An Approach to the A Ring of Vitamin D *via* Sequential Carbometalation/Anion Capture

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Summary: An intramolecular palladium catalyzed carbometalation followed by anion capture achieves construction of model comprising the A ring of vitamin D. The synthesis of appropriate bromoenyne (10) for successful implementation of strategy is also described.

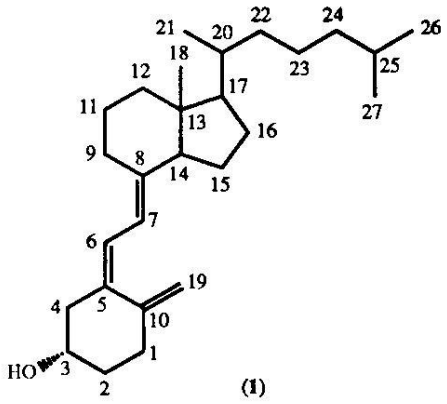
Introduction

Because of the highly interesting structure and important therapeutic value, considerable attention has been focussed on the chemistry of vitamin D (1) [1-14].

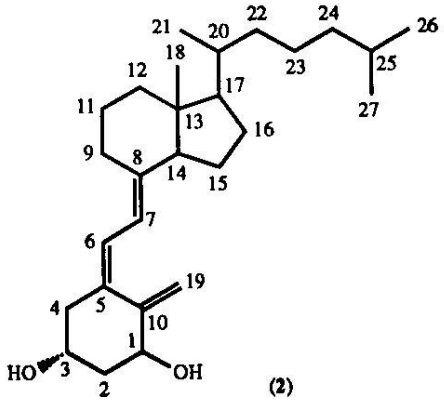
It has been shown that the primary requirement for activity in vitamin D analogues is the presence of 1α-hydroxy group [15]; synthetic 1α-hydroxy cholecalciferol (2) [16] is now being used in the clinical treatment of nephritic bone disease in humans [17]. These facts have made vitamin D an attractive target for the both total synthesis and for the design of analogues which mimic its considerable biological activity. Much attention has been directed towards the synthesis and reactivity of the A ring having diene system of vitamin D [18]. The numbering system is according to the reference [19].

Many efforts have been devoted for preparation of a variety of cyclic compounds making use of Pd-catalyzed intramolecular functionalization of olefins and acetylenes [20-26].

We have recently described the use of Pd-salt for implementation of sequential carbometalation anion capture [27]. Because of pharmacological importance of vitamin D, we wish to report a new approach to achieve construction of the A ring of vitamin D.



(1)



(2)

Results and Discussion

Condensation of *tert*-Butyl acetate (3) with 2,3-dibromopropene (4) in the presence of LDA afforded the *t*-Butyl-3-bromo-3-pentenoate (5). The latter was reduced with lithium aluminium hydride to give the corresponding alcohol (6). Partial oxidation of (6) led to the corresponding aldehyde (7) by using pyridinium chlorochromate in CH_2Cl_2. The latter was reacted with propargyl magnesium bromide (8) to obtain the corresponding alcohol (9). The latter was reacted with *tert*-butyl-di-methylsilyl chloride

(TBDMSCl) in the presence of imidazole to afford the corresponding silylether (10). The total synthesis of substrate (10) is depicted in Scheme-1.

Reaction of bromoenyne (10) with two or three equivalent of alkyl stannane (11) in the presence of a catalytic amount of Pd $(PPh_3)_4$ (10 mol %) [27] resulted in complete conversion of (10) to a single major product to which structure (12) was assigned from spectroscopic data (Scheme-2).

It means this reaction has led in a single operation to the construction of the C5-C10 and C6-C7 bonds (see formulae 1 and 2) with complete control of the C5-C6 exocyclic geometry based on the literature precedent for *syn* carbometalation of alkynes [28-33].

Experimental

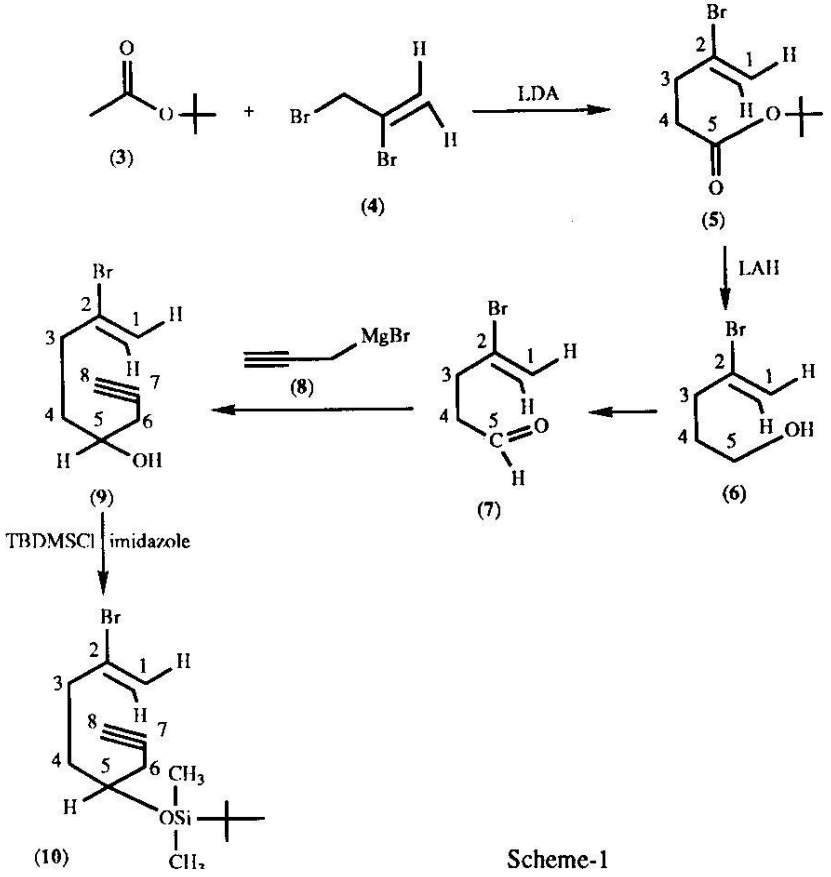
General aspects

The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a 300 MHz QE-300 spectrometer with $CDCl_3$. Aldrich 99% D and internal standard (unless otherwise indicated). The chemical shifts are given in δ values. The ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra were obtained on a 75.5 MHz QE 300 with deuterochloroform and internal standard. The chemical shifts are given in δ values. Mass spectra were obtained on a VG-7070 at 70 eV unless otherwise noted.

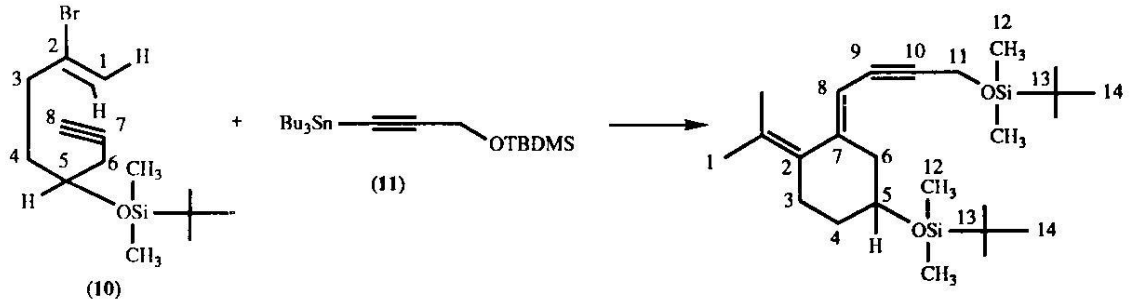
All experiments involving air and/or moisture sensitive materials were carried out under an inert atmosphere of nitrogen which was dried prior to use by passage through a column of KOH layered with $CaSO_4$. THF, Et_2O were distilled over sodium and benzophenone. Flash chromatography was performed using silica gel (Sigma 230-400 mesh).

tert-Butyl-3-bromo-3-pentenoate (5)

A mixture of diisopropylamine (13.29 ml, 0.103 mol) (distilled from CaH_2) and dry THF (100 ml) was cooled to -78°C. To this solution under N_2, 2.37 M *n*-BuLi (43 ml, 0.103 mole) was added dropwsie. This nearly colorless solution was stirred



Scheme-1



Scheme-2

for 30 min then *tert*-Butylacetate (11.6 ml, 0.086 mol) was added and the reaction mixture was stirred for further 30 min. followed by addition of 2,3-dibromopropene (20.49 g. 0.103 mol) *via* a 20 gauge cannula. The reaction mixture was kept stirring at -78°C for 1 h and then quenched by the slow addition of a saturated solution of ammonium chloride. The product was extracted with ether, the ethereal layer washed with brine and water, dried and freed of solvent. The residue was subjected to column chromatography over silica gel using 20:1 pet ether:ether to afford the title compound (yield 6.3 g, 31%) ^{1}H-NMR ($CDCl_3$) δ 1.1 (s, 9H, 7-H_9) 2.45 (t, 2H, 3-H_2) 3.7 (t, 2H, 4-H_2) 5.4 (d, 1H, 1-H), 5.6 (d, 1H, 1-H); Mass spectrum M^+, m/z 234.

4-Bromo-4-penten-1-ol (6)

The compound (5) (2.60 g; 0.11 mol) was dissolved in THF (40 ml) at °C; a solution of 1M $LiAlH_4$ (27 ml) was added dropwise. The reaction mixture was quenched with the addition of dilute hydrochloric acid (5%). The product was extracted with ether, dried and evaporated to dryness. The residue was column chromatographed over silica gel by using 4:1 pet ether:ether to yield the tilte compound (yield 980 mg, 54%) ^{1}H-NMR ($CDCl_3$) δ 1.65 (s, 1H, 5-OH), 1.8 (m, 2H, 4-H_2), 3.6 (t, 2H, 3-H_2), 3.7 (t, 2H, 5-H_2), 5.4 (d, 1H, 1-H), 5.6 (d, 1H, 1-H); (mass spectrum) M^+, m/z 164.

3-Bromo-3-pentenal (7)

The compound (6) (500 mg, 3 mmol) was dissolved in CH_2Cl_2 (15 ml) and pyridinium chlorochromate was added at room temperature, and stirred for 2 h. The reaction mixture was filtered through SiO_2. The solvent was evaporated under reduced pressure to afford the title compound (yield, 400 mg, 81%) ^{1}H-NMR ($CDCl_3$) δ 2.6 (t, 2H, 3-H_2), 2.8 (t, 2H, 4-H_2), 5.4 (d, 1H, 1-H), 5.65 (d, 1H, 1-H), 9.8 (s, 1H, 5-H); (mass spectrum) M^+, m/z 162.

7-Bromo-7-ene-1-octyn-4-ol (9)

Magnesium (120 mg) and mercuric chloride (2 mg) were suspended in dry ether (10 ml). To this mix -ture propargyl bromide (8) (385 mg) was added. The reaction mixture was sitrred at room temperature for 1 h and then the temperature was decreased to -78°C. At this temperature a solution of aldehyde (7) (250 mg) in ether, was added. After 10 min the reaction was quenched by slow addition of saturated solution of ammonium chloride. The product was extracted with ether, dried and evaporated off. The residue was subjected to column chromatography over silica gel using 9:1 pet ether: ether to afford the title compound (yield 200 mg, 64%), ^{1}H-NMR ($CDCl_3$) δ 1.3 (s, 1H, 5-OH) 2.1 (s, 1H, 8-H), 2.4 (m, 4H, 4-H_2 and 6-H_2) 2.6 (t, 2H, 3-H_2), 3.8 (m, 1H, 5-H), 5.4 (d, 1H, 1-H) 5.6 (d, 1H, 1-H); (mass spectrum), M^+, m/z 202.

[(2-Bromo-5-penten-1-yl)-(4-butyn-1-yl)]-tert-butyl dimethylsilyl ether (10)

The compound (9) (200 mg, 1.97 mol), TBDMSCI (300 mg, 3.94 m mol) and imidazole (201 mg; 5.91 m mol) were dissolved in DMF (6 ml) and stirred at room temperature for 2h. DMF was washed off with water and the product was extracted with a mixture of pet ether:ether (80:20). The crude was flash chromatographed over silica gel to afford the title compound (yield 175 mg; 55%) ^{1}H-NMR ($CDCl_3$) δ 0.18 (s, 6H, 9H_6) 0.8 (s, 9H, 11-H_9) 2.1 (s, 1H, 8-H), 2.4 (m, 4H, 4-H_2 and 6-H_2), 2.6 (t, 2H, 3-H_2), 3.8 (m, 1H, 5-H), 5.4 (1H, 1-H) 5.6 (d, 1H, 1-H).

tert-Butyldimethylsilyl-4(3')Z-[(1-tert-butyldimethyl silyl- 4-en-3-cyclohexylidinyl ether]-butyn-2-yl ether (12)

A solution of (10) (100 mg, 0.31 mmol) dissolved in THF (2 ml) was added to tetrakis (triphenylphosphine) palladium (O) (0.031 mmol) followed by (11) (526 mg, 1.15 mmol) in THF (1 ml). The resulting solution was heated to 40°C for 12 h. The solution was directly chromatographed on SiO_2 using 20:1, petroleum ehter: ether to afford the title compound, (yield 55 mg, ^{1}H-NMR ($CDCl_3$) δ 0.1 (s, 12H, 12-H_{12}) 0.9 (s, 18H, 14-H_{18}), 1.2 1.4 (m, 4H, 4-H_2 and 6-H_2), 1.6 (t, 2H, 3-H_2), 3.5 (m, 1H, 5-H), 4.65 (s, 2H, 11-H_2) 6.9 (s, 1H, 8-H) 7.1 and 7.2 (2-d, 2H, 1-H_2). ^{13}C-NMR (75 MHz $CDCl_3$) 145 C_9, 136.62 C_{10}, 1135.86 C_7, 128.29 C_2, 126.88 C_1, 123.4 C_8, 68.45 C_5, 39.56 C_4, 28.22 C_3, 26.75 C_6, 25.89 C_{11}, 25.62 C_{14}, 3.62 C_{12}, -4.64 C_{13}; (mass spectrum) M^+ m/z 406.

References

1. H. F. Deluca, *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, **33**, 2211 (1974).
2. R. M. Wing, W. H. Okamura, M. R. Pirio, S. M. Sine and A. W. Norman, *Science*, **189**, 939 (1974).
3. D. E. M. Lawson, D. R. Fraser, E. Kodicek, H. R. Morris and D. H. Williams, *Nature* (London), **230**, 228 (1971).
4. H. F. Delucas and H. K. Schnoes, *Ann. Rev. Biochem.*, **45**, 631 (1976); J. K. Wichmann, H. F. Deluca, H. K. Schones, R. L. Horst, R. M. Shepard and N. A. Jorgensen, *Biochemistry*, **18**, 4775 (1979).
5. B. Lythgoe, *Chem. Soc. Rev.*, **9**, 449 (1980).
6. M. Sheves and Y. Mazur, *J. Am. Chem. Soc.*, **97**, 6249 (1975).
7. M. Scheves and Y. Mazur, *J. Chem. Soc. Comm.*, **21**, (1977).
8. M. Scheves and Y. Mazur, *Tetrahedron Lett.*, 2987 (1976).
9. M. Scheves, B. Sialom and Y. Mazur, *J. Chem. Soc. Comm.*, 554 (1978).
10. M. L. Hommond, A. Mourino and W. H. Okamura, *J. Am. Chem. Soc.*, **100**, 4907 (1978).
11. D. J. Aberhart, J. Y. R. Chu and A. C. T. Hsu, *J. Org. Chem.*, **41**, 1067 (1976).
12. J. K. Wichmann, H. E. Paaren, M. A. Fivizzani, H. K. Schnoes and H. F. Deluca, *Tetrahedron Lett.*, **21**, 4667 (1980).
13. R. Malatesta, C. Willis and P. A. Hackett, *J. Am. Chem. Soc.*, **103**, 6781 (1981).
14. H. Nemoto, X. Mungwu, H. Kurobe, M. I har and K. Fukumoto, *Tetrahedron Lett.*, **24**, 4257 (1983).
15. W. H. Okamura, M. N. Metra, D. A. Proesal and A. W. Norman *Biochem. Biophys. Res. Commun.*, **65**, 24 (1975).
16. K. Mingwu, M. M. Midland and W. H. Okamura, **55**, 4381 (1990) and reference cited.
17. W. Norman, K. Schaefer, H. G. Grigoleit, D. Von Herrath and E. Ritz, Vitamin D and problems related to uremic bone disease. Walter de Gruyter New York (1975).
18. H. Nemoto, K. Suzuki, M. Tsubuki, K. Minemura, K. Fukumoto, T. Kametani and H. Furuy, *Tetrahedron*, **39**, 1123 (1983).
19. E. G. Baggiolini, J. A. Lacobelli, B. M. Hennessy A. D. Batcho, J. F. Sireno and M. R. ushokovic, *J. Org. Chem.*, **51**, 3098 (1986).
20. L. S. Hegedus, P. O. Winton and S. J. Varaprath, *J. Org. Chem.*, **46**, 2215 (1981) some other examples are listed therein.
21. K. Utimoto, H. Miwa and H. Nozaki, *Tetrahedron Lett.*, **22**, 4277 (1981).
22. J. R. Norton, K. E. Shenton and J. Schwartz, *Tetrahedron Lett.*, **51**, (1975).
23. T. F. Murray and J. R. Norton, *J. Am. Chem. Soc.*, **101**, 4107 (1979).
24. T. F. Murray, E. G. Samsel, V. Varma and J. R. Norton, *J. Am. Chem. Soc.*, **103**, 7525 (1981).
25. R. C. Larock, N. Berios-Pena and K. Norayaman, *J. Org. Chem.*, **55**, 3447 (1990).
26. M. M. Heravi and M. Bakavoli, *Heterocycles* (submitted).
27. J. M. Nuss, B. H. Levine, R. A. Rennels and M. M. Heravi, *Tetrahedron Lett.*, 5243 (1991).
28. F. T. Luo, F. L. Chou and R. T. Wang, *J. Org. Chem.*, **55**, 4846 (1990).
29. B. Burns, R. Grigg, D. Ratanannukul, V. Sridhawan, P. Steveneson and J. Wurakum, *Tetrahedron Lett.*, 4329 (1988).
30. R. Grigg, S. Sukirthalingam and V. Sridharan, *Tetrahedron Lett.*, 2545 (1991) and references therein.
31. J. K. Stile, *Angew Chem. Int. Ed. Engl.*, **25**, 508 (1986).
32. J. M. Huggins and R. G. Bergman, *J. Am. Chem. Soc.*, **101**, 4410 (1979).
33. A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron*, **41**, 5121 (1985).