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A NOVEL STEREOSELECTIVE SYNTHESIS OF A CHIRAL KEY INTERMEDIATE FOR THE PREPARATION OF VITAMIN D_3

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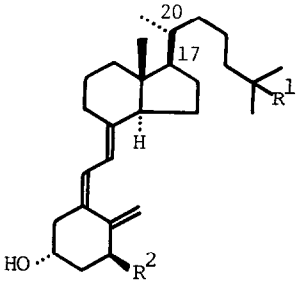
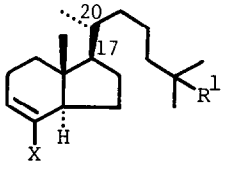
Summary: The cyclopentanone 3a, a key intermediate in the synthesis of vitamin D_3 and its metabolites, has been prepared in optical active form using (S)-γ-trityloxymethyl-γ-butyrolactone (6) as a chiral building block.

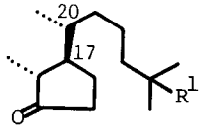
Because of the clinical importance of vitamin D_3 (1a) and its metabolites 1b, c, particularly 1,25-dihydroxyvitamin D_3 (1b), in the treatment of bone disease, the practical synthesis of these compounds has attracted great interest[1]. Vitamin D_3 (1a) and the metabolites 1b, c possess common C(17)-R and C(20)-R configurations of which assembly is one of the most crucial problems in construction of the C/D-ring fragment 2. Therefore, various imaginative methods for proper elaboration of these asymmetric centers have been explored so far[2]. For the purpose of attaining one solution to this problem, we chose the cyclopentanone 3 as a synthetic goal which appears to represent a useful precursor[3] for the synthesis of vitamin D_3 metabolites.



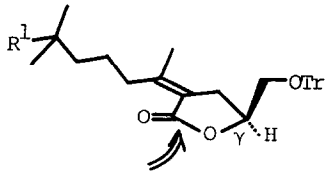
1 a) $R^1=R^2=H$
b) $R^1=R^2=OH$
c) $R^1=H$, $R^2=OH$



2 C/D-ring fragment
(X=OH, CHO, or p-$TsCH_2$
R^1=H or OH)



3 a) R^1=H
b) R^1=OH



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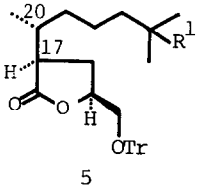

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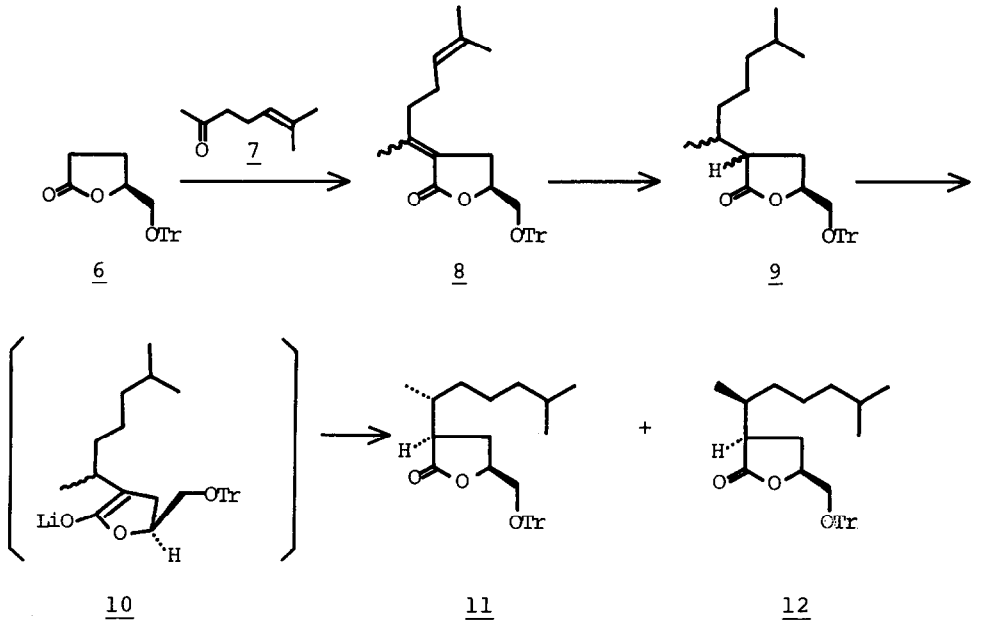
3

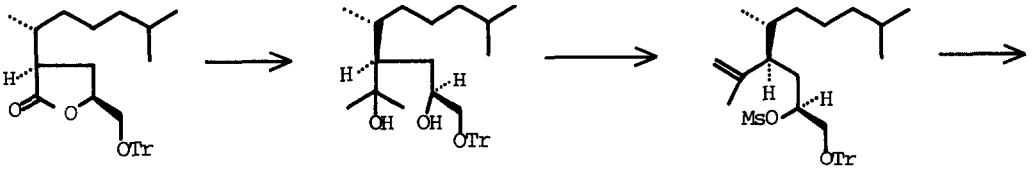
Tr=Ph_3C

Our synthetic plan centered around the chiral unsaturated lactone 4 in which the bulky trityloxymethyl group at γ-position should enable to introduce the chiralities of C(17) and C(20) at the same time through the established stereoselective hydrogenation[4]-kinetic protonation[5] sequence.

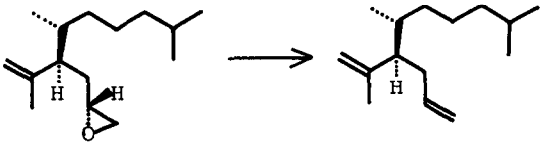
The (S)-γ-trityloxymethyl-γ-butyrolactone (6), prepared from L-glutamic acid[7], was subjected to aldol reaction with 2-methyl-2-heptene-6-one (7) in the presence of lithium diisopropylamide (THF, -78 °C), followed by dehydration with thionyl chloride (pyridine, 0 °C) giving rise to the unsaturated lactone 8[7] as a 3 : 1 isomeric mixture[8] in 99 % yield. Without separation, hydrogenation of 8 (H_2, PtO_2, EtOH, room temperature), followed by kinetic protonation of the lithium enolate 10 prepared from 9 (LDA, THF, -78°C then sat. Na_2SO_4, - 78 °C) allowed stereoselective construction of the required chiralities to give the desired lactone 11, $[\alpha]_D^{20}$ + 11.1° (c 1.24, $CHCl_3$) in 63 % overall yield from 8 along with 16 % yield of the isomeric lactone 12, $[\alpha]_D^{20}$ + 20.9° (c 1.22, $CHCl_3$)[9].



Having the key chiral lactone 11 in hand, conversion of 11 into the cyclopentanone 3a was then investigated. Treatment of 11 with methyllithium (THF-Et_2O, 0 °C) gave the diol 13, $[\alpha]_D^{20}$ + 3.8° (c 1.26, $CHCl_3$) in 62 % yield. The diol 13 was subjected to mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C) with simultaneous dehydration of the tertiary hydroxy moiety furnishing the mesylate 14[10], $[\alpha]_D^{20}$ + 40.3° (c 1.60, $CHCl_3$) in 73 % yield. After acidic methanolysis of 14 (conc. HCl, MeOH, room temperature), treatment with potassium carbonate gave the epoxide 15, $[\alpha]_D^{20}$ + 27.6° (c 1.41, $CHCl_3$), which was directly reduced using sodium iodide and zinc under buffered conditions[12] (AcONa, AcOH, 0 °C) to afford the diene 16, $[\alpha]_D^{20}$ + 14.7° (c 1.16, $CHCl_3$) in 67 % overall yield from 14.



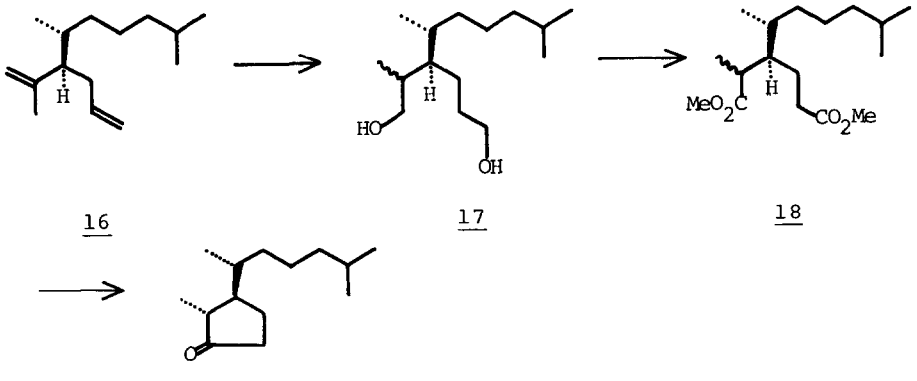
11 13 14



15 16

Hydroboration of 16 with dicyclohexylborane (THF, 0 °C), followed by oxidative work-up (H_2O_2, NaOH, room temperature) afforded the diol 17 as an inseparable epimeric mixture in 91 % yield. The diol 17 was successively subjected to Jones oxidation (acetone, 0 °C) and esterification (conc. H_2SO_4-MeOH, reflux) giving the diester 18 in 60 % yield. Finally, Dieckmann condensation (KH, THF, reflux), followed by decarbomethoxylation[13] (LiI·$2H_2O$, γ-collidine, 170 °C) furnished the cyclopentanone 3a, $[\alpha]_D^{20}$ - 48.7° (c 0.83, $CHCl_3$) (lit.[2a] - 43.6° (c 0.5, $CHCl_3$)), mp 167 °C (semicarbazone) (lit.[2a] 157 °C), in 83 % yield. The spectral data (^{13}C-NMR, IR) of 3a were identical with those reported[2a,14].

The study outlined above demonstrates an effective chiral route to side chain-construction of vitamin D_3 as well as various steroids[15] and the method developed is also applicable to the synthesis of required intermediates (i.e., 3b) for the derivatives of vitamin D_3 possessing modified side chains. Further synthetic studies to convert 3a into the C/D-ring fragment 2 are under investigation.



16 17 18

3a

References and Notes

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7. Satisfactory spectral (NMR, IR, MS) and analytical (high resolution MS) data were obtained for all new compounds.
8. The ratio was determined by HPLC (column LS-320K: Et_2O/hexane (1 : 12)). The major product was presumed to be the Z-isomer by comparison of two olefinic methyls located at δ 1.83 (ca. 2.3 H) and δ 2.35 (unclear) in its ^{1}H-NMR.
9. As a result, completion of the synthesis of 3a from 11 made the structure of 11 unambiguous. Concerning 12, this compound was assumed to be the epimer of 11 at C(20), because kinetic protonation of 12 did not bring about any significant change.
10. Reductive removal[11] of the mesylate moiety of 14 with lithium triethylborohydride (THF, reflux) was unsuccessful.
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14. Although the valid proof of the stereochemistry of the epimerizable α-position to the carbonyl group in 3a could not be obtained, we believe that our synthetic 3a would be the thermodynamically more stable trans-isomer because the existence of the corresponding cis-isomer was not recognized in its ^{13}C-NMR; ($CDCl_3$) ppm: 221.4 (s), 50.3 (d), 46.9 (d), 39.3 (t), 37.3 (t), 34.8 (d), 32.6 (t), 28.0 (d), 25.2 (t), 23.4 (t), 22.8 (q), 22.5 (q), 17.8 (q), 14.1 (q).
15. For a review on steroid side chain construction: M. D. Piatak and J. Wicha, Chem. Rev., 78, 199 (1978).

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