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Toward an Analogue of the Transition State of PreD_3–D_3 Isomerization: Stereoselective Synthesis of Linearly Fused 6-8-6 Carbocyclic Systems[1]

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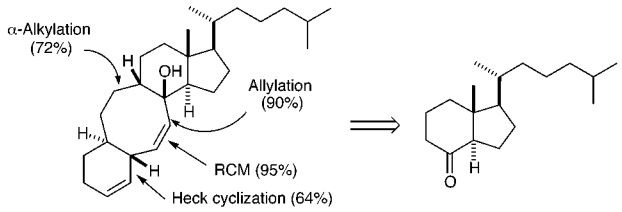
ABSTRACT



A stereoselective synthesis of 6-8-6 fused carbocyclic systems based on enol alkylation, ketone allylation, RCM, and Heck cyclization was developed to obtain compounds with a carbon framework that mimics the putative transition structure of the isomerization of previtamin D_3 to vitamin D_3.

Interest in polycyclic systems containing an eight-membered ring stems both from the synthetic challenge associated with their construction and from the wide-ranging biological activities of many such compounds.[2] We have recently embarked on the preparation of 6-8-6 fused carbocyclic systems with a view to obtaining steroid-like compounds of type **I** (Figure 1),[3] which as Figure 2 shows in the case of **Ib**, mimic [1,7]-H TS, the putative cyclic transition state of the isomerization[4] of previtamin D_3 (preD_3) to vitamin D_3 (D_3) (note in particular the good match between the C3 hydroxy groups, the CD bicyclic systems, and the diene systems). Our hope is that understanding of the mechanism of this transformation may be furthered by study of the active sites of isomerization-catalyzing antibodies raised against compounds of this type.[6] As locked 6-*s*-*cis* analogues of 1α,-

(1) This paper is partially based on the doctoral thesis of Eva María Codesido, University of Santiago de Compostela, 2001.

(2) For reviews, see: (a) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, pp 73−115. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (c) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777−2849. (d) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609. (e) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−990.

(3) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483−1486.

(4) This isomerization, one of two successive pericyclic reactions in the photobiogenesis of vitamin D_3 (Figure 1),[5] consists of a thermally induced antarafacial [1,7]-sigmatropic hydrogen shift from C19 to C9. For studies of the mechanism of this physiologically important transformation, see: (a) Havinga, E. *Experientia* **1973**, *29*, 1181−1192. (b) Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I.; Norman, A. W. *J. Steroid Biochem. Mol. Biol.* **1995**, *53*, 603−613. (c) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1999**, *274*, 4174−4179.

(5) Henry, H. L.; Norman, A. W. Metabolism of Vitamin D. In *Disorders of Bone and Mineral Metabolism*; Coe, F. L.; Favus, M. J., Eds.; Raven Press: New York, 1991; pp 149−162.

(6) The catalytic antibody strategy is a powerful method for the design of enzymes that achieve transformations that are rare or do not occur in nature; see: (a) Schultz, P. G.; Lerner, R. A. *Science* **1995**, *269*, 1835−1842. (b) Wentworth, P.; Janda, K. D. *Curr. Opin. Chem. Biol.* **1998**, *2*, 138−144. (c) Hilvert, D. *Top. Stereochem.* **1999**, *22*, 83−135.

(7) The biological functions of the hormonally active form of D_3, 1α,-25-dihydroxyvitamin D_3,[5] are now thought to include promotion of cell differentiation, inhibition of tumor cell proliferation, and induction of functions related to the immunological system. For some studies of the biological activity of this hormone, see: (a) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200−257. (b) *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop, Inc.; Riverside, CA, 1997.

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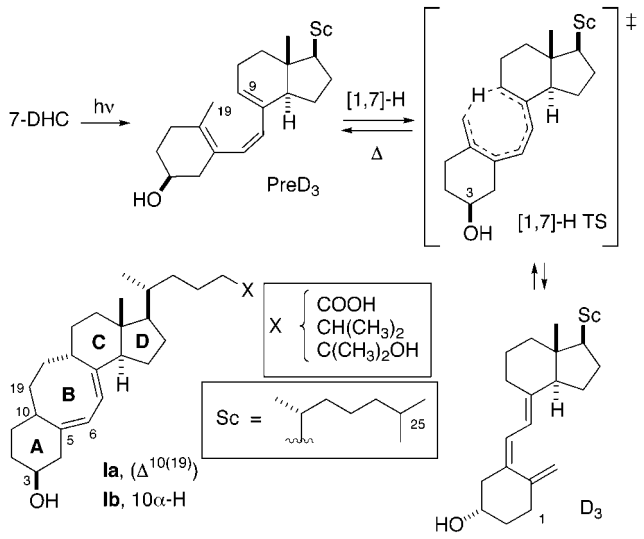


Figure 1. Putative mechanism of the [1,7] sigmatropic hydrogen shift of $PreD_3-D_3$ isomerization and the structure of the [1,7]-H TS analogues **I**.

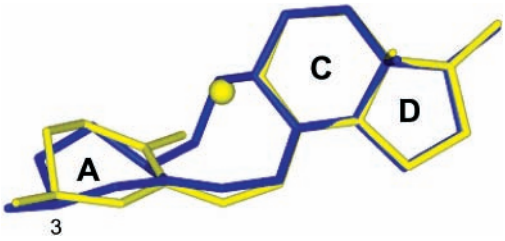


Figure 2. The polycyclic system **Ib** (blue) superimposed on the putative transition state structure of the $PreD_3-D_3$ isomerization reaction ([1,7]-H TS, yellow).

$25\text{-}(OH)_2\text{-}D_3$,[7–9] vitamin D analogues with this central eight-membered ring might also be useful for studying nongenomic vitamin D responses.

As potentially fast, versatile approaches to **I** that might allow the introduction of further functional groups, we set out to evaluate the strategies shown in Figure 3, both of which are based on an RCM[10] reaction forming the C5–C6[11] double bond and an intramolecular Heck[12] cyclization for construction of ring A.[13] We envisaged that in both cases the initial RCM would involve the less substituted double bonds, producing the appropriate precursor for the final Heck

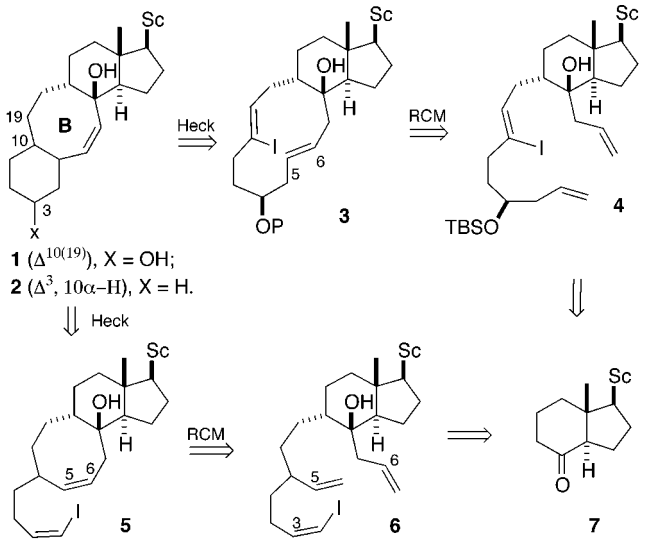


Figure 3. The synthetic approaches to **1** and **2** investigated in this work.

cyclization. The RCM precursors **4** and **6** would be easy to prepare by stereoselective alkylation and allylation of Grundmann's ketone (**7**).[14] Here we present the results of our preliminary studies of these approaches, which show that the second strategy (via **6** and **5**) has substantial potential for stereoselective construction of complex polycyclic frameworks.

We initially aimed at compound **1** because of the presumed ease of obtaining precursor **4** from **7** and the allyl bromide derived from the known alcohol **8** (Scheme 1).[13] Following formation of the 12-membered ring by RCM of triene **4**, a subsequent intramolecular Heck reaction ought to produce the 6-8 fused bicyclic system of **1** because of the usual preference for 6-*exo* cyclization of Heck reactions.[12,15] As expected, alkylation of the kinetic enolate of **7** (formed by LDA treatment at −78 °C) with bromide **9**, followed by allylation of the resulting ketone, gave alcohol **4**.[16] However,

(8) The involvement of a $preD_3 \rightleftharpoons D_3$ type of equilibrium in nongenomic activities is hinted at by experimental results suggesting that these activities are mediated by membrane receptors for $1\alpha,25\text{-}(OH)_2\text{-}PreD_3$ as well as by $1\alpha,25\text{-}(OH)_2\text{-}D_3$; see: (a) Norman, A. W.; Okamura, W. H.; Farach-Carson, M. C.; Allewaert, K.; Branisteanu, D.; Nemere, I.; Muralidharan, K. R.; Bouillon, R. *J. Biol. Chem.* **1993**, *268*, 13811−13819. (b) Okamura, W. H.; Midland, M. M.; Norman, A. W.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I. *Ann. N.Y. Acad. Sci.* **1995**, *761*, 344−348.

(9) While this manuscript was under revision the synthesis of an analogue of $1\alpha,25\text{-}(OH)_2\text{-}D_3$ bearing an eight-membered ring B has been published: Hayashi, R.; Fernández, S. Okamura, W. H. *Org. Lett.* **2002**, *4*, 851−854.

(10) For reviews of metathesis, see: (a) Fürstner, A. *Angew. Chem., In. Ed.* **2000**, *39*, 3012−3043. (b) Chang, S.; Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413−4450. For a recent view of the synthesis of medium-sized rings by RCM, see: (c) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. For a more general review of the synthesis of medium-sized rings, see: (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.

(11) For convenience, steroid numbering is used.

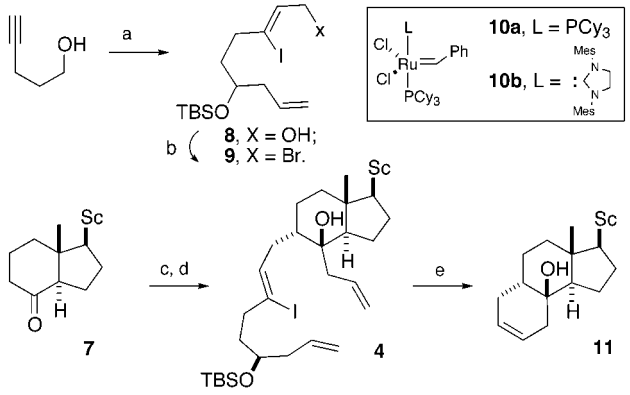
(12) For recent uses of intramolecular Heck reactions for the construction of 6−7 fused bicyclic systems, see: (a) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590−5591. For recent reviews of this reaction, see: (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (c) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 6. (d) de Meijere, A.; Meyer, F. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3. (e) Link, J. T.; Overman, L. E. *CHEMTECH* **1998**, 19−26. (f) Neghisi, E.-i.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 6, 365−393.

(13) Preliminary studies had shown the viability of the Heck cyclization of iododiene **8**; see: Codesido, E. M.; Cid, M. M.; Castedo, L.; Mouriño, A.; Granja, J. R. *Tetrahedron Lett.* **2000**, *41*, 5861−5864.

(14) Mascareñas, J. L.; Sarandeses, L.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485−3498.

(15) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Neghisi, E.-i. *J. Am. Chem. Soc.* **1992**, *114*, 10091−10092.

Scheme 1[a]

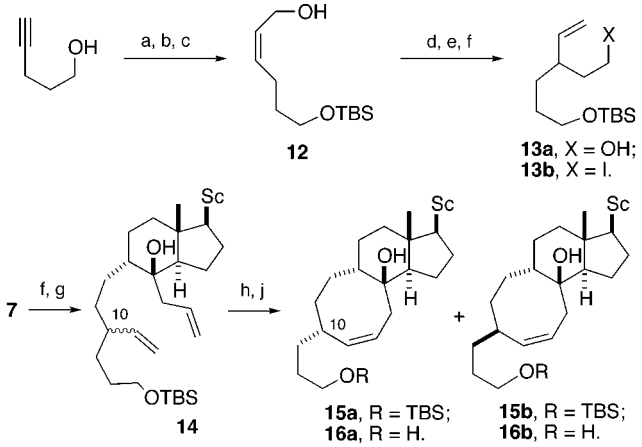


[a] (a) Reference 13; (b) PPh_3, CBr_4, CH_2Cl_2, 89%; (c) LDA, **9**, THF, −78 °C, 42%; (d) allylMgBr, THF 85%; (e) **10a**, CH_2Cl_2, Δ, 70%.

when this compound was subjected to RCM conditions using Grubbs' catalyst (**10a**) or **10b**,[17] instead of **3** we obtained only compound **11**, formation of the six-membered ring having prevailed over macrocyclization even though it involved reaction with the more substituted olefin.

We therefore turned to the second approach, focusing on the preparation of compound **2** (Figure 3). The key step here had initially been envisaged as formation of the central eight-membered ring by RCM of triene **6**, but in view of the unexpected cyclization behavior of **4** we decided to install the vinyliodide moiety only after the RCM (Scheme 2). As

Scheme 2[a]



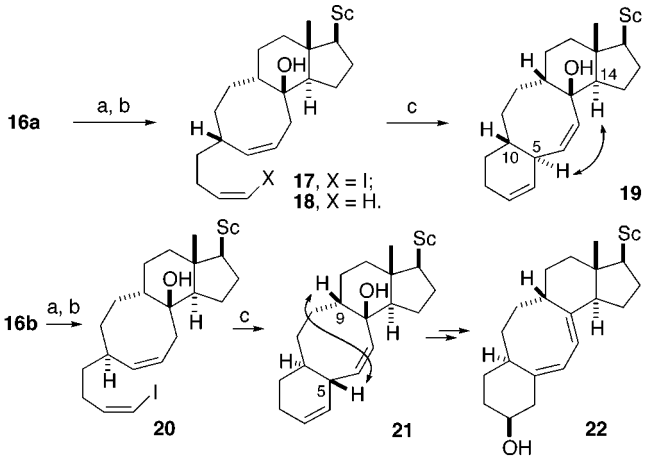
[a] (a) TBSCl, Im, CH_2Cl_2, 92%; (b) *n*BuLi, THF, $(H_2CO)_n$, 82%; (c) H_2/Lindlar, hexanes, 83%; (d) CH_2=CHOBu, $Hg(OAc)_2$, 160 °C; (e) $NaBH_4$, MeOH, 69% (from **12**); I_2, PPh_3, Im, 76%; (f) KHMDS, **13b**, DMF/toluene (1:1), −80 °C, 72%; (g) allylMgBr, THF 82%; (h) **10a**, CH_2Cl_2, Δ, 6 days, 95%; (j) TBAF, THF, 87%.

alkylating agent we therefore synthesized iodide **13b** from 4-pentyn-1-ol. After protection of 4-pentyn-1-ol with TBSCl, metalation of the silyl ether, and entrapment of the alkynyllithium with *p*-formaldehyde, the resulting propargyl alcohol was semihydrogenated to compound **12** in 63% overall yield. Condensation with butyl vinyl ether in the presence of $Hg(OAc)_2$, followed by Claisen rearrangement and in situ reduction with sodium borohydride, provided alcohol **13a** in 69% yield from **12**. After exposure of this alcohol to triphenylphosphine, imidazole, and iodine, the resulting iodide **13b** was reacted with the kinetic enolate of **7** (formed by reaction with potassium hexamethyldisilazide in 1:1 DMF/toluene at −80 °C),[18] and the resulting ketone was allylated, giving diene **14** in 59% yield (from **7**) as an inseparable 1:1 mixture of C10-epimers.

RCM of **14** with catalyst **10a** (20%) was successful though slow, the cyclooctene derivatives **15a** and **15b** being obtained in 95% overall yield as an inseparable mixture after 1 week in refluxing CH_2Cl_2. The use of benzene or the more reactive catalyst **10b** did not significantly decrease the reaction time, which was much longer than in previous RCM assemblies of eight-membered rings in similar systems.[3] Clearly, the additional substituents at the allyl position slow the reaction regardless of the stereochemistry at C10.[19] Fortunately, after deprotection of **15a**/**15b** with tetrabutylammonium fluoride, the resulting alcohols **16a** and **16b** were easily separated, although it was not possible to establish the configuration of these compounds at C10 by NMR experiments.

Oxidation of isomer **16a** with PCC and subsequent olefination by Stork's method[20] produced the (*Z*)-vinyl iodide **17** in 72% yield (Scheme 3). Heck reaction using palladium

Scheme 3[a]



[a] (a) PCC, CH_2Cl_2, (56% from **16a**, 66% from **16b**); (b) $Ph_3P^+CH_2I\ I^-$, NaHMDS, THF, (72% for **17**, 70% for **20**); (c) $Pd(PPh_3)_4$, CH_3CN, Δ, (15% for **19**, 64% for **21**).

tetrakistriphenylphosphine in refluxing acetonitrile for 2 h yielded compound **19** as a single isomer, but in only 15%

(16) The relative stereochemistry of **4** was determined by NOE experiments as in ref 3.

(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(18) Palomo, C.; Oiarbide, M.; Mielgo, A.; González, A.; García, J.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett.* **2001**, *3*, 3249−3252.

(19) The **15a**/**15b** ratio was almost 1:1 after 48 and after 76 h. For an example of stereocontrolled RCM, see: Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376−2378.

yield, the major product being the protonated compound **18** (>40% yield). Other catalyst systems did not improve the reaction yield. The relative stereochemistry at C5 and C10 was established on the basis of the coupling of the C5 proton to those on C6 and C10, C5−H appearing as a triplet[21] with a *J* value of 9.3 Hz, which in cyclohexanes is characteristic of *trans* axial-axial orientation. The *R* configuration of C10 was established when a substantial cross-peak between H14 and H5 in a NOESY experiment showed them to be *cis* to each other.

Finally, oxidation and olefination of the second of the isomeric alcohols, **16b**, afforded (*Z*)-vinyl iodide **20** in 70% yield, and intramolecular Heck reaction of this compound gave, as the only product, a 64% yield of the *trans*-bicyclo compound **21**, the relative stereochemistry of which was shown by an NOE enhancement between H5 and H9 suggestive of a *cis* relationship and an H5−H10 coupling constant of 9.3 Hz indicating *trans* axial-axial orientation (Scheme 3). Compound **21** is the isomer required for preparation of the transition state analogue **22**.

In conclusion, we have shown that tricyclo[10.4.0.0^{4,9}]-hexadecane systems can be stereoselectively constructed by appropriately combining enol alkylation,[22] ketone allylation,[23] RCM, and Heck cyclization. Whether the product is a *cis-cisoid-trans* or a *cis-transoid-trans* system is determined by the stereochemistry of the alkylating agent, which in our case ultimately derives from a Claisen rearrangement.[24] It is envisaged that this approach will allow access to general 6-8-*n* fused systems starting from *n*-membered cycloalkanones. We are currently completing the route to potential haptens **I** with a view to employing them to elicit catalytic antibodies.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds **13a**, **16a**, **16b**, **17**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.
(21) H4−H5 coupling was close to zero.
(22) For some examples of stereoselective enol alkylation, see: (a) Hughes, D. L. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 34.1. For a review of asymmetric protonation of enolates, see: (b) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 34.2.
(23) For a recent study of the diastereoselectivity of cycloalkanone alkylation, see: (a) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377−1386. (b) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337−1376.
(24) For reviews of asymmetric Claisen rearrangement, see: (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. For recent reports of enantioselective catalytic Claisen rearrangement, see: (c) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911−2912. (d) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700−4703.