A Convenient Synthesis of (24*S*)-1α-Hydroxyvitamin D_2

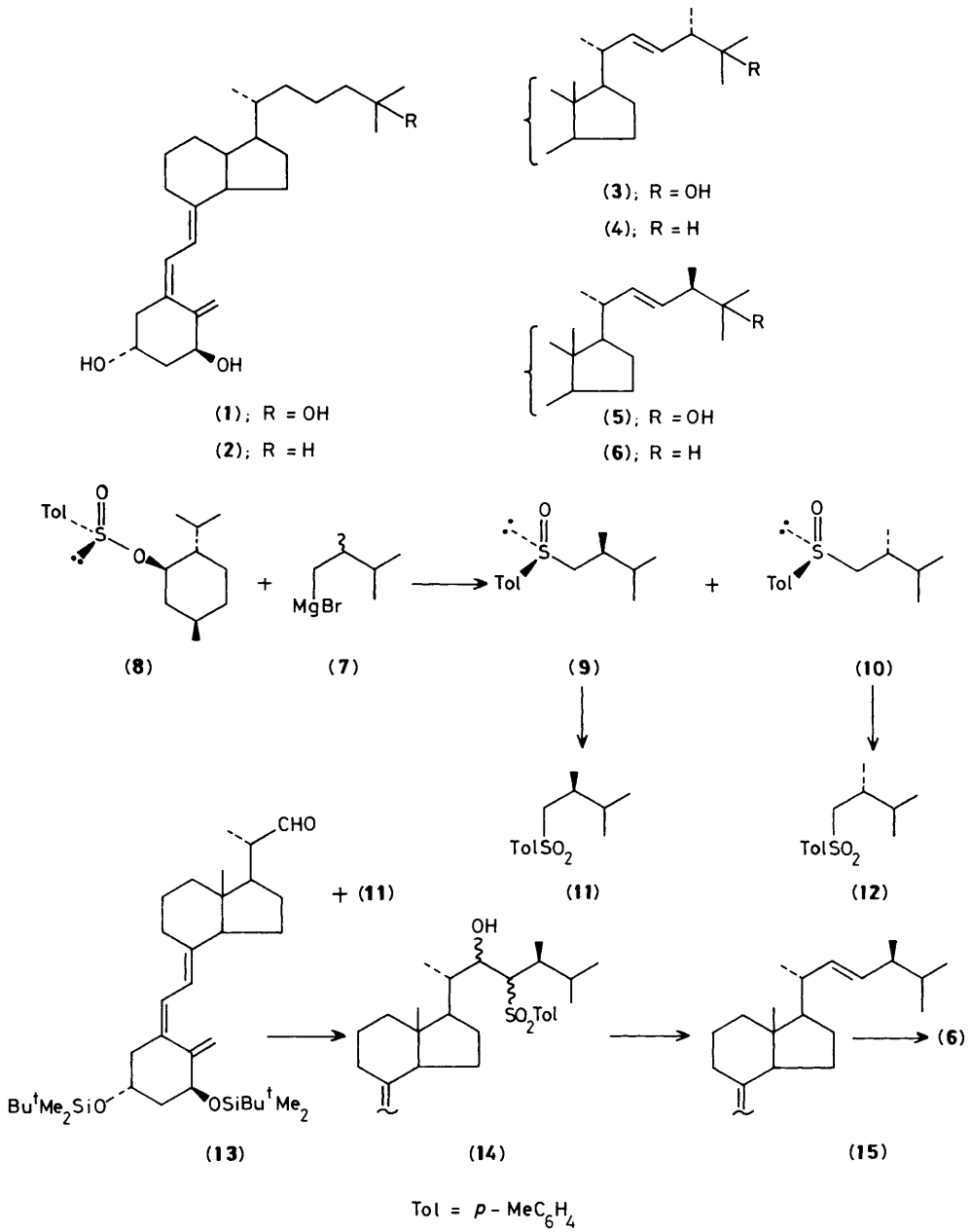
Kato L. Perlman, Heinrich K. Schnoes, and Hector F. DeLuca

Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin-Madison, WI 53706, U.S.A.

A new method was developed for the synthesis of (2*R*)- and (2*S*)-2,3-dimethylbutyl *p*-tolyl sulphone from a chiral sulphinate ester, and applied to the synthesis of (24*S*)-1α-hydroxyvitamin D_2; this new 24-epimer of vitamin D_2 has a distinct biological activity profile, differing qualitatively from that known for the (24*S*)-isomer.

1α,25-Dihydroxyvitamin D_3 (**1**), the natural vitamin D-derived hormone, and its 25-deoxy analogue, 1α-hydroxyvitamin D_3 (**2**) mediate both intestinal calcium absorption and the mobilization of calcium from bone, and the corresponding vitamin D_2 derivatives, 1α-25-dihydroxyvitamin D_2 (**3**) and 1α-hydroxyvitamin D_2 (**4**) (C-24 stereochemistry as in D_2 or ergosterol) exhibit an analogous pattern of biological activity.[1,2] In contrast, the C-24-epimer, (24*R*)-1α,25-dihydroxyvitamin D_2 (**5**), elicits an at best minimal bone mobilization response, but does promote intestinal calcium absorption, as well as the calcification of bone.[2] This unique and therapeutically valuable activity spectrum of (**5**) pointed to the corresponding 25-deoxy analogue, 1α-hydroxy-24-*epi*-vitamin D_2 (**6**) as an important synthetic target, since it has been found that the absence of a 25-hydroxy group [as in analogues (**2**) and (**4**)] is associated with reduced toxicity and superior pharmacokinetics of the respective products. In this Communication, we describe the synthesis of (24*S*)-1α-hydroxyvitamin D_2 (**6**), which has been tested and found to have biological activity similar to that of (24*R*)-1α,25-dihydroxyvitamin D_2 (**5**).

Whereas 1α-hydroxyvitamin D_2 [(**4**), 24*R* stereochemistry] is directly accessible by C-1-hydroxylation of readily available D_2,[3] synthesis of the desired 24*S* analogue (**6**) required construction of the epimeric side chain, and hence the preparation of the appropriate chiral side chain fragment.



Both (*R*)- and (*S*)-2,3-dimethylbutyl phenyl sulphone have been prepared as synthons for steroid side-chain construction. However, all reported syntheses are long, elaborate, multi-step procedures.[4—8] We now report a more direct and simple synthesis of the analogues chiral tolylsulphones and their use for the preparation of our target compound, (24*S*)-1α-hydroxyvitamin D_2 (**6**).

2,3-Dimethylbutylmagnesium bromide[9—11] (**7**) was converted in good yield into a diastereoisomeric mixture of (2*S*)-2,3-dimethylbutyl (*S*)-*p*-tolyl sulphoxide (**9**) and the (2*R*)-isomer (**10**) by the S_N2 displacement of the *O*-menthyl group of (−)-menthyl (+)(*R*)-*p*-toluenesulphinate (**8**)[12] in tetrahydrofuran. As expected, only two diastereoisomers were formed with inversion of configuration at sulphur (70% yield). Diastereoisomers (**9**) and (**10**) were separated by column chromatography or by h.p.l.c. and then separately oxidized with 3-chloroperoxybenzoic acid to the desired (*S*)- and (*R*)-2,3-dimethylbutyl *p*-tolyl sulphones (**11**) and (**12**) (yield 90%). Since the optical rotation of the corresponding phenyl sulphones was known from the literature,[4—7] we tentatively assigned to the (+)-tolyl sulphone the (2*S*), and to the (−)-isomer the (2*R*), configuration.† The final proof came after converting the (2*S*)-*p*-tolyl sulphone (**11**) to the (24*S*)-1α-hydroxyvitamin D_2 (**6**). The above procedure, yielding chiral sulphone synthons from racemic alcohol in three standard reactions plus one separation step, provides a simple and efficient approach to the required sulphone intermediates, which should be generally applicable to the preparation of a variety of synthetically useful chiral reactants.

The addition of side-chain fragment (**11**) to 1α-hydroxyvitamin D C-22-aldehyde (**13**) was accomplished as in our previously reported synthesis of vitamin D side-chain anal-

† (2*S*)-Sulphoxide (**9**) $[\alpha]_D^{20}$ −153.5° (*c* 4, $CHCl_3$) and (2*R*)-sulphoxide (**19**) $[\alpha]_D^{20}$ −444.8° (*c* 4, $CHCl_3$). (2*S*)-Sulphone (**11**) $[\alpha_D^{20}$ = +17° (*c* 3.5, $CHCl_3$) and (2*R*)-sulphone (**12**) $[\lambda]_D^{20}$ −19° (*c* 1.4, $CHCl_3$).

ogues.[13] Condensation of aldehyde (**13**) with the deprotonated (2*S*)-*p*-tolylsulphone (**11**) provided (**14**) (60% yield), and after desulphonylation with Na–Hg in buffered tetrahydrofuran–methanol, the protected diol (**15**) (50% yield). Removal of the protecting groups by tetrabutylammonium fluoride in tetrahydrofuran gave (24*S*)-1α-hydroxyvitamin D_2 (**6**) (65% yield).

Not surprisingly, the new D_2 epimer (**6**) and the previously known 1α-hydroxyvitamin D_2 (**4**) have very similar chromatographic and spectral properties, but they are distinguishable by slight differences in chromatographic behaviour and the ^1H n.m.r. patterns. H.p.l.c. co-injection of (**6**) with authentic (**4**) separated the two compounds, with (**6**) eluting at 21, and (**4**) at 22 min (C_{18}-reverse phase, 4.6 × 25 cm column, MeCN/H_2O 85/15). The ^1H n.m.r. spectra (500 MHz) of (**4**) and (**6**) are nearly superimposable, except for a slight upfield shift of the resonances for the side-chain double bond protons in (**6**) compared to (**4**). For both compounds, the C-22,23 protons give rise to a seven-line multiplet, centred in the spectrum of (**4**) at δ 5.131, and of (**6**) at δ 5.113. Likewise, as expected, the mass spectra of (**4**) and (**6**) are essentially identical. In preliminary experiments, epimer (**6**), like the previously prepared 1α,25-dihydroxy-24-*epi*-vitamin D_2 (**5**), elicited an intestinal calcium transport response in vitamin D-deficient rats, but showed little, if any, bone mobilization activity; more extensive testing will be required to define the full activity profile of this analogue, and these results will be reported elsewhere.

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