Vol.4 No.3
Summer 1993

AN APPROACH TO THE A RING OF VITAMIN D ANALOGUES VIA SEQUENTIAL CARBOMETALATION/ ANION CAPTURE

M.M. Heravi[1] and J.M. Nuss[2]

[1]*Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Islamic Republic of Iran*
[2]*Department of Chemistry, University of California, Riverside CA 9252*

Abstract

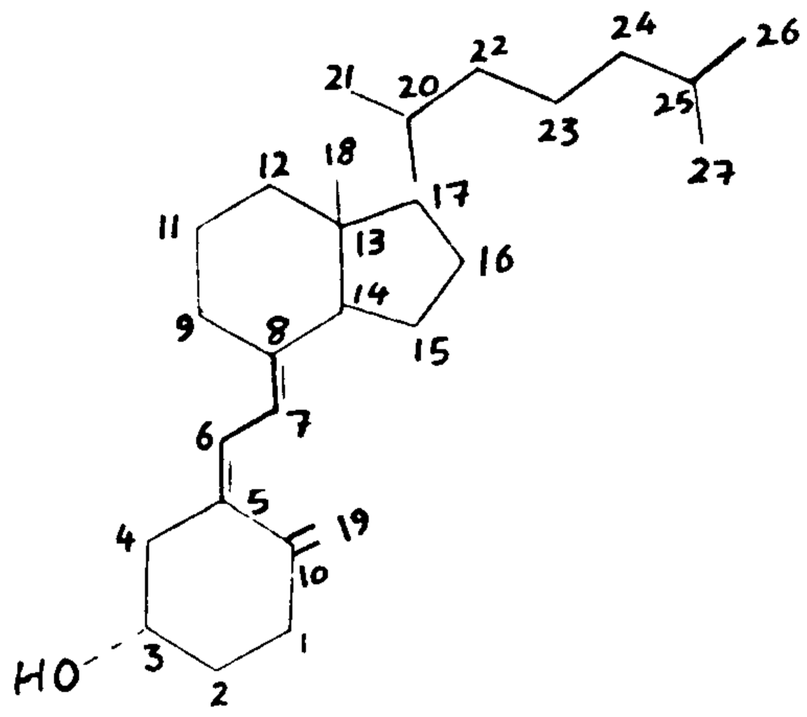
An intramolecular palladium catalysed carbometalation followed by anion capture achieves construction of a model comprised of the A ring of Vitamin D oxygen analogues.

Introduction

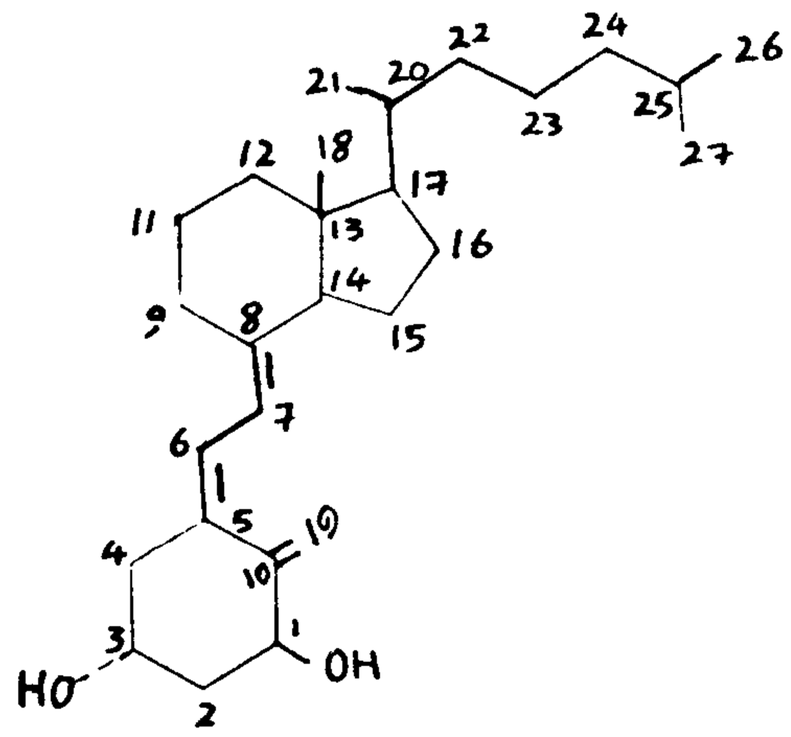
Because of its highly interesting structure and important therapeutic value, considerable attention has been directed toward the chemistry of Vitamin D(1) causing the discovery of highly biologically active vitamin D derivative [1-4] and increased activity in its synthetic chemistry [5-14].

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

Now we wish to report a new approach to achieve construction of the oxygen analogue of the A ring.



(1)



(2)

Keywords: A ring of vitamin D; Carbometalation/ Anion capture

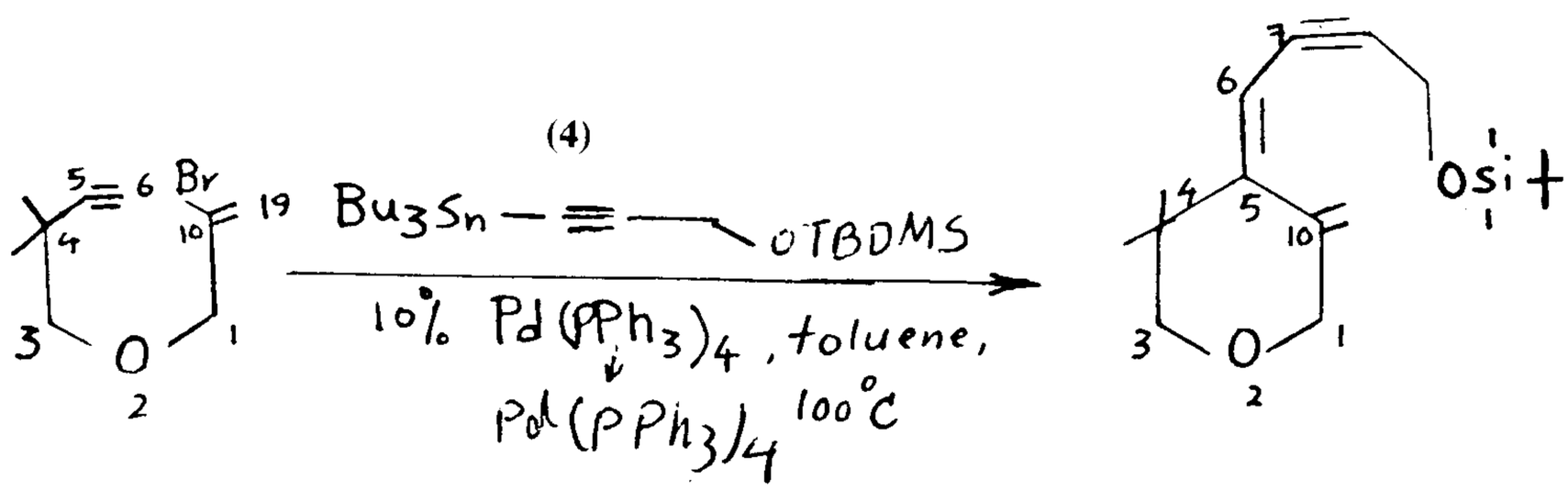
Results and Discussion

The strategy is described in Scheme I. This strategy can easily access structurally modified for the A ring of the oxygen analogues of vitamin D. The plan involved utilizing an intramolecular carbometalation to form the bond between C_5 and C_{10} . This was immediately followed by the intramolecular capture of the resultant (z) organometallic by an alkyne tin from the C_6[20-23].

Reaction of bromoeneyne (**3**) with two or three equivalents of alkynyl stannane (**4**) in the presence of a catalytic amount of pd $(pph_3)_4$ (10mol%) results in the complete conversion of (**3**) to a single product assigned from spectroscopic data as the desired cyclization product (**5**). Capillary gas chromatographic examination of the crude reaction mixture reveals (**5**) and n-Bu_3SnBr as the only volatile product. It means this reaction has led in a single operation to the construction of the C_5-C_{10} and C_6-C_7 bonds with complete control of the C_5-C_6 exocyclic geometry based on the literature precedent for syn carbometalation of al-kynes [20-25].

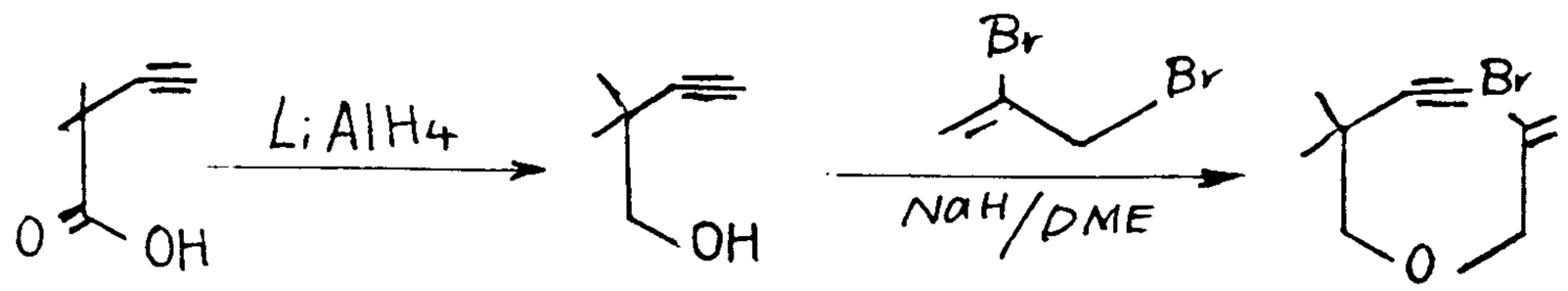
The requisite substrate (3) was synthesized from the reaction of 3,3-Dimethyl-3-butyn-1- o1 (6) with 2,3-dibromopropene in the presence of NaH in DME. The alcohol (6) was prepared by the reduction of known corresponding acid (7) [26] with $LiAlH_4$(Scheme 2).

The compound (**4**) was prepared from propargyl alcohol in two steps. The latter was first protected with TBDMSC1 to afford (**8**) and then the protected alcohol (8) was reacted with tributyl tin chloride in the presence of n-BuLi in THF to give (4) (Scheme 3).



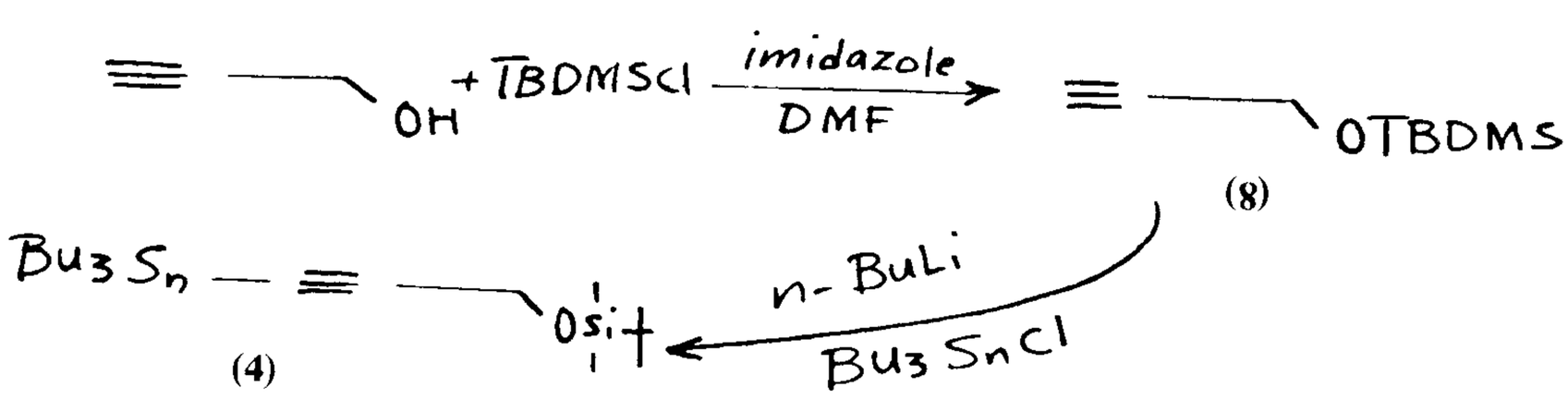
(3) (5)

Scheme 1



(7) (6) (3)

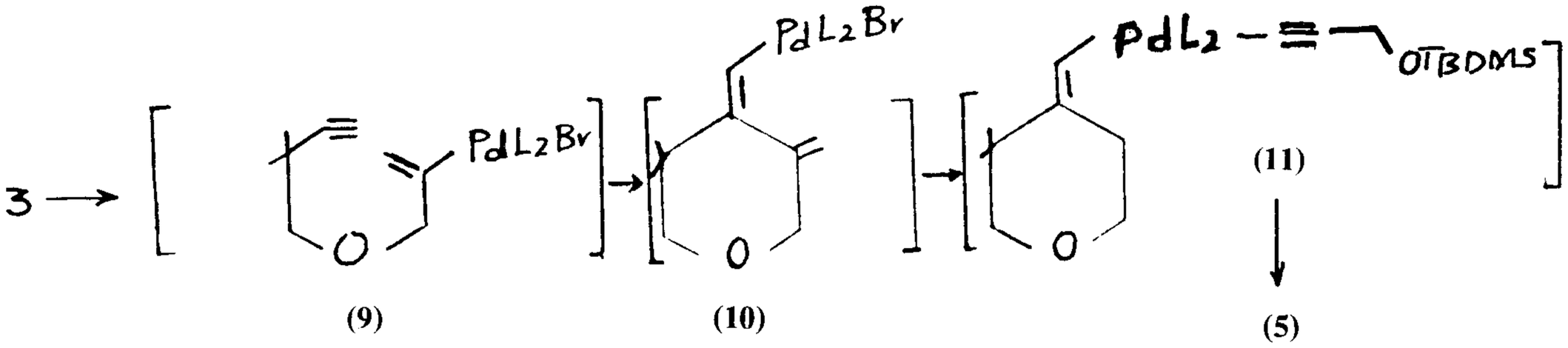
Scheme 2



(8) (4)

Scheme 3

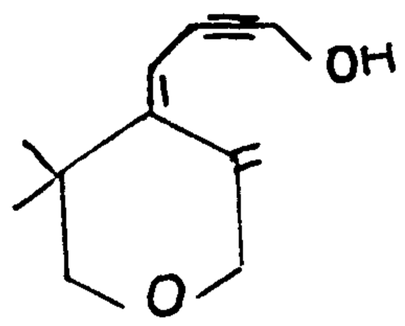
It is presumed (Scheme 4) that the reaction proceeds by initial oxidation addition of palladium (0) to the C-Br bond to afford (**9**). Complexation to alkyne and migratory insertion proceeding in a syn fashion then to give a second vinyl palladium species (**10**) having the correct C_5-C_6 olefin geometry. The highly effective concentration of the alkyne proximal to the metalcarbon bond in (**9**) has made intramolecular carbometalation favored compared to the intermolecular capture of (**9**) by (**4**) (Stille type coupling) [23]. This phenomenon has been noted previously [20-22]. Transmetalation of (**10**) with the alkynyl tin (**4**) provides (**11**), reductive elimination affords (**5**) and regenerated palladium (0) [23].



(**9**) (**10**) (**11**) (**5**)

Scheme 4

The compound (**5**) was deprotected by using HF in acetonitrile to afford the corresponding alcohol (**12**).



(**12**)

Further studies now in progress are aimed at using the appropriate bromoeneyne, to perform an intramolecular carbometalation/ capture sequence.

Experimental Section

The ^1H nuclear magnetic resonance spectra were recorded at 300 MHZ with deuteriochloroform ($CDCl_3$, Aldrich 99.8%D) as solvent and internal standard (unless otherwise indicated). Mass spectra (MS) were obtained at an electron ionization voltage of 20 ev unless otherwise noted. Flash column chromatography, using nitrogen, was performed on silicagel. Anhydrous sodium sulphate was used for drying solution.

2,2-Dimethyl-3-butyn-1-o1 (6)

To a solution of 2,2-dimethyl-3-butynoic acid (500 mg; 4.46 mmol) in THF (20ml) at 0°C, lithium aluminium hydride (250 mg; 6.5 mmol) was slowly added. The reaction mixture was stirred at room temperature overnight and then a saturated solution of NH_4Cl was added. The mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered off and evaporated to dryness at low pressure.The crude was subjected to column chromatography (silica gel 9:1, pet ether: ether) to give **the title compound** (280 mg; 63%) ^1H NMR, δ, 1.2 (S,6H, CH_3) 2.18 (S, 1H, ≡ CH), 3.4 (S,2H, OCH_2): ms:m/z ,M^+98.

2-Bromo-2-propen-1-y1- 3,3-dimethyl 4 butyn-1-y1 ether(3)

2,2-Dimethyl-3-butyn-1-o1(200 mg; 2.04 mmol) was dissolved in DME (20 ml). To this solution sodium hydride (73mg; 3.06 mmol or 122mg of 60% in oil) was added portionwise. To this slurry solution 2,3-Dibromopropene (602mg; 3.06 mmol) was added via cannula at 0°C. The reaction mixture was stirred at room temperature for 12 hrs under N_2.To this mixture, water was added dropwise, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic solvents were dried over Na_2SO_4. After filtration and evaporation under reduced pressure the crude was subjected to column chromatography **(Silica gel, 40:1, pet ether: ether) to afford the title compound** (250 mg; 56%). ^1H NMR, δ1.2 (S, 6H, CH_3), 2.8 (S, 1H, ≡CH), 3.38 (S,2H, -OCH_2) 4.2 (S, 2H- OCH_2), 5.6 (d, 1H, syn=CH), 6.00 (d,H, anti=CH) ms, m/z M^+218.

Tert-Butyldimethylsilyl propargyl ether (8)

Propargyl alcohol (5g; 0.689 mol) was dissolved in DMF (50 ml), tert-Butyldimethyl silylchloride (16g; 0.1mol) and imidazole (6.8g; 0.1 mol) were added portionwise and the reaction mixture was stirred at room temperature for 12 hrs. Water was then added and the mixture was extracted with 80:20 pet ether:ether. The combined solvents were dried over Na_2SO_4 and filtered off. After evaporation, the crude was subjected

to column chromatography using pet ether:ether 40:1 to afford **the title compound** (6.5g; 43%) ^{1}HNMR; δ 0.1(S, 6H, Si- CH_3) 0.8 (S, 9H, Si-tBu), 2.2 (S, 1H, ≡ CH), 4.3 (S, 2H, - OCH_2).

t-Butyldimethylsilyl [tributylstannyl] propargyl ether(4)

t-Butyldimethylsilyl propargyl ether (5g; 0.03 mol) was dissolved in THF (120 ml). To this solution under N_2 and at 0^{o}C n-BuLi (0.036 mol, 14 ml of 2.5 M solution in ether via syringe was added dropwise. The mixture was stirred for 30 min. at 0°C and then tributyltin chloride (9.75 g; 0.03 mol) in THF (10 ml) was added via cannula. The reaction mixture was stirred for 2hrs and then poured on to ice. The mixture was extracted with ether. The organic layer was dried over Na_2SO_4 , filtered and evaporated to dryness. The residue was subjected to fractional distillation (140-145°C, 12mm) to give **the title compound** (6.3g; 45%), ^{1}H NMR; δ 0.1 (S, 6H, Si-CH_3); 0.8 (S, 9H,tBu) 0.9 (t, 9H; CH_3), 1.0 (t, 6H, CH_2) 1.3 (m, 6H, CH_2): 1.6 (q.6H, CH_2); 4.25 (s, 2H, O- CH_2).

tert-Butyldimethylsilyl 4(4') Z-[3,3-dimethyl-pyran-5-enebutyn-2-yl ether (5)

2-Bromo-2-propen-1-yl 2,2-dimethyl-3-butyn-1-yl ether (100 mg; 0.46 mmol) was dissolved in toluene (1.5 ml) and added to tertrakis (triphenyl phosphin) palladium (0) (5_3mg; 0.046 mmol) followed by the addition of tert-Butyl dimethyl si-3-lyl [tributyl stannyl] propargyl ether (527 mg; 1.15 mmol) in toluene (1.5 ml). Undecane (113 µlit) was then added as a standard for monitoring the reaction with G.C. The resulting solution was then heated to 100°C for 2 hrs in a Schlank Tube under N_2. The reaction mixture was filtered through celite. The solution was evaporated to dryness and subjected to column chromatography using 40:1, pet ether:ether to afford the title compounds (66mg; 46%), ^{1}H NMR ($CDCl_3$), δ 0.1 (S, 6H, Si2CH_3) 0.9 (S, 9H, SitBu) 1.3 (S, 6H, CH_3) 3.6 (S, 2H, OCH_2 in ring) 4.6 (S, 2H, OCH_2 ring), 4.8 (S, 2H, -OCH_2) 6.9 (S, 1H, = CH, H_6) 7.25 and 7.4 (2d, 2H, = CH_2, C_{19}).

4(4') Z-4 [3,3-dimethyl-pyran-5-en-] yl 2-butyn-1-o1 (12)

tert-Butyldimethylsilyl 4(4') z[3,3-dimethyl-pyran-5-en] butyn-2-yl ether (60 mg; 0.21 mmol) was dissolved in HF (10.4 µlit of 48% solution) and acetonitile (2 ml). The reaction mixture was stirred for 4 hrs at room temperature. To this mixture, a solution of Na_2Co_3 (5 ml, 5%) was then added and extracted with ether. The solvent was dried over Na_2SO_4 and filtered off. After the evaporation of solvent under reduced pressure, the crude was subjected to column chromatography using 4:1 pet ether:ether to afford **the title compound.** (18 mg; 58%). ^{1}HNMR ($CDCl_3$), δ 1.3 (S,6H, CH_3), 3.6 (S,2H, OCH_2 ring) 4.6 (S, 2H, -OCH_2 ring), 4.8 (S, H, OH), 7. (S, H, = CH; H_6), 7.2 7.3 (2d, 2H, = CH_2, H_{19}) m.s, m/z,M^+162.

Acknowledgements

Support of this research from the University of California, Riverside is gratefully acknowledged.

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