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CHIRAL RING A SYNTHONS FOR VITAMIN D SYNTHESIS

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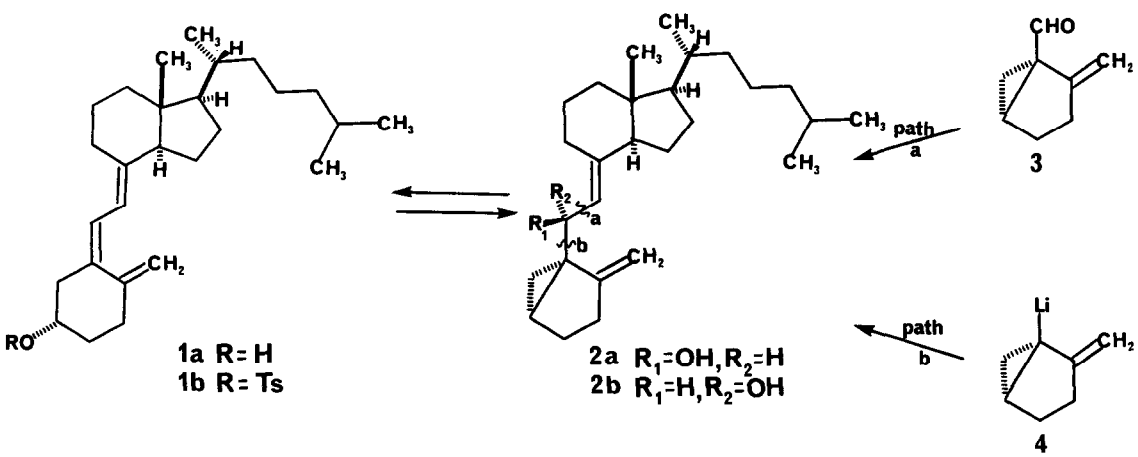
Summary - A unique approach to Vitamin D compounds via chiral bicyclo - [3.1.0]-hexane derivatives is described.

In the preceding paper,[1] we reported our total synthesis of Vitamin D_3. We communicate herein further details of our synthetic strategy for the construction of ring A.[2] In 1975 Mazur[3] reported the formation of cyclovitamin D_3 by the solvolysis of vitamin D_3 tosylate 1b. Of great interest was the observation that both epimers of C-6 alcohol 2a,b on solvolysis gave back only vitamin D_3 (i.e., with the Z-double bond and β-C-3 epimer.)

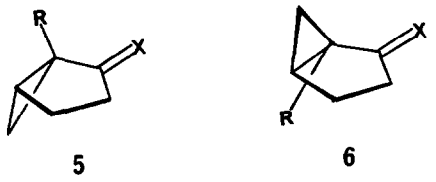


Such high stereoselection was rationalized in terms of the preferred formation of a single cyclopropylcarbinyl cation intermediate.

The implication for synthesis can clearly be seen, wherein, in a retrosynthetic sense, either path a or path b could be used for the attachment

of ring A to a fully elaborated steroid C/D ring system. Obviously, in either approach, the ring A synthon 3 or 4 must be available in chiral form. In this paper we report the successful implementation of both approaches which make available optically active synthons of the correct absolute configuration for steroid synthesis.

We begin the first approach with known[4] keto-esters, 5a and 6a. The

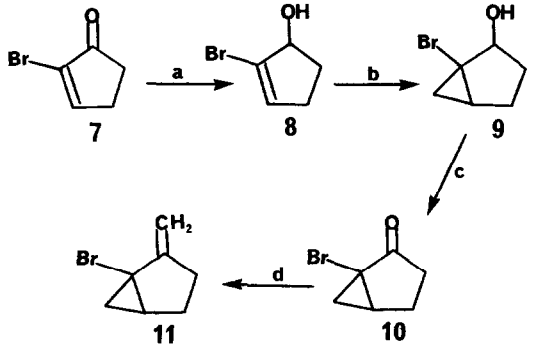


5 6

a R=CO_2menthyl, X= O
b R=CO_2menthyl, X= CH_2
c R=CH_2OH , X= CH_2

diastereomers 5a and 6a had previously been separated and the absolute configuration of each had been determined.[4] Thus 5a corresponds to the isomer of Rf^5 = 0.27 and possesses the natural steroid configuration and 6a corresponds to the isomer of Rf^5 = 0.23. Keto-ester 5a was converted to methylene derivative 5b by Wittig (72%) or Peterson olefination (49%). Reduction of 5b gave alcohol 5c ($[\alpha]_D$= -63°), and PCC oxidation produced 3 in 89% overall yield.

Scheme I shows the synthesis of the key intermediate for investigation of pathway b. The known[6] 2-bromocyclopentenone 7 was reduced with LAH/$AlCl_3$ 3:1

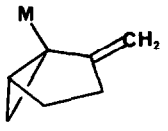


7 8 9 10 11

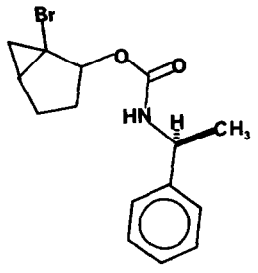
Scheme I

a. LAH, $AlCl_3$; 90%
b. Et_2Zn, CH_2I_2; 94%
c. PCC; 88%
d. $Ph_3P^+CH_3Br^-$, KOtBu, HOtBu, THF; 84%

to give 8. Cyclopropanation, oxidation (PCC) and methylenation produced bromide 11. Compound 11 readily formed the Grignard (Mg/ether) 12a or lithium reagent (t-butyl lithium) 4. Resolution was accomplished by



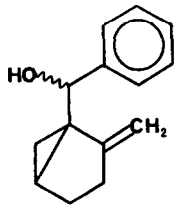
12 M=MgBr
4 M=Li



13a α-cyclopropane
13b β-cyclopropane

the formation of Pirkle carbamate derivatives[7] of 9 followed by chromatography (13a, Rf = 0.31 and 13b Rf = 0.29).[8] Both enantiomeric alcohols 9 were converted into reagent 12a by the reactions in Scheme I. Carboxylation of 12 followed by LAH reduction gave 6c ($[\alpha]_D = {}^{+}73^{o}$) starting from diastereomer 13b and 5c ($[\alpha]_D = -67^{o}$) the desired Ring A absolute configuration starting from diastereomer 13a.

When 3 is allowed to react with phenyl lithium, 14 is produced in 60% yield. Alternatively, if 12 reacts with benzaldehyde, the same alcohol 14 (mixture of epimers) is produced.



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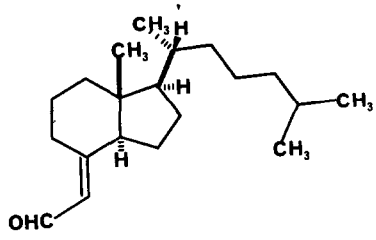
While extensive model studies (including 1-hydroxylated systems) will be reported in due course, reagent 4 has already figured prominently in our

asymmetric synthesis of vitamin D_3.[1] The known vitamin D_3 derived aldehyde 15 was reacted with 4 in THF to produce cyclovitamins 2a/2b. Solvolysis gave pure vitamin D_3 in 45% overall yield.



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References and Notes

1. S.R. Wilson and M.S. Haque, Tetrahedron Lett., 25, 3147 (1984).

2. A related strategy has recently been reported in this journal: H. Nemoto, X-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto and T. Kametani, Tet. Lett., 4257-4260 (1983).

3. (a) M. Sheves and Y. Mazur, J. Am. Chem. Soc., 97, 6240 (1975).
(b) M. Sheves and Y. Mazur, Tetrahedron Lett., 2987 (1976).

4. D.F. Taber, A. Saleh and W. Korsmeyer, J. Org. Chem., 45, 4699-4702 (1980).

5. Silica Gel (10% ethyl acetate/90% hexane).

6. S.J. Brana, A.B. Smith, III, J. Am. Chem. Soc., 100, 7767 (1978).

7. W.H. Pirkle, K.A. Simmons and C.W. Boeder, J. Org. Chem., 44, 4891 (1979).

8. Silica Gel (15% ethyl acetate/85% hexane).

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