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An 8π Electron Electrocyclization Leading to a 9,19-Methano-Bridged Analogue of 1α,25-Dihydroxyvitamin D_3

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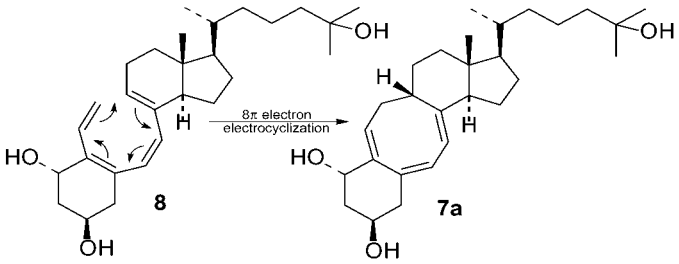
ABSTRACT



Lindlar semihydrogenation of a vitamin D type trienyne leads spontaneously to 9α,19-methano-1α,25-dihydroxyvitamin D_3. The intermediate tetraene resulting from the reduction undergoes a rapid, stereoselective 8π electron electrocyclization affording a novel steroid containing a linearly fused ABC (six-eight-six) 1,3,5-cyclooctatriene carbon framework.

The steroid hormone 1α,25-dihydroxyvitamin D_3 (**1a**, 1,25-D3) spontaneously tautomerizes via a [1,7]-sigmatropic hydrogen shift to the extent of about 5% at equilibrium to 1α,25-dihydroxyprevitamin D_3 (**3a**, 1,25-PreD3) (Scheme 1).[1] The hormone **1a**, the bioactive metabolite of **1c** formed via **1b**, is potent in both genomic and rapid (nongenomic) actions, processes considered to be mediated via binding of steroid to a nuclear vitamin D receptor (n-VDR) and a putative membrane receptor (m-VDR), respectively.[2] It has been observed that the tautomer 1,25-PreD3 (**3a**) is able to fully mimic the membrane actions of 1,25-D3 but has little action at the nuclear level.[3] It has also been shown that 1α,-25-dihydroxylumisterol$_3$ (**4a**, 1,25-Lumi), the 6π electron electrocyclized photoproduct of **3a**, also exerts selective action at the membrane level.[4] The selectivity of **3a** and **4a** toward membrane actions of 1,25-D3 has therefore suggested that the higher energy, spectroscopically invisible cisoid conformation of 1,25-D3, namely, **2a**, mediates membrane actions via selective m-VDR binding.[5] A recent X-ray study

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(2) (a) Bouillon, R.; Okamura, W. H.; Norman, A. W. Structure−Function Relationships in the Vitamin D Endocrine System. *Endocr. Rev.* **1995**, *16*, 200−257. (b) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: San Diego, 1997. (c) *Vitamin D: Physiology, Molecular Biology, and Clinical Applications*; Holick, M. F., Ed.; Humana Press: Totowa, 1999.

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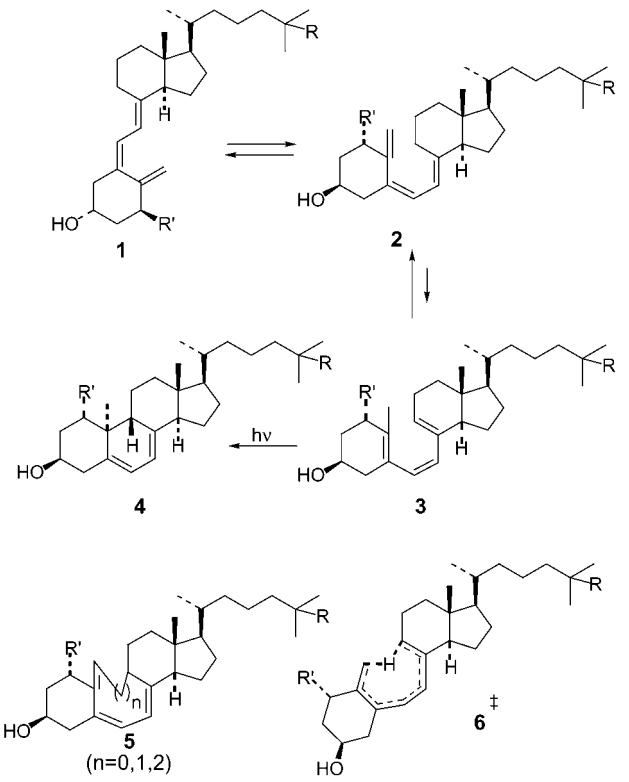
Scheme 1[a]

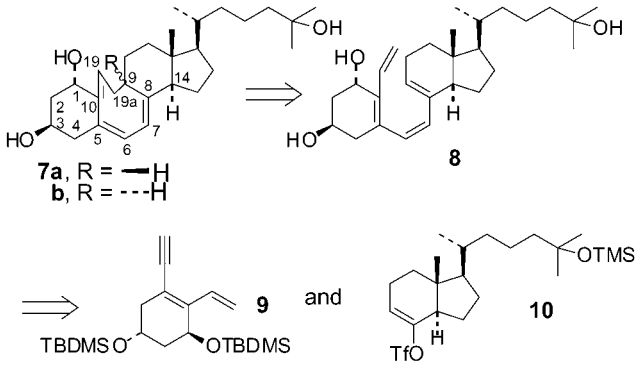


[a] **a**, R = R′ = OH; **b**, R = OH, R′ = H; **c**, R = R′ = H.

of 1,25-D3 bound to its n-VDR has revealed that the transoid conformation of the hormone (i.e., **1a**) is the active nuclear conformer.[6]

Thus, rotation about the 6,7-single bond of the seco-steroid vitamin D skeleton may play an important role in modulating the different biological activities of vitamin D. It became of interest to further probe the less well investigated membrane actions of 1,25-D3 via development of a synthesis of a series of 9,19-bridged vitamin D molecules of the type **5**.[7] This kind of polyene conformationally "locking" strategy has been used by Nakanishi and others in probing the biological activities of retinoids (vitamin A).[8] As is apparent from the transition state structure **6** for the sigmatropic shift of **1** to **3**, analogues of the type **5** have also recently engendered interest as transition state mimics for the development of catalytic antibodies for this particular type of pericyclic process.[7,9] It is the purpose of this Letter to describe the first synthesis of an analogue in this series possessing the full vitamin D triene skeleton, namely, the 9,19-methano-bridged system **7** (i.e., **5**, $n = 1$) (Scheme 2).

Scheme 2



It was envisaged that synthesis of **7** could be achieved by conrotatory 8π electron electrocyclization[10] of **8**, a previtamin derivative related to **3a** wherein its C-10 methyl is replaced by a vinyl group. Transition metal mediated cross-coupling of the A-ring dienyne **9** with enol triflate **10** followed by Lindlar reduction was anticipated to lead to the desired **7**, albeit of uncertain stereochemistry at C-9.

It was also anticipated that A-ring dienyne **9** could be synthesized from the bromoenol triflate **13**,[11] which was accessed from the known C_2-ketone **11** (Scheme 3). The latter, obtainable in six steps from (−)-quinic acid,[12] was α-brominated (LHMDS and then Br_2 to afford **12**, 87%) and

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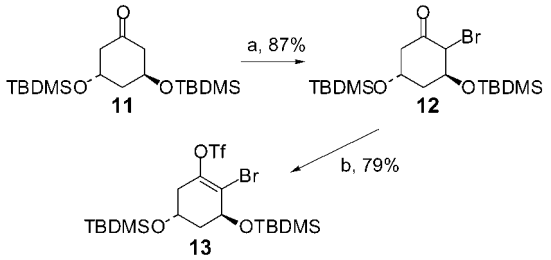
Scheme 3[a]

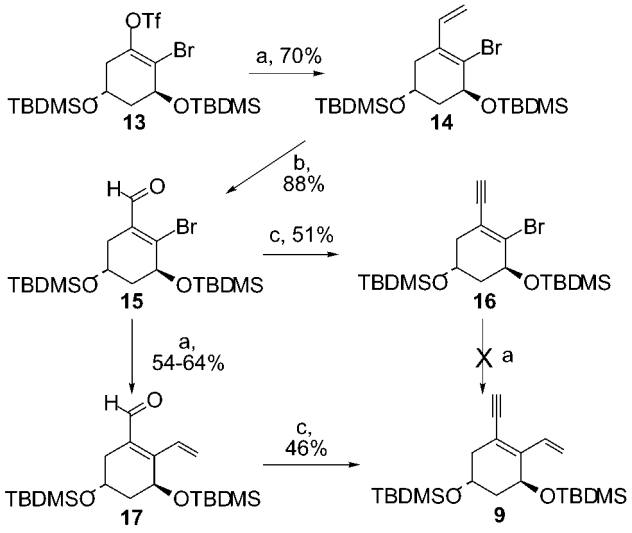


[a] (a) LHMDS, THF; Br_2, CH_2Cl_2; (b) KHMDS, THF−HMPA; $PhNTf_2$.

then transformed into **13** (KHMDS, THF, HMPA followed by $PhNTf_2$, 79%). Formation of the latter was critically dependent upon using HMPA as cosolvent.

Direct alkynylation reactions of **13** under either the Stille (using alkynylstannanes with $Pd(PPh_3)_4$ or Pd_2dba_3 with or without addends such as PPh_3, $AsPh_3$, and/or LiCl) or Sonogashira (using terminal alkynes with $Pd(PPh_3)_4$, $(PPh_3)_2Pd(OAc)_2$, $(PPh_3)_2PdCl_2$, $Pd(OAc)_2/PPh_3$ or $PdCl_2/PPh_3$) coupling conditions have thus far proven singularly unsuccessful in our hands.[13] Surprisingly, vinylation of **13** (Scheme 4) using the Farina modification[14] of the Stille process

Scheme 4[a]

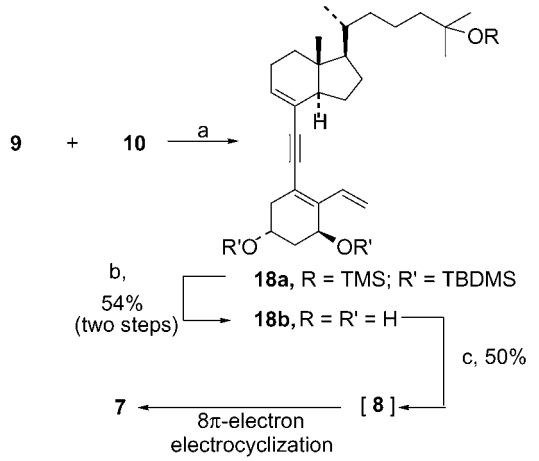


[a] (a) CH_2=$CHSnBu_3$, Pd_2dba_3, $AsPh_3$, LiCl, NMP; (b) OsO_4, $NaIO_4$, THF−H_2O; (c) $TMSCHN_2$, LHMDS, THF.

(tributylvinylstannane, Pd_2dba_3, $AsPh_3$, LiCl, NMP, 35 °C, 14 h) produced the bromodiene **14** in 70% yield. Oxidative cleavage (OsO_4, $NaIO_4$, 88%) afforded bromoaldehyde **15**, which upon elongation ($TMSCHN_2$, BuLi, 51%) afforded bromoenyne **16**. The latter however could not be vinylated directly to produce the desired **9** (using the same Farina−Stille process). This dienyne could however be obtained by reversing the sequence. Namely, **15** was vinylated first (54−64% yield using the same Farina−Stille process) to produce **17**, which in turn could be transformed to the desired dienyne **9** ($TMSCHN_2$, BuLi, 46%).

Standard Sonogashira coupling of dienyne **9** with the CD fragment **10** [$(PPh_3)_2Pd(OAc)_2$, CuI, Et_2NH, DMF] followed by direct desilylation (TBAF, THF) afforded the trienyne **18b** in 54% yield (Scheme 5).[15] Most interestingly, Lindlar

Scheme 5[a]



[a] (a) $(PPh_3)_2Pd(OAc)_2$, CuI, Et_2NH, DMF; (b) TBAF, THF; (c) H_2, Lindlar cat. quinoline, MeOH.

reduction of **18b** (H_2, Lindlar catalyst, quinoline, MeOH, <25 °C, <1 h; and <25−33 °C during workup and purification, ∼30 min) afforded the electrocyclized 9,19-methano-bridged product **7** directly as a single diastereomer in 50% yield. Aside from the identification of the product as the cyclized product **7**, even from a cursory examination of its ^1H and ^{13}C NMR spectra, its UV spectrum [λ_{max} 253 nm (ϵ 2400)] was particularly diagnostic. Whereas the parent

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hormone **1a** and its various metabolites (e.g., **1b** and **1c**) characteristically exhibit λ_{max} (EtOH) 264 nm ($\epsilon \sim 19\,000$),[15b,d] 1,3,5-cyclooctatrienes exhibit λ_{max} values near 250 nm with notably attenuated extinction coefficients of $\epsilon \sim 2000$.[16]

In retrospect, the facility with which the presumed octatetraene **8** undergoes cyclization is not surprising. The parent (3*Z*,5*Z*)-1,3,5,7-octatetraene cyclizes even at −78 °C[17] while similar dimethyl-capped systems (the various (4*Z*,6*Z*)-2,4,6,8-decatetraenes) cyclize at temperatures ranging from −10 to +65 °C.[18] It is also possible that the strain imparted by the positioning of a $\Delta^{8,9}$-double bond in the *trans*-hydrindane skeleton of **8** may also play a role in accelerating the 8π electron electrocyclization.[19] That this presumed conrotatory electrocyclization produces mainly if not exclusively a single diastereomer, namely, the 9α epimer **7a**, can be rationalized on the basis of the analysis shown in Figure 1. This epimer can be considered to result from a stereoelectronically favored axial attack (**19**) rather than an equatorial coupling (**19′**).[20]

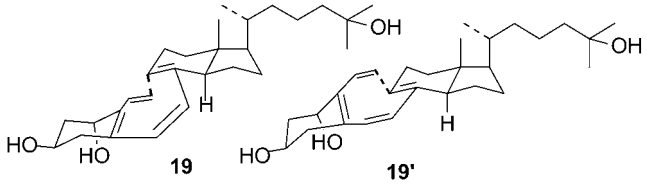

Figure 1. Possible transition state conformations for the formation of **7a** (via axial attack, **19**) and **7b** (via equatorial attack, **19′**) from electrocyclization of tetraene **8**.

The stereochemistry of the cyclized product as **7a** was tentatively established through a series of 1D and 2D ^{1}H and ^{13}C NMR studies. That the C-9 proton of the observed product is β oriented, and hence equatorial, to the chairlike C-ring of **7a** is based on the observation of a $J_{eq,eq}$ and a $J_{eq,ax}$ pair of vicinal splittings[21] by the protons on C-11 to that on C-9. The epimer **7b** should have exhibited a large $J_{ax,ax}$ and a small $J_{ax,eq}$ splitting[21] of the C-9 proton by the protons at C-11, which were not detected. Moreover, in the NOESY spectrum, a cross-peak was detected between H-14α and an H-19a proton but not the H-9 proton. A detailed NMR analysis is presented in the Supporting Information.

Finally, it is noted with interest that 1,3,5-cyclooctatrienes are notorious for their propensity to undergo rather facile disrotatory 6π electron electrocyclization to their bicyclo-[4.2.0]octa-2,4-diene counterparts.[10a,22] This extrathermal conduit can limit the use of 8π electron electrocyclizations in eight-membered ring syntheses. It is noteworthy that **7a** shows little tendency toward such a cyclization under ambient conditions,[23] possibly because a strained spirocycle would result. Thus the exploration of 8π-electron cyclizations of suitably substituted octatetraenes analogous to **8** in applications to medium ring synthesis is a novel feature of the results described herein.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http//pubs.acs.org.

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(22) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc*. **1982**, *104*, 5560−5562 and the preceding three papers in the series.

(23) Heating **7a** in ethanol-d_6 at 65 °C (1.8 h) leads to no discernible changes (NMR monitoring).