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# A Short, Efficient Route to 1-Hydroxylated Vitamin D Ring A Fragments

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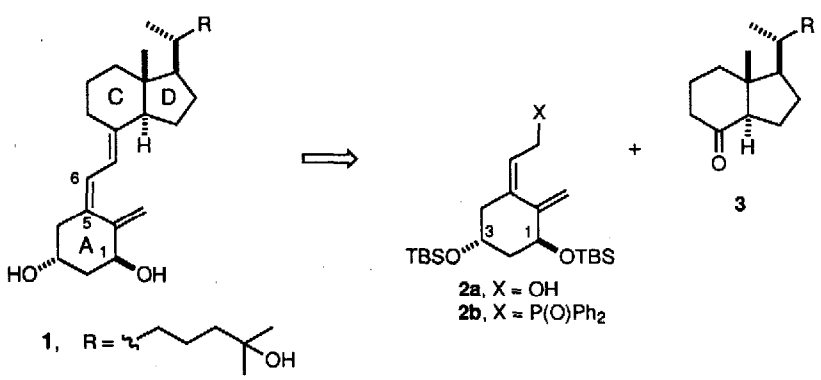
***Abstract:*** The *bis*-exocyclic conjugated diene system of vitamin D ring A synthons is efficiently constructed by means of a palladium-catalyzed intramolecular cyclization of the (*Z*)-iodoalkene resulting from the stereoselective hydrometallation-iodinolysis of propargylic alcohol **9**.

Current evidence suggests that 1α,25-dihydroxyvitamin $D_3$ (**1**), the hormonally active form of vitamin $D_3$, is not only involved in calcium homeostasis, but also plays a role in the modulation of a number of fundamental cellular processes.[1] In particular, it has been found that the hormone is a potent inhibitor of proliferation and inducer of differentiation of several malignant cells.[1,2] Unfortunately, the therapeutic utility of the hormone for the treatment of cancers and skin disorders is limited as a consequence of its calcemic effects. Therefore, much of current research in this area is focused on the design and synthesis of analogues that can induce selective or differential biological responses.[3]

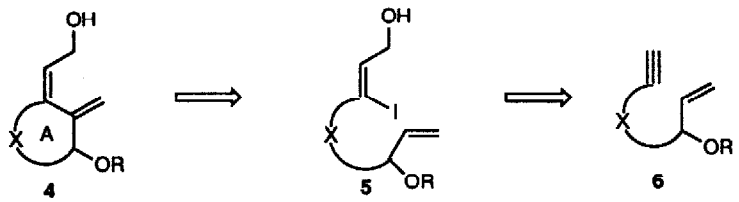
On the basis of Lythgoe's convergent approach to ~~accede to~~ the triene system of vitamins D (Scheme I),[4] Hoffman La Roche's group developed an elegant synthesis of hormone **1** using **2b** (readily prepared from dienol **2a**) as a convenient precursor of the ring A synthon.[5a] Since then, several alternative methods for the synthesis of **2a** from available chiral cyclohexanes have been devised.[5] Although these methods are highly efficient in controlling 1,3-diol stereochemistry, most of them suffer from three significant drawbacks: (1) a large number of steps and low overall yield; (2) inefficient control of the *Z*-stereochemistry of the 5,6-double bond; and (3) scant scope for obtaining modified ring A frameworks.




Scheme I

For preparing a wider variety of analogues of the hormone, a simpler and quicker route to **2a** and other ring A synthons is clearly needed.[6] We envisaged that the scant flexibility of the methods mentioned above might be overcome by using acyclic compounds as starting materials. While our research was in progress this belief was borne out by the report of a noteworthy synthesis of a racemic precursor of **2a** based on the palladium-catalyzed intramolecular cyclization of a vinyl bromide to an α,β-unsaturated ester.[7]

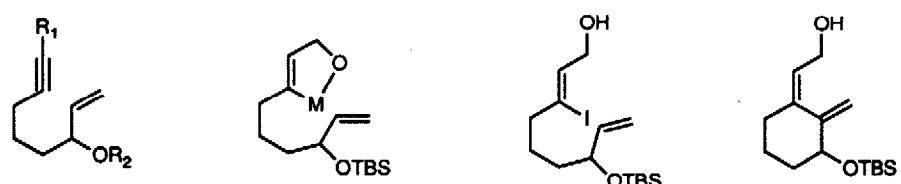
Our preliminary efforts in this matter have led to the development of a new, short entry to 1-hydroxylated vitamin D ring A synthons from acyclic enynes.[8] The key feature of the strategy is the formation of the exocyclic conjugated diene system through an intramolecular Heck cyclization of a (Z)-iodoalquene (**5**).




Scheme II

In this communication we describe the application of the strategy for the synthesis of the model dienol **12**.[9] Propargylic alcohol **9** was prepared in 4 steps from 5-hexyn-1-ol, as follows. The aldehyde obtained by PDC oxidation of 5-hexyn-1-ol was treated with vinyl magnesium bromide in THF to obtain the alcohol **7**, which was protected as its *t*-butyldimethylsilyl ether **8** (TBSCl, imidazole, DMF, 67 % overall yield from 5-hexyn-1-ol). This compound (**8**) was then treated with *n*-BuLi in THF at -78 °C, and the resulting acetylide was trapped with *p*-formaldehyde affording the propargylic alcohol **9** in 85 % yield.[10]

The transformation of **9** into the required (Z)-vinyl iodide was first carried out by Corey's reductive iodination method ($LiAlH_4$, NaOMe, $I_2$).[11] We subsequently found that Denmark's modification of this procedure was milder and more efficient.[12] Reaction of **9** at room temperature with Red-Al (1.5 equiv., 3.4 M solution in toluene) and subsequent addition of a solution of freshly sublimed $I_2$ in THF gave exclusively the (Z)-iodoalkene **11** in 84 % yield. Although the mechanism of this reaction is still unclear, it is assumed that its regio- and stereoselectivity are a consequence of the formation of a metallacycle intermediate such as **10**.[12]




**7**, $R_1 = R_2 = H$
**8**, $R_1 = H$, $R_2 = TBS$
**9**, $R_1 = CH_2OH$, $R_2 = TBS$

**10**, M = Al $(OCH_2CH_2OCH_3)_2$ **11** **12**

Iodoalkene **11** is satisfactorily cyclized to **12** in 73 % yield by treatment with 10 mol % of Pd $(OAc)_2$, 20 mol % of $PPh_3$ and 2 equiv. of $AgCO_3$ in $CH_3CN$ at room temperature for 3 days.[13] The reaction is faster when the mixture is refluxed (2 hours, 70 % yield). Interestingly, a cleaner, more efficient reaction occurred using 5 mol % of $Pd(PPh_3)_4$ as catalyst and $Et_3N$ (1 equiv.) as base (87 % isolated yield after refluxing for 1.5 h).[14] It is noteworthy that no byproducts derived from 7-*endo* cyclization or double bond isomerization were detected.[14]

The fact that the coupling reaction is so efficient and selective eventhough the double bond is not activated, is clearly due to the restricted conformational mobility resulting from its intramolecular nature. The (Z)-stereochemistry of compound **12** was confirmed by NOE $^1$H NMR spectroscopy and by comparison of its $^1$H NMR spectrum with that of the compound obtained by Hoffman La Roche's group.[9]

In summary, a short and versatile approach for regio- and stereoselective synthesis of *bis*-exocyclic conjugated dienes has been developed. It allows syntheses of ring A fragment precursors of hormone **1** that are simpler and more direct than related approaches previously reported which required the use of activated olefines for cyclization.[7a] In view of current progress in the control of acyclic stereochemistry, our approach should lead to the shortest known synthesis of **2a** and to the preparation of previously unaccessible ring A-modified derivatives of **1**. The results we obtain in pursuing these goals will be reported in due course.

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## References and Notes

1. (a) DeLuca H. F. *FASEB J.* **1988**, *2*, 224. (d) Minghetti, P. P.; Norman A. W. *FASEB J.* **1988**, *2*, 3043. (b) Reichel, H; Koeffler,H. P.; Norman, A.W. *New. Eng. J. of Med.* **1989**, *320*, 980. (c) DeLuca, H. F.; Burmester, J.; Darwish, H.; Krisinger, J. *Comprehensive Medicinal Chemistry*; Pergamon Press: New York, NY, **1990**, Vol. 3, 1129. (d) *Vitamin D: Gene Regulation, Structure Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R.; Thomasset, M. Eds.; Walter de Gruyter and Co: Berlin, **1991**.

2. (a) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Science (Washington, D.C.)* **1984**, *224*, 1438. (b) Suda, T. *Proc. Soc. Exp. Biol. Med.* **1989**, *191*, 215.

3. In recent years a broad range of 1-hydroxylated analogues of **1** have been prepared, some of which have only slight calcemic effects and have been shown to be promising drugs for treatment of psoriasis and certain of cancers: (a) Ikekawa, N. *Med. Chem. Rev.* **1987**, *7*, 333. (b) Abe, J. Morikawa, M.; Miyamoto, K.; Kaiho, S.; Fukushima, M.; Miyaura, C.; Abe, E.; Suda, T. Nishii, Y. *FEBS Lett.* **1987**, *226*, 58. (c) Ostrem, V. K.; Lau, W. F.; Lee, S .H.; Perlman, K.; Prahl, J.; Schnoes, H. K.; DeLuca, H. F. *J. Biol. Chem.* **1987**, *262*, 14164. (d) Shiuey, S. J., Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040. (e) Zhou, J.; Norman, A. W.; Lubbert, M.; Collins, E. D.; Uskokovic, M. R.; Koeffler, H. P. *Blood* **1989**, *74*, 82. (h) Perlman, R. R.; Sicinski, H. K.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823. (i) Figadere, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452. (j) Kissmeyer, A-M.; Binderup. L. *Biochem. Pharmacology* **1991**, *41*, 1601. (k) Zhou, J-Y; Norman, A. W.; Akashi, M.; Chen, D-L.; Uskokovic, M. R.; Aurrecoechea, J. M.; Dauben, W. H.; Okamura, W. H.; Koeffler, H. P. *Blood* **1991**, *78*, 75.

4. (a) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc. Perkin Trans. I* **1978**, 590. (b) Kociensky, P. J.; Lythgoe, B. *J. Chem. Soc. Perkin Trans. I* **1978**, 1290. (c) Lythgoe, B. *Chem. Soc. Rev.* **1981**, 449.

5. (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (b) Hatakeyama, S.; Numata, H.; Osanai, K.;Takano, S. *J. Org. Chem.* **1989**, *54*, 3515. (c)

Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577. (d) Posner, G. H.; Nelson, T. D. *J. Org. Chem.* **1991**, *56*, 4339. (e) Kiegiel, J.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057.

6. Although it is known that the dihydroxylated ring A is a crucial structural feature of the hormone, little research has been done on the effects of modifying the ring A skeleton on biological activity. However, several substituted ring A fragments have been synthesized. (a) For a review see ref 3a. (b) Okano, T.; Tsugawa, N; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 1444. (c) Miyamoto, K.; Kubodera, N.; Ochi, K; Matsunaga, I.; Muruyama, E. Eur. Pat. Appl. EP 184,206; *Chem. Abstr.* **1986**, *105*, 115290y. (d) De Costa, B. R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc. Chem. Commun.* **1989**, 325. (e) Nishii, Y, Abe, J.; Kobayashi, T.; Okano, T.; Tsugawa, N.; Slatopolsky, E.; Brown, A. J.; Dusso, A.; and Raisz, L. G. in *Vitamin D: Gene Regulation, Structure Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R; Thomasset, M. Eds.; Walter de Gruyter and Co: Berlin, **1991**, pp 289.

7. (a) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937. A radical approach that unfortunately does not ensure the Z-stereochemistry of the 5,6-double bond has also been reported: (b) Batty, D.; Crich, D.; Fortt, S. M. *J. Chem. Soc. Chem. Commun.* **1989**, 1366. (c) Batty, D.; Crich, D. *J. Chem. Soc. perkin Trans. I* **1991**, 2895.

8. Before submission of this paper an excellent new strategy for the synthesis of vitamin D systems from acyclic ring A precursors was reported: Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924.

9. Uskokovic, M. R.; Baggiolini, E.; Shiuey, S.-J.; Iacobelli, J; Hennessy, B. in *Vitamin D: Gene Regulation, Structure Function Analysis and Clinical Application*; Norman, A. W.; Bouillon, R; Thomasset, M. Eds.; Walter de Gruyter and Co: Berlin, **1991**, pp138.

10. All new compounds gave satisfactory $^{1}H$ and $^{13}C$ NMR and high resolution mass spectra.

11. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.

12. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

13. (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J Org. Chem.* **1987**, *52*, 4130. (b) Larock , R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

14. (a) Negishi, E-I; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (b) O'Connor, B.; Zhang, Y.; Negishi, E-I *Tetrahedron Lett.* **1988**, *29*, 3903.

15. The intramolecular cyclization of vinylhalides to unactivated olefins has only briefly been investigated in the past, and it is usually accompanied by the formation of isomeric mixtures: Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1073.

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