A Practical Convergent Route to (23*S*,25*R*)-1α,25-Dihydroxyvitamin D_3 26,23-Lactone

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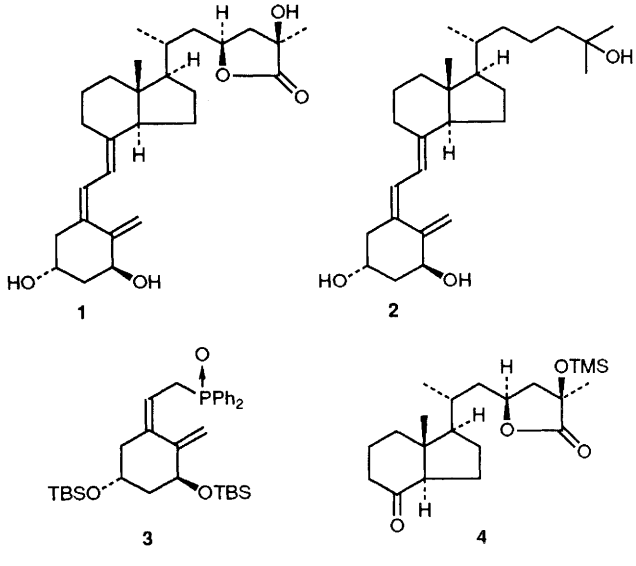
The Ireland–Claisen rearrangement of the lactate **8**, prepared from the Inhoffen–Lythgoe diol **5**, followed by iodolactonisation allowed easy access to the *C–D*-ring fragment **4**, from which a novel convergent synthesis of (23*S*,25*R*)-1α,25-dihydroxyvitamin D_3 26,23-lactone **1** has been accomplished *via* coupling with the *A*-ring fragment **3**.

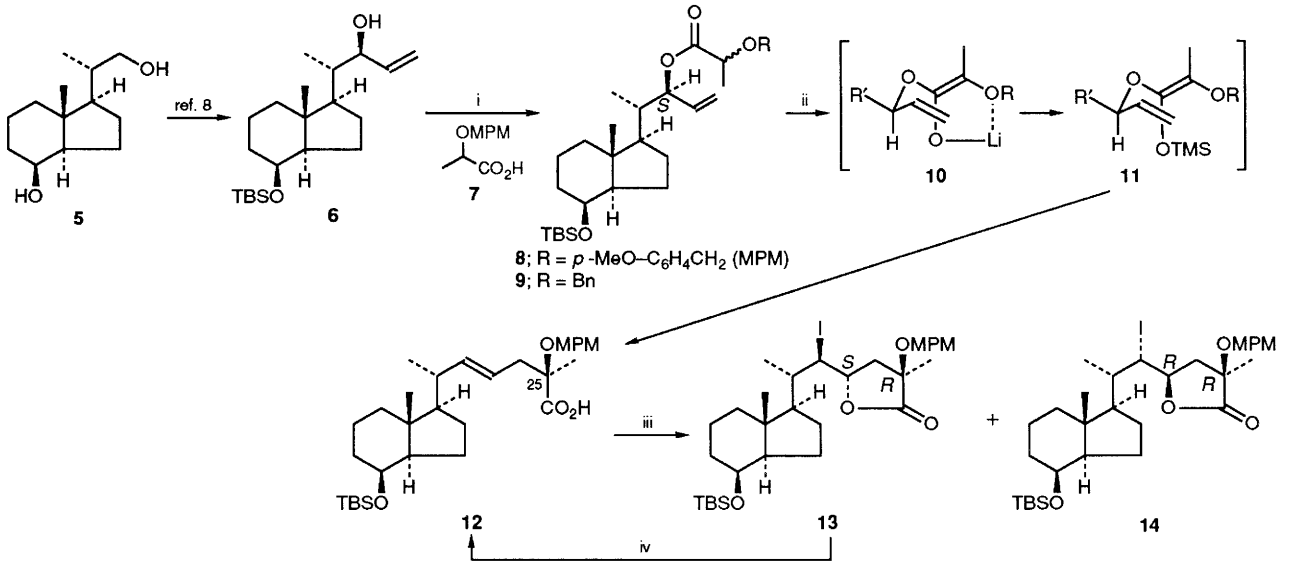
Of the active vitamin D_3 metabolites, (23*S*,25*R*)-1α,25-dihydroxyvitamin D_3 26,23-lactone **1** (calcitriol lactone),[1] a major metabolite of 1α,25-dihydroxyvitamin D_3 **2**,[2] has attracted considerable attention because of its unique biological activities. For example, this compound is known to exhibit inhibitory action on bone resorption induced by **2**[3] as well as stimulatory action on bone formation,[4] suggesting a potential utility for the treatment of bone disease such as osteoporosis. However, its biological function remains largely unclear mainly because access to sufficient amounts of **1** is not easy. Much effort,[5] therefore, has been devoted to developing an efficient method for the preparation of **1** to make biological evaluation possible. For the synthesis of **1**, we focused our attention on the *C–D*-ring fragment **4**, since the preparation of the *A*-ring fragment **3**[7] and the Lythgoe[6] type Wittig–Horner coupling of both fragments are already well established.[5a] We report here a new facile synthesis of the *C–D*-ring fragment **4** which translates the Roche's convergent route[5a] to **1** into a more practical process.

The known allyl alcohol **6**,[8] easily available from the Inhoffen–Lythgoe diol **5** (5 steps, 50% yield), was converted to the lactate **8**† in 93% yield by reaction with racemic 2-*p*-methoxybenzyloxypropionic acid **7**‡ using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho CDI) as a dehydrating agent.[9] Upon deprotonation of **8** with lithium diisopropylamide (LDA) followed by silylation, the Ireland–Claisen rearrangement[10,11] took place smoothly at room temperature to give the carboxylic acid **12** almost quantitatively. This transformation was shown to

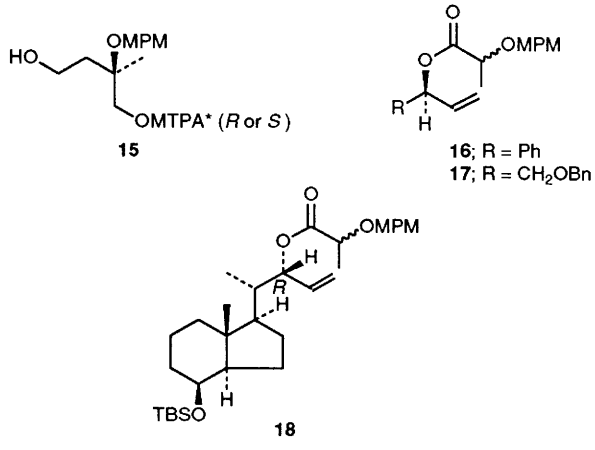


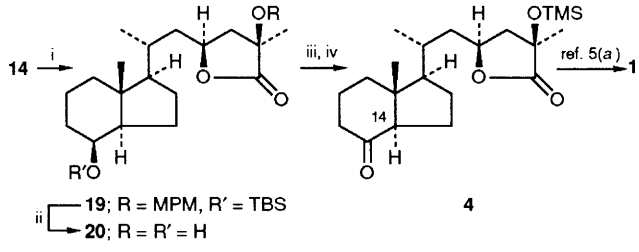
† All new isolated compounds exhibited satisfactory spectral (^{1}H NMR, IR, MS) and analytical data.

‡ Prepared from racemic ethyl lactate by *p*-methoxybenzylation (Ag_2O, MPMCl, Et_2O) followed by hydrolysis (NaOH, MeOH) and used without purification.



Scheme 1 *Reagents and conditions*: i, **7**, morpho CDI, 4 Å molecular sieves, CH_2Cl_2; ii, LDA, tetrahydrofuran (THF), −78 °C, then add TMSCl, −78 °C → room temp., iii, I_2, 2,4,6-collidine, MeCN, −30 °C; iv, Zn, MeOH, reflux (TBS = Bu^tMe_2Si; Bn = $PhCH_2$; TMS = Me_3Si)





Scheme 2 *Reagents and conditions*: i, Bu^n_3SnH, azoisobutyronitrile (AIBN) (catalyst), THF, reflux; ii, 46% HF, MeCN; iii, Pt (catalyst), O_2, sodium lauryl sulfate (catalyst), 1:1 diglyme–H_2O, 55 °C; iv, *N*-(trimethylsilyl)imidazole, CH_2Cl_2

proceed with 85% diastereoisomeric excess (d.e.) by ^1H NMR (500 MHz) analysis of the (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters **15**§ derived from **12**. Interestingly, the rearrangement of the benzyl ether **9** was found to proceed with rather poorer diastereoselectivity (70% d.e.), although the yield was almost quantitative. It is assumed that increase in Lewis basicity of the alkoxy group would result in higher diastereoselection due to the increasing preference for forming the *Z*-silyl ketene acetal **11** *via* the chelated lithium enolate **10**. For comparison with the results mentioned above, we also undertook the rearrangement of the lactates **16** and **17**. In both cases, the reaction turned out to be very sluggish at room temperature and the corresponding rearranged carboxylic acids were produced in less than 5% yield even after 2 days. These results suggest that the bulky hydrindan unit would cause a sufficiently close approach of the two double bonds for rearrangement to occur without heating for steric reasons. It is also interesting that the (22*R*)-lactate **18** was found to undergo facile rearrangement with the same degree of diastereoselectivity as observed for **8** giving rise to the C-25 epimer of **12** preferentially. This means that the chirality of the C-22 asymmetric centre including the hydrindan moiety exerts little influence on the diastereoselection.

The carboxylic acid **12** thus obtained was then subjected to iodolactonisation without purification. According to the method developed by Yamada and coworkers,[5d] the carboxylic acid **12** was treated with iodine in the presence of 2,4,6-collidine in acetonitrile at −30 °C¶ to give the (23*S*)-iodolactone **13**, m.p. 167–168 °C (EtOH), $[\alpha]_D^{29}$ + 12.6 (*c* 0.980, $CHCl_3$), the (23*R*)-iodolactone **14**, $[\alpha]_D^{29}$ + 47.5 (*c* 1.240, $CHCl_3$), and an unidentified iodolactone possibly derived from the (25*S*)-carboxylic acid, in a ratio of 23:70:7 in 93% yield from the lactate **8**.‖ After separation of these isomeric iodolactones by silica gel column chromatography, treatment of the undesired (23*S*)-lactone **13** with zinc in boiling methanol followed by iodolactonisation gave a 1:3.5 mixture of **13** and **14** in 78% yield, establishing a route for recycling **13**. As a result, the desired (23*R*)-iodolactone **14** was obtained from **8** in 78% overall yield through the Ireland–Claisen rearrangement, iodolactonisation, and one recycle of **13**.

Reduction of **14** with tri-n-butyltin hydride followed by simultaneous removal of both protecting groups of **19**, $[\alpha]_D^{29}$

§ Prepared by the following four-step sequence: (i) CH_2N_2, Et_2O, (ii) $LiAlH_4$, THF, (iii) (*R*)- or (*S*)-MTPACl, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, (iv) OsO_4 (catalyst)–$NaIO_4$, aq. THF, then $NaBH_4$.

¶ The diastereoselectivity turned out to be somewhat temperature dependent (*e.g.* 0 °C, **13**:**14** 1:2).

‖ The observed diastereoselectivity can be interpreted by the reaction mechanism postulated by Yamada and coworkers; see ref. 5(*d*). Note that iodolactonization of **12** under standard conditions (*e.g.* I_2, sat. $NaHCO_3$–THF or MeCN) resulted in poor diastereoselection (**13**:**14** 3:2).

+ 34.1 (*c* 0.690, $CHCl_3$), with aqueous hydrofluoric acid gave the diol **20**, m.p. 129–130 °C (benzene–hexane), $[\alpha]_D^{29}$ + 28.7 (*c* 0.985, $CHCl_3$), in 78% yield. The diol **20** was then converted to the ketone **4**, $[\alpha]_D^{29}$ −8.9 (*c* 1.165, $CHCl_3$), in 88% yield by oxidation[5c] using platinum black as a catalyst under oxygen and then silylation. It is noteworthy that PCC oxidation of **20** was always accompanied by epimerisation of the C-14 asymmetric centre, while the platinum catalysed oxidation did not cause any epimerisation at all.

From the *C–D*-ring fragment **4** thus obtained, the total synthesis of calcitriol lactone **1** was achieved by Wittig–Horner coupling with **3** followed by deprotection according to the Roche's procedure (90% yield).[5a] The synthetic **1**, $[\alpha]_D^{31}$ + 24.1 (*c* 1.480, EtOH) [lit[5a] +24.66 (*c* 0.73, EtOH)], exhibited spectral properties (^{1}H NMR, IR, MS, UV) in accord with those reported,[5a,d]

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References

1 N. Ohnuma, K. Bannai, H. Yamaguchi, Y. Hashimoto and A. W. Norman, *Arch. Biochem. Biophys.*, 1980, **204**, 387; Y. Tanaka, J. K. Wichmann, H. E. Paaren, H. K. Schnoes and H. F. DeLuca, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 6411.

2 S. Hatakeyama, K. Sugawara, H. Numata and S. Takano, *J. Org. Chem.*, 1991, **56**, 461, and references therein.

3 M. Kiyoki, N. Kurihara, S. Ishizuka, S. Ishii, Y. Hakeda, M. Kumegawa and A. W. Norman, *Biochem. Biophys. Res. Commun.*, 1985, **127**, 693.

4 S. Ishizuka, M. Kiyoki, N. Kurihara, Y. Hakeda, K. Ikeda, M. Kumegawa and A. W. Norman, *Mol. Cell. Endocrinol.*, 1988, **55**, 77.

5 (*a*) P. M. Wovkulich, E. G. Baggiolini, B. M. Hennessy, M. R. Uskokovic, E. Mayer and A. W. Norman, *J. Org. Chem.*, 1983, **48**, 4433; (*b*) S. Ishizuka, J. Oshida, H. Tsuruta and A. W. Norman, *Arch. Biochem. Biophys.*, 1985, **242**, 82; (*c*) W. S. Johnson and M. F. Chan, *J. Org. Chem.*, 1985, **50**, 2598; (*d*) K. Yamamoto, M. Shimizu, S. Yamada, S. Iwata and O. Hoshino, *J. Org. Chem.*, 1992, **57**, 33.

6 For a review, see: B. Lythgoe, *Chem. Soc. Rev.*, 1980, 449.

7 (*a*) E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1982, **104**, 2945; (*b*) S. Hatakeyama, H. Numata, K. Osanai and S. Takano, *J. Org. Chem.*, 1989, **54**, 3515; (*c*) S. Kobayashi, J. Shibata, M. Shimada and M. Ohno, *Tetrahedron Lett.*, 1990, **31**, 1577; (*d*) K. Nagasawa, Y. Zako, H. Ishihara and I. Shimizu, *Tetrahedron Lett.*, 1991, **32**, 4937.

8 P. M. Wovkulich, F. Barcelos, A. D. Batcho, J. F. Sereno, E. G. Baggiolini, B. M. Hennessy and M. R. Uskokovic, *Tetrahedron*, 1984, **40**, 2283.

9 *Cf.* B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.

10 R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.

11 For the Ireland–Claisen rearrangement of lactate derivatives, see: P. A. Bartlett, D. J. Tanzella and J. F. Barstow, *J. Org. Chem.*, 1982, **47**, 3941.