics; introduction of such $\Delta^{16,17}$ unsaturation usually is achieved via a Lewis acid-catalyzed *ene* reaction of a 17-ethylidene unit with an aldehyde (Eq. (1)).[7] Recently, Mouriño and co-workers reported an effective procedure involving stereocontrolled organocuprate S_N2' reactions with C,D-ring allylic carbamates to form 16-ene units carrying a specific side-chain (Eq. (2)).[8] Now we report that C,D-ring, enantiomerically pure, allylic alcohol **4**, easily prepared from known C,D-ring chiron **2**,[9] stereoselectively undergoes five types of [3,3]-sigmatropic rearrangements forming 16-ene products with natural C-20(*S*) stereochemistry. These rearrangements produce synthetically versatile side-chain units with different C-23 carbonyl groups: an aldehyde, an ester, a ketone, an α-phenylthioketone as well as a 23 sulfone (Scheme 1).[10] It is noteworthy that 16-ene side-chain sulfone analogs of calcitriol (**1**) have recently been shown to have pharmacologically desirable therapeutic potential.[11]



(1)

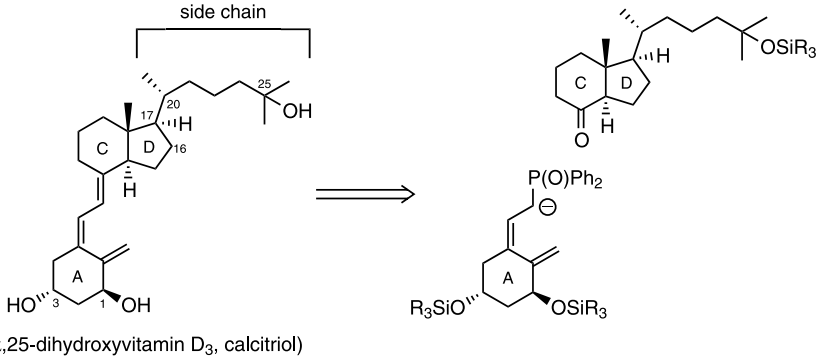


Figure 1.

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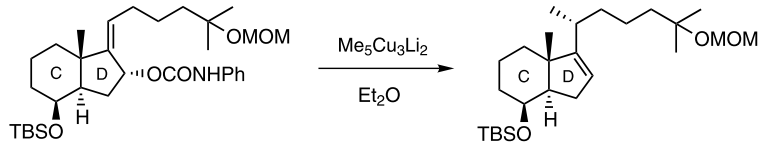
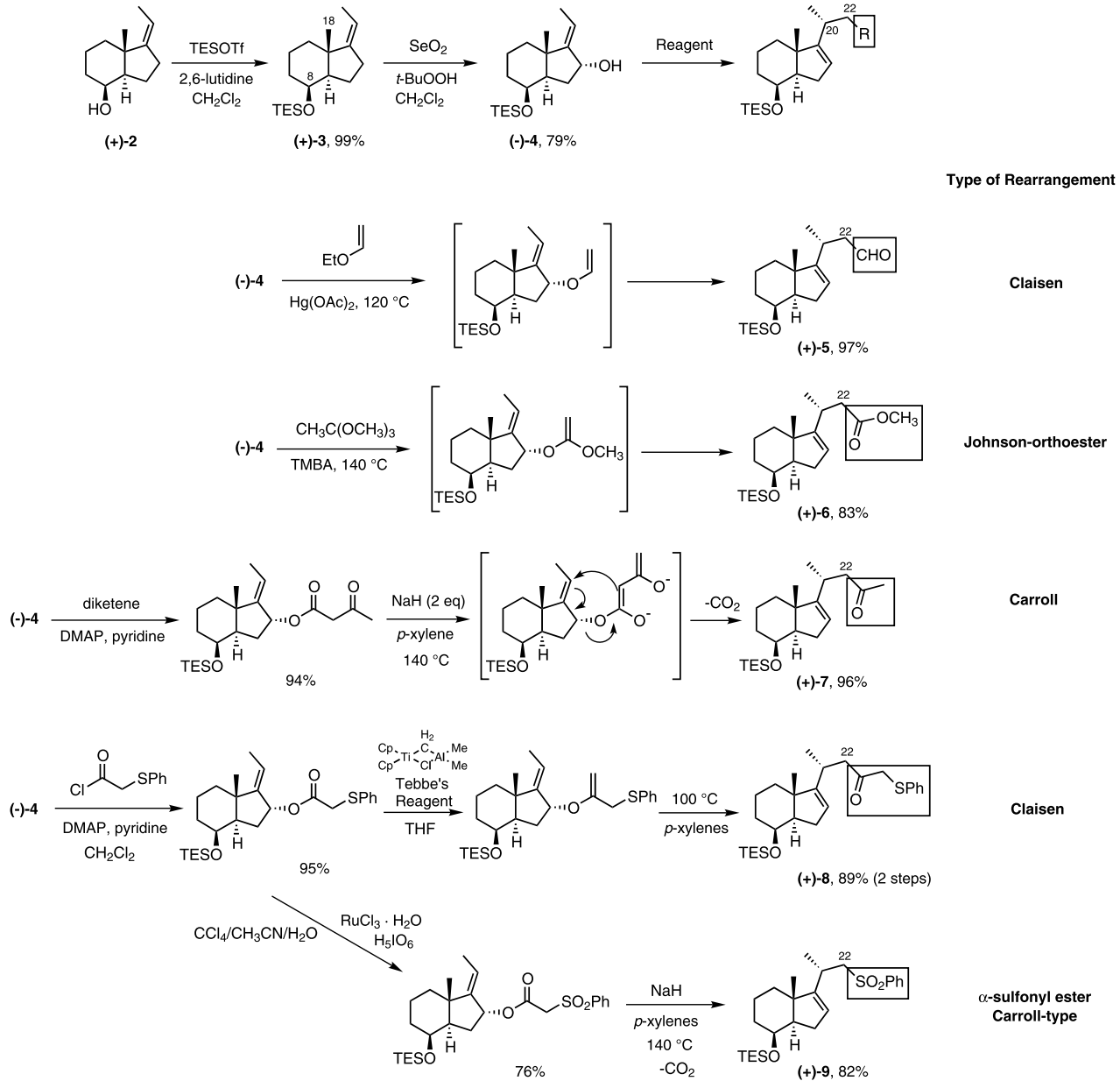
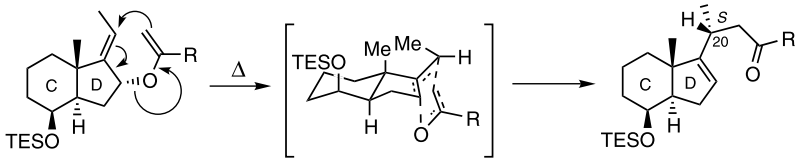


(2)

In developing a general method for preparing 16-ene C,D-ring synthons with natural C-20(*S*) stereochemistry, we envisioned various allylic vinyl ethers undergoing [3,3]-sigmatropic rearrangement on the α face of the D-ring (Eq. (3)). D-ring allylic vinyl ethers of this type have previously been shown to undergo rearrangement in steroidal, but not vitamin D, systems.[12,13] As seen in Eq. (3), this rearrangement proceeds via a 6-membered ring, chair-like transition state giving the natural absolute stereochemistry at C-20. In order to achieve these rearrangements, by either stepwise or in situ preparation of an appropriate allylic vinyl ether, we produced



Scheme 1.



(3)

allylic alcohol **4** (Scheme 1). This allylic alcohol was synthesized stereoselectively[14] from known ethylidene D-ring **3** via a selenium dioxide oxidation[15] in 79% yield. The *ene*-like SeO_2 oxidation occurs exclusively on the α face of the D-ring due to the steric hindrance of both the β-C-18 methyl group and β-C-8 triethylsiloxy group.[16,17] With allylic alcohol **4** in hand, five different [3,3]-sigmatropic rearrangements were achieved (Scheme 1).[18]

Reaction of allylic alcohol **4** with ethyl vinyl ether and mercury diacetate afforded the desired enol ether, which underwent thermal rearrangement in situ to give known aldehyde **5**, isolated and purified in 97% yield, with only one diastereomer detected by ^{1}H NMR spectroscopy. This aldehyde **5** is a synthetically useful intermediate for the formation of a number of vitamin D_3 analogs.[9,11,19] Aldehyde **5** has previously been prepared from ethylidine **2** in five steps (37% overall yield);[9] in sharp contrast, however, only three steps (76% overall yield) characterize the new methodology shown in Scheme 1 for preparation of aldehyde **5**. Obtaining the single C-20(*S*) diastereomer of aldehyde **5** further supports the C-16(*R*) absolute stereochemistry of the starting allylic alcohol **4**. Next, a Johnson-orthoester Claisen rearrangement[20] was achieved by reaction of alcohol **4** with trimethyl orthoacetate in the presence of a catalytic amount of 2,4,6-trimethylbenzoic acid. This reaction afforded methyl ester **6** in 83% yield, as determined by both ^{1}H NMR and gas chromatography (GC) using an internal standard; no other diastereomer was detectable by GC. An anion-assisted Carroll reaction was performed via the β-keto ester prepared in 94% yield from the reaction of **4** with diketene (Scheme 1). This β-keto-ester formed a dianionic intermediate upon reaction with 2 equiv. of sodium hydride and then smoothly underwent rearrangement and in situ decarboxylation at 140°C to give the 16-ene-23-methyl ketone **7**, isolated and purified in 96% yield. Synthesis of a 16-ene-25-sulfide C,D-ring side chain was accomplished via a Claisen rearrangement of an allylic vinyl ether containing the desired sulfide side chain (Scheme 1). Thus, converting allylic alcohol **4** into an α-sulfide ester using (phenylthio)acetyl chloride proceeded in 95% yield. Using Tebbe's reagent, this ester was then methenylated to form the corresponding allylic vinyl ether, which thermally rearranged into the β-keto phenyl sulfide **8** in 89% yield.[21] Finally, 23-sulfone **9** was prepared through a Carroll-like rearrangement[22] of an α-phenyl sulfone ester in 59% overall yield (Scheme 1).

In summary, we have shown that diversely functionalized 16-ene vitamin D_3 side-chain units, with natural C-20(*S*) stereochemistry, are easily accessible through a number of different [3,3]-sigmatropic rearrangements using enantiomerically pure allylic alcohol **4**. These rearrangements proceed in high yield and with high stereocontrol, and they provide synthetically versatile side-chain units useful for subsequent elaboration into many different and pharmacologically desirable analogs of calcitriol (**1**).

Acknowledgements

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18. Characteristic data are as follows: **(–)-4**: mp 38–41°C; $[\alpha]_D^{25}$ –20.9 (*c* 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (dq, J=7.2, 1.2 Hz, 1H), 4.43 (d, J=6.4 Hz, 1H), 4.13 (d, J=2.8 Hz, 1H), 2.24 (dt, J=12.0, 3.2 Hz, 1H), 1.97 (ddd, J=13.2, 6.4, 0.8 Hz, 1H), 1.87 (dt, J=13.2, 4.0 Hz, 1H), 1.84–1.76 (m, 1H), 1.75–1.66 (m, 1H), 1.71 (dd, J=7.2, 1.2 Hz, 3H), 1.61–1.53 (m, 1H), 1.51–1.40 (m, 4H), 1.08 (s, 3H), 0.94 (t, J=8.0 Hz, 9H), 0.55 (q, J=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.19, 118.17, 73.48, 69.33, 49.11, 44.39, 38.20, 34.76, 34.40, 20.18,

17.79, 13.04, 6.88, 4.85; IR ($CHCl_3$, cm^{-1}) 3341, 2997, 2876, 1379, 1107, 1019; HRMS m/z (M^+) calcd 333.2220 for $C_{18}H_{34}O_2SiNa^+$ found 333.2233. **(+)-5**: $[\alpha]_D^{25}$ +38.8 (*c* 7.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (t, $J=2.4$ Hz, 1H), 5.30 (t, $J=1.6$ Hz, 1H), 4.11 (m, 1H), 2.75–2.66 (m, 1H), 2.58 (dd, $J=8.0$, 2.8 Hz, 1H), 2.41 (dd, $J=7.4$, 2.0 Hz, 1H), 2.24 (tt, $J=13.2$, 1.2 Hz, 1H), 1.92–1.83 (m, 2H), 1.77–1.61 (m, 3H), 1.53–1.44 (m, 2H), 1.43–1.35 (m, 1H), 1.06 (d, 3H), 1.03 (s, 3H), 0.94 (t, $J=8.0$ Hz, 9H), 0.55 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.09, 158.68, 121.78, 68.79, 54.94, 49.93, 46.89, 35.90, 34.80, 30.75, 26.59, 22.00, 18.98, 18.02, 6.91, 4.88. **(+)-6**: $[\alpha]_D^{25}$ +34.8 (*c* 0.795, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, $J=1.6$ Hz, 1H), 4.11 (m, 1H), 3.64 (s, 3H), 2.62 (m, 1H), 2.51 (dd, $J=14.8$, 6.8 Hz, 1H), 2.36 (dd, $J=14.8$, 8 Hz, 1H), 2.23 (m, 1H), 1.95–1.83 (m, 2H), 1.75 (m, 1H), 1.67 (m, 1H), 1.61 (m, 1H), 1.50–1.33 (m, 4H), 1.02 (d, $J=6.8$, 3H), 1.00 (s, 3H), 0.94 (t, $J=8.0$ Hz, 9H), 0.55 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.23, 159.09, 120.59, 68.86, 54.91, 51.35, 46.91, 41.49, 35.84, 34.86, 30.76, 28.68, 21.76, 18.63, 18.05, 6.92, 4.88. **(+)-7**: $[\alpha]_D^{25}$ +36.6 (*c* 0.635, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (m, 1H), 4.11 (d, $J=2.0$ Hz, 1H), 2.69–2.60 (m, 2H), 2.48–2.41 (m, 1H), 2.27–2.19 (m, 1H), 2.11 (s, 3H), 1.91–1.83 (m, 2H), 1.78–1.74 (m, 1H), 1.69–1.58 (m, 2H), 1.50–1.42 (m, 1H), 1.42–1.33 (m, 1H), 1.01 (s, 3H), 0.99 (d, $J=6.8$ Hz, 3H), 0.94 (t, $J=8.0$ Hz, 9H), 0.55 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.53, 159.58, 120.53, 68.85, 54.95, 50.78, 46.91, 35.91, 34.82, 30.71, 30.40, 27.59, 21.82, 18.84, 18.05, 6.92, 4.89; HRMS m/z (M^+) calcd 373.253325 for $C_{21}H_{38}O_2SiNa^+$ found 373.25229. **(+)-8**: $[\alpha]_D^{25}$ +28.6 (*c* 0.765, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.17 (m, 1H), 5.23 (m, 1H), 4.07 (m, 1H), 3.62 (d, $J=1.6$ Hz, 2H), 2.81 (dd, $J=15.6$, 6.0 Hz, 1H), 2.64 (m, 1H), 2.57 (dd, $J=16.0$, 7.6 Hz, 1H), 2.15 (tt, $J=13.2$, 1.6 Hz, 1H), 1.91–1.77 (m, 2H), 1.72–1.63 (m, 2H), 1.59–1.54 (m, 1H), 1.48–1.37 (m, 2H), 1.31 (dt, $J=12.8$, 3.6 Hz, 1H), 0.95 (d, $J=7.2$ Hz, 3H), 0.92 (s, 3H), 0.92 (t, $J=8.0$ Hz, 9H), 0.53 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.70, 159.44, 134.91, 129.38, 129.04, 126.68, 120.60, 68.83, 54.94, 47.45, 46.89, 44.20, 35.83, 34.81, 30.68, 27.50, 21.82, 18.75, 18.02, 6.93, 4.89; HRMS m/z (M^+) calcd 418.256695 for $C_{27}H_{42}O_2SSiNa^+$ found 481.25422. **(+)-9**: $[\alpha]_D^{25}$ +18.6 (*c* 0.520, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.64 (m, 1H), 7.56 (m, 2H), 5.24 (m, 1H), 4.07 (m, 1H), 3.27 (dd, $J=14.0$, 3.6 Hz, 1H), 3.18 (dd, $J=14.0$, 9.2 Hz, 1H), 2.70 (m, 1H), 2.16 (t, $J=13.2$, 1H), 1.87–1.77 (m, 2H), 1.67–1.52 (m, 2H), 1.46–1.36 (m, 2H), 1.27 (m, 1H), 1.21 (d, $J=7.2$ Hz, 3H), 0.93 (t, $J=8.0$ Hz, 3H), 0.89 (s, 3H, 0.53 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.18, 140.13, 133.48, 129.19, 127.89, 122.30, 68.69, 62.54, 54.74, 47.07, 35.51, 34.68, 30.75, 26.97, 21.67, 18.86, 17.90, 6.90, 4.86; HRMS m/z (M^+) calcd 471.235960 for $C_{25}H_{40}O_3SSiNa^+$ found 471.232612.

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