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A New Synthetic Route to 1,25-Dihydroxy-vitamin D_3‡

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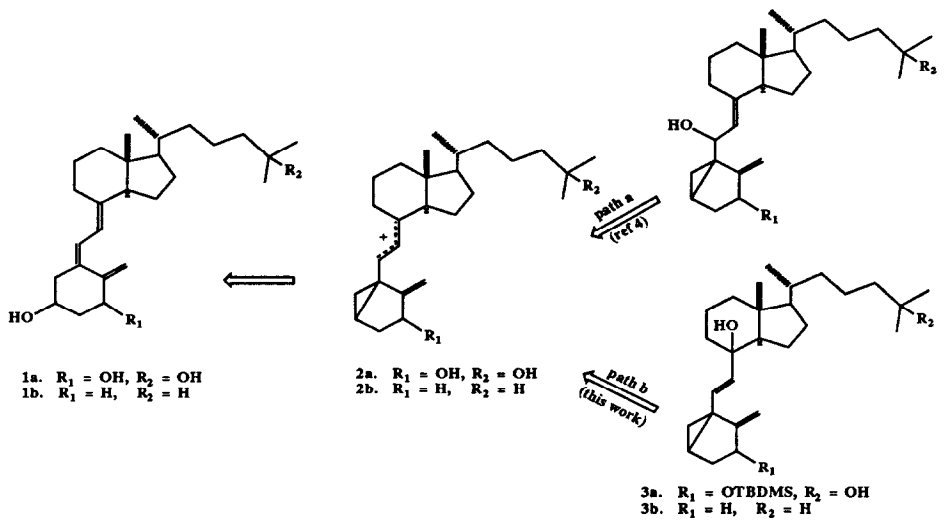
Summary: A synthesis of 1,25-dihydroxy-vitamin D_3 using a new acetylenic Ring-A precursor is described. Ring-A synthons **4a** or **4b** can be prepared in homochiral form by a diastereoselective diazoester cyclization.

The synthesis of calcitriol (the vitamin D calcium homeostasis hormone) **1a**[1a,b] has taken on renewed importance because of newly uncovered and extremely promising cell differentiation and anti-proliferative activities. For example, an important contemporary treatment[2] for psoriasis involves the topical application of **1a**. While hormonal doses require microgram amounts of **1a**, much greater quantities are needed to adequately provide for large scale external use. These new developments point to a need for more efficient syntheses.[3a,b]



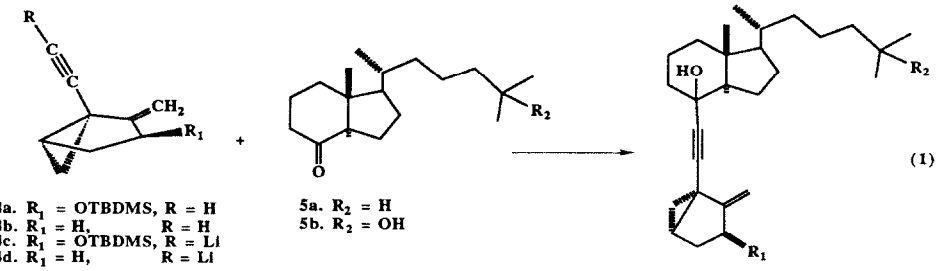
Scheme I

We have previously reported[4] a cyclopropyl carbinol solvolysis route (Scheme I, path a) to vitamin D_3, **1b**.

‡ Dedicated to the late Dr. Enrico G. Baggiolini of Hoffman La Roche.

Further development of this method has led to the synthesis of **1b** and the active form of the hormone, 1,25-dihydroxy-vitamin D_3, **1a**, via a more efficient alternative route (Scheme I,path b) involving the same allylic cation **2a,b**.

This construction involves as a key step addition of the lithio acetylene **4c** or **4d** to the readily accessible Grundmann ketones **5a** or **5b** which produces cyclopropylacetylenes **6a** or **6b** respectively (eq 1).



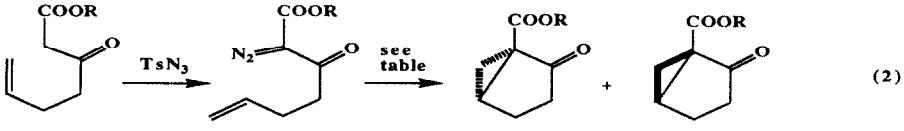
(1)

4a. R_1 = OTBDMS, R = H
4b. R_1 = H, R = H
4c. R_1 = OTBDMS, R = Li
4d. R_1 = H, R = Li

5a. R_2 = H
5b. R_2 = OH

6a. R_1 = OTBDMS, R_2 = OH
6b. R_1 = H, R_2 = H

The first challenge of our new approach was to develop a route to ring A precursors **4a** and **4b** in optically active form. Our earlier synthesis[4] began with menthyl ester **9a** which was converted to menthyl diazoester **8a**. Cyclization gave a 1:1 mixture of diastereomers **9a/10a** which could be separated by HPLC (eq 2). Compound **9a/10a** was obtained in this way in 63 % yield from **7a**, but the overall efficiency was limited by what was actually a rather difficult chromatographic separation[5] (Waters Prep-500 with recycle).



(2)

7a. R = menthyl
7b. R = NB

8a. R = menthyl
8b. R = NB

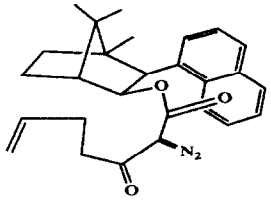
9a. R = menthyl
9b. R = NB

10a. R = menthyl
10b. R = NB

We now report a greatly improved process for stereoselective cyclization using a new chiral auxiliary 1(S)-3(S)-exo-hydroxy-2(S)-exo-naphthyl-bornane (NB).[6] Ester **8b**[7] can be cyclized selectively with several

Table I: Diastereoselectivity for Equation 2[8]

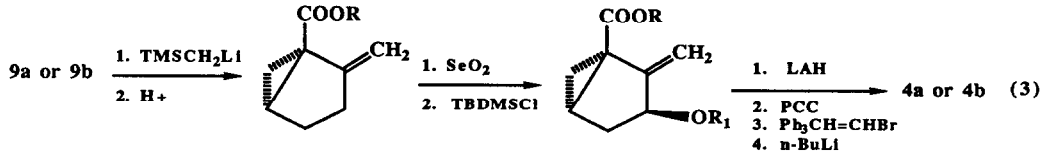
Substrate 8b



Catalyst (toluene reflux 1 hr)	Ratio 9b/10b	Yield (%)
Rh(III)TPPCl-H_2O (0.1%)	63 : 27	76
Rh(III)OEPCl-H_2O	80 : 20	58
Rh(III)TPPCl-H_2O (5%)	91 : 9	88

catalyst modifications. Conditions examined are reported in Table I, the best results leading to cyclization 91/9 in favor of desired isomer **9b**. While TLC separation of the NB series **9a/9b** is much easier than the corresponding menthyl analogs (ΔRf = 0.03 for **9a/10a** vs.ΔRf = 0.11 for **9b/10b**), more importantly pure **9b** can be obtained by crystallization.[9]

Introduction of a protected 1-alpha-hydroxy substituent into our ring A fragment is shown in equation 3.



11a. R = menthyl
11b. R = NB

12a. R = menthyl, R_1 = H
12b. R = menthyl, R_1 = OTBDMS

The exomethylene group may be introduced using either Wittig or Peterson olefination chemistry (87-92 %) to produce either **11a** or **11b**. Introduction of the 1-alpha-hydroxy substituent involves oxidation of **11a** with SeO_2, followed by TBDMS protection (60% overall). Conversion of **12a** to key acetylenic intermediate **4a** was accomplished using Ph_3P=CHBr (84%)[10] followed by treatment with n-butyllithium. In general, lithio intermediate **4d** was directly captured with Grundmann ketone **5a**[11] to produce acetylene **6a** in 56% yield. Coupling of 1-alpha-hydroxy intermediate **4c** with 25-hydroxy-Grundmann ketone **5b**[12] produces acetylene **6a** in 50% yield.[13] The reduction of acetylenes **6a** or **6b** to the corresponding allylic alcohols **3a**(89%) or **3b**(95%) can be accomplished using LAH modified with NaOMe.[14] These carbinols could be solvolysed to the triene systems using conditions previously described.[4] When **3b** was heated in 50% aqueous dioxane containing ~1% p-TsOH, vitamin D **1b** was formed in 43% yield. The product was an 8:2 mixture of *cis/trans* isomers about the 5,6-double bond. Similar reaction of 1-hydroxy analog **3a**, lead both to solvolysis and loss of the TBDMS protecting group resulting in the formation of 1,25-dihydroxy-vitamin D_3 **1a** in 64% yield. No trace of the undesired *trans* -isomer could be detected. Compound **1a** was directly compared (TLC, proton and ^{13}C NMR) to authentic material provided by Dr. E. Baggiolini of Hoffman La Roche.

In summary, we have reported herein a new method for the synthesis of vitamin D derivatives from the classic C/D fragments known as Grundmann ketones. This method has also been employed in the synthesis of rather divergent 1-alpha-hydroxy vitamin D analogs using other ketones.[15] Quite surprisingly, such compounds show biological activity[16] suggesting that vitamin D receptor subtypes may be specifically targeted.

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1a. "Vitamin D: Molecular, Cellular and Chemical Endocrinology," proceedings of the Seventh Workshop on Vitamin D, Rancho Mirage, CA, Norman, A. W., Schaefer, K., Grigoleit, H.,-G., Herrath, D. V., Eds, Walter de Gruyter, Berlin, 1988.

1b. For a comprehensive collection of reviews on vitamin D and its actions see: *Steroids* **49**, 1-123 (1987).

2. M. F. Holick, *Proc. Soc. Exp. Biol. Med.*, **191**, 246-257 (1989).

3a. For some recent synthetic approaches see G. H. Posner and C. M. Kinter, *J. Org. Chem.*, **55**, 3967-3969 (1990) and references cited therein.

3b. "Stereospecific Syntheses of Vitamin D", S. R. Wilson and A. Yasmin in *Studies in Natural Products Chemistry*, Atta Ur-Rahman, Ed., Elsevier Science Publishers, Amsterdam, in press.

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5. A. M. Venkatesan, Ph D. Thesis, New York University, 1987; C. E. Augelli-Szafran, Ph. D. Thesis, New York University, 1988.

6. Preparation of 1(S)-3(S)-exo-hydroxy-2(S)-exonaphthyl-bornane (NB) involves addition of 1-naphthyl magnesium bromide to (-)-camphor followed by dehydration, hydroboration and oxidation to the ketone (in 6 % overall yield). Reduction with LAH gave NB in 82% yield. NB is the enantiomer of an auxillary reported: D. F. Taber, J. C. Amedio, Jr., and K. Raman, *J. Org. Chem.*, **53**, 2968-2971 (1988).

7. Prepared in 96% yield by DMAP catalyzed ester interchange (refluxing toluene) with methyl 3-oxo-6-heptenonate.

8 The abbreviations TPP and OEP stand for tetraphenylporphrin and octaethylphorphyrin respectively.

9. Determination of diastereoselectivity and correlation of the menthyl and NB series involved LAH reduction of **11a** and **11b** to produce a chiral (non-racemic) alcohol previously reported.[4]

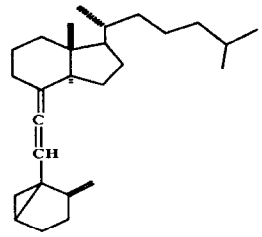
10. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769-3772 (1972)

11. B. Lythgoe, D. A. Roberts and I. Waterhouse, *J.C.S. Perkin I*, 2608-2612 (1977).

12. G. A. Leyes and W. H. Okamura, J. *J. Am. Chem.* Soc., **104**, 6099-6109 (1982).

13. Two equivalents of **4c** was employed in the reaction with **5b**. The resulting equivalent of acetylene **4a** could be isolated and reused.

14. Cf. E. J. Corey and W. T. Borden, *Tetrahedron Lett.*, 313-316 (1984). If LAH alone was used, acetylene **6b** was reduced to allene ***i***.[5]



i

15. S. R. Wilson, A. M. Venkatesan and C. E. Augelli-Szafran in reference 1a.

16. A. Kutner, K. L. Perlman, A. Lago, R. R. Sicinski, H. K. Schnoes and H. F. DeLuca, *J. Org. Chem.*, **53**, 3450-3457 (1988).

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