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Access to [6.4.0]Carbocyclic Systems by Tandem Metathesis of Dienynes. A Step toward the Synthesis of a PreD_3–D_3 Transition State Analogue†

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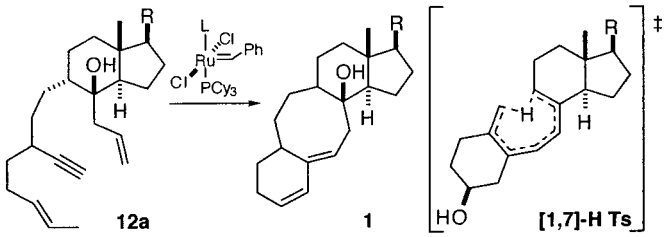
ABSTRACT



A new approach to the synthesis of linearly fused 6–8–6 tricarbocyclic systems, tandem ring-closing metathesis of dienynes, allows access to compounds with a carbon framework analogous to the proposed transition state of the isomerization of previtamin D_3 to vitamin D_3.

The photobiogenesis of vitamin D_3 in the skin consists of two successive pericyclic reactions (Figure 1): a UV-B-induced electrocyclic ring opening of 7-dehydrocholesterol (7-DHC) to produce previtamin D_3 (preD_3), followed by a thermally induced isomerization of the latter to vitamin D_3 (D_3) by means of an antarafacial [1,7]-sigmatropic hydrogen shift from C19 to C9. D_3 is subsequently transported to the liver and kidney, where it is transformed into its biologically active form, 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2$-D_3).[1,2] The involvement of a preD_3 ⇌ D_3 type of equilibrium in the biological activity has been suggested by experimental results hinting at the existence of uncharacterized membrane receptors for both 1α,25-$(OH)_2$-PreD_3 and 1α,25-$(OH)_2$-D_3 associated with nongenomic activity.[3]

Although preD_3−D_3 transformation is one of the best known examples of a concerted reaction that occurs in vivo,[4] its mechanism has not yet been completely elucidated. For example, recent studies have revealed that both the kinetics and thermodynamics of this equilibrium differ significantly in many anisotropic microenvironments (such as lipid membranes)[5] from their behavior in isotropic media where,

† This paper is dedicated to Prof. Barry M. Trost in honor of his 60th birthday.

(1) 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.

(2) (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.

(3) The nongenomic actions refer to rapid biological responses mediated by a membrane receptor and believed to be independent of direct interaction with the genome as, for example, transcaltachia. For studies implicating the PreD_3−D_3 equilibrium in biological activity, 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.; Dormanen, M. C.; Nemere, I. *Ann. N.Y. Acad. Sci.* **1995**, *761*, 344−348.

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(5) (a) Tian, X. Q.; Chen, T. C.; Matsuoka, L. Y.; Wortsman, J.; Holick, M. F. *J. Biol. Chem.* **1993**, *268*, 14888−14892. (b) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1995**, *270*, 8706−8711. (c) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1999**, *274*, 4174−4179.

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like other concerted reactions, no solvent effect was observed.[6] In the hope that investigation of the mechanism of this physiologically important transformation will be facilitated by studying the active site of a tailor-made enzyme, we have embarked on the development of catalytic antibodies for this process.[7] To this end we require molecules capable of eliciting an immune response producing such antibodies, and we envisaged that compounds of the type **I** (e.g., **Ia**), in which the eight-membered ring B mimics the putative cyclic transition state of the PreD$_3$−D$_3$ isomerization reaction ([1,7]-H Ts), might be a suitable family of potencial haptens (Figure 1).

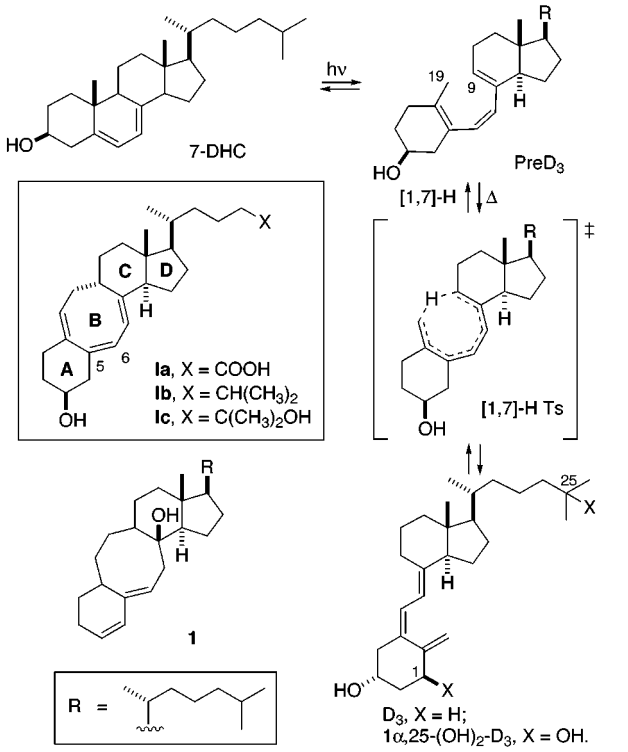


Figure 1. Photobiogenesis of vitamin D$_3$ and analogues of the proposed transition state of preD$_3$−D$_3$ isomerization.

Furthermore, compounds of the type **I**, such as **Ic**, might also be useful as locked analogues of the 6-*s*-*cis* conformer of 1α,25-(OH)$_2$-D$_3$ in studies of the nongenomic responses.[8] In this letter we describe the synthesis of compounds **1**, which exhibit the basic carbon framework of these type of systems **I**.

Our initial strategy for the preparation of the tetracyclic system of compounds **I** is outlined in Figure 2. The key step

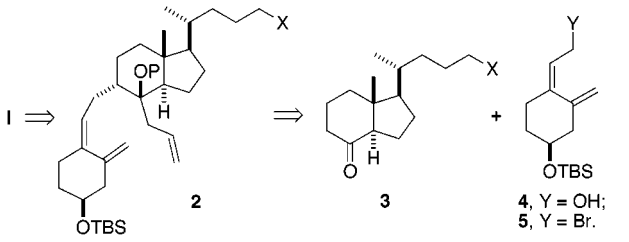
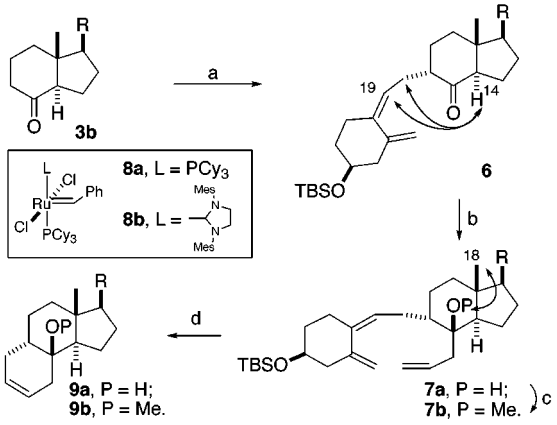


Figure 2. Synthetic approach for the preparation of haptens **I**.

involves the construction of the eight-membered ring by ring-closing metathesis (RCM) of triene **2**.[9] We envisaged that the RCM would take place through the less substituted double bond to form the C5−C6 bond of **I**.[10] Compound **2** would be prepared by alkylation of the kinetic enolate of **3** with bromide **5** (easily prepared from alcohol **4**),[11] followed by allylation of the ketone group.

To test the viability of this strategy we decided to prepare compound **Ib**, using Grundmann's ketone (**3b**) as starting material (Scheme 1).[12] The kinetic enolate formed by LDA

Scheme 1[a]



[a] (a) (i) LDA, THF, −78 °C, (ii) **5**, 85%; (b) allylMgBr, THF, 88%; (c) HK, MeI, 18-crown-6, THF, 85%; (d) **8b**, CH_2Cl_2, △, 90% (**9a**), 87% (**9b**).

treatment at −78 °C was trapped at the least hindered face with freshly prepared bromide **5**, affording ketone **6** in 85% yield.[13] Treatment of **6** with allylmagnesium bromide gave

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

(10) For convenience, steroid numbering is used.

(11) For enantioselective synthesis of **4**, see: Codesido, E. M.; Cid, M. M.; Castedo, L.; Mouriño, A.; Granja, J. R. *Tetrahedron Lett.* **2000**, *41*, 5861−5864.

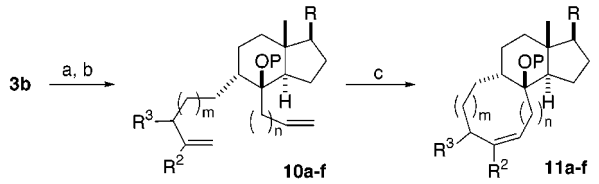
(12) Ketone **3b** is readily obtained by ozonolysis of vitamin D$_3$; see: Mascareñas, J. L.; Sarandeses, L.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485−3498.

alcohol **7a** in almost quantitative yield. The relative stereochemistry of these newly generated stereocenters was confirmed by inspection of the NMR (NOE, NOESY) spectra of **6** and **7b**. The NOE relationship between H14 and both H19 and the neighboring allyl protons in compound **6** (Scheme 1) reflects the axial (α) orientation of the enolate alkylation, while the significant interaction between Me18 and the OMe group in the NOESY spectrum of **7b** confirmed their *cis* relationship.

Unfortunately, when **7a** or the methyl ether **7b** were submitted to RCM conditions using Grubbs' catalyst (**8a**), they were recovered unaltered; while treatment with the more reactive ruthenium catalyst **8b**[14] furnished compounds **9a** and **9b** in very high yield, i.e., formation of the six-membered ring prevailed over formation of the eight-membered ring, even though it involved reaction with the more substituted olefin. This result was not completely unexpected, because the formation of eight-membered rings is especially difficult. In particular, it has become increasingly apparent that the formation of cyclooctene by metathesis requires a conformationally predisposed diene or an adequately oriented polar functional group acting as an internal ligand.[10c,15] Furthermore, our cyclization precursor is a 1,2-*cis* disubstituted cyclohexane, and previous studies have shown that substrates of this kind undergo RCM to [6.4.0] systems less easily than the corresponding *trans* systems.[16] In our case, and to further check if cyclooctene formation by RCM was indeed a viable alternative for our synthetic purposes, we prepared compounds **10a**−**f** (Table 1), for which the otherwise preferred cyclohexene pathway is not possible because they have no internal double bond. Additional issues of interest were to unveil how substitutents on the olefin and the presence of a cyclohexyl precursor of ring A of **I** would affect the course of the RCM reaction.

The results of this study are listed in Table 1. Substrates **10a**, **10d**, and **10e** afforded the desired eight-membered ring (entries 1, 5, and 6). Entries 2 and 3 show that a methylene group ($n = 1$) between the olefin and the bicyclic system is required: substrates **10b** and **10c** failed to cyclize regardless of changes of solvent and catalyst and protection of the hydroxyl group. For the *gem*-disubstituted terminal olefins **10d** and **10e**, catalyst **8b** was required for RCM (entries 4−6). The attempted ring closure of the cyclohexyl derivative **10f** [$R^2-R^3 = (CH_2)_4$, entry 7] failed completely, lengthy reaction in refluxing benzene bringing about metathetic dimerization. These results show that formation of the eight-membered ring by RCM is possible, but they also suggest that the constrains introduced by the cyclohexane ring do not allow adoption of the conformation necessary for the annulation.

Table 1. RCM Studies for Formation of Eight-Membered Ring



a) KHMDS, $CH_2=CR^2CHR^3(CH_2)_mCH_2$-I, DMF/toluene (1:1), -78 °C, 50-65%; b) $CH_2=CH(CH_2)_nMgBr$, THF, 0 °C, 80-95%; c) 15% Ru catalyst (**8a**, **8b**), CH_2Cl_2, Δ.

entry	substrate	P	R^2	R^3	*m*	*n*	catalyst	yield %[a]
1	**10a**	H	H	H	1	1	**8a**	86
2	**10b**	H	H	H	2	0	**8a**/**8b**	nd[b]
3	**10c**	Me	H	H	2	0	**8a**/**8b**	nd[b]
4	**10d**	Me	Me	H	1	1	**8a**	nd[b]
5	**10d**	Me	Me	H	1	1	**8b**	92
6	**10e**	H	Me	H	1	1	**8b**	89
7	**10f**	Me	$(CH_2)_4$		1	1	**8b**	nd[b]

[a] Isolated yields of **11**. [b] nd = not detected in reaction crude by ^{1}H NMR (a variety of solvents were used).

In view of the above results we planned a new approach in which initial formation of the ring B by RCM was to be followed by a second cyclization to generate ring A (Figure 3). Specifically, we hoped for tandem RCM of dienyne **12a**.[17]

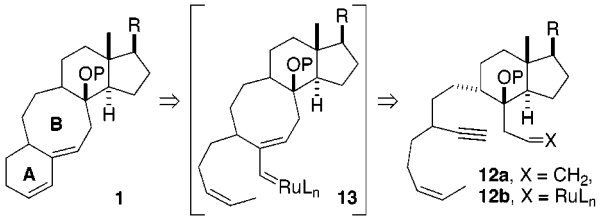


Figure 3. The proposed tandem metathesis approach.

Although there was no precedent for the formation of a [6.4.0] bicycle by RCM of dienynes,[18] the observed readiness of **10a**, **10d**, and **10e** to form the eight-membered ring led us to expect that intramolecular enyne metathesis of carbene **12b** would give the first ring plus the regenerated carbene

(13) Bromide **5** was prepared in 81% yield by treatment of alcohol **4** with triphenylphosphine and carbon tetrabromide in dichloromethane.

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

(15) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660. (c) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc* **2000**, *122*, 2742−2748.

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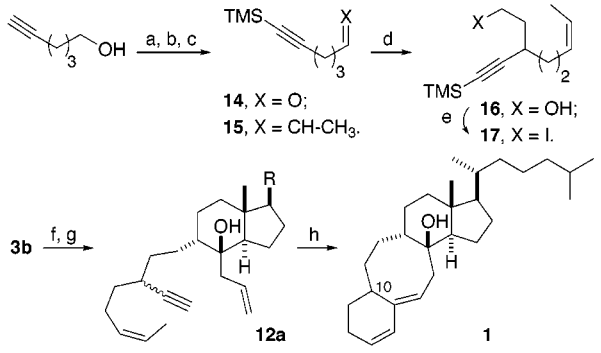
(17) (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801−10802. (b) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073−1081. (c) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291−4298. (d) Fürstner, A.; Liebl, M.; Hill, A. F.; Wilton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601−602.

(18) For recent eight-membered heterocycle ring formation using enyne metathesis, see: Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543−545.

13 and that a second diene RCM of **13** would produce ring A. The methyl group on the terminal olefin was expected to favor formation of the eight-membered ring by starting the process at the monosubstituted double bond.

The iodide needed for enolate alkylation, **17**, was prepared from 5-hexyn-1-ol in four steps (Scheme 2). After alkyne

Scheme 2[a]



[a] (a) (i) *n*-BuLi, THF, TMSCl, (ii) AcOH, 97%; (b) PDC, CH_2Cl_2, 72%; (c) $Ph_3PCH_2CH_3^+Br^-$, *n*-BuLi, THF, 0 °C, 88%; (d) *n*-BuLi, ethylene oxide, THF, 28%; (e) I_2, PPh_3, imidazole, 75%; (f) (i) KHMDS, **17**, DMF/toluene (1:1), −80 °C; (ii) TBAF, THF, 65% (two steps); (g) allylMgBr, THF, −80 °C, 82%; (h) **8a**, CH_2Cl_2, △, 48%, 6.5:1 diastereomeric mixture at C10.

silylation of 5-hexyn-1-ol by treatment with 2 equiv of *n*-BuLi, followed by trapping of the resulting dianion with trimethylsilyl chloride and washing with acetic acid to remove the trimethylsilyloxy group, oxidation of the resulting alcohol with PDC afforded aldehyde **14**. Wittig alkenation of **14** provided enyne **15**, and the propargyl carbanion of **15**, formed by deprotonation with *n*-BuLi, was alkylated with ethylene oxide at 0 °C to obtain alcohol **16**,[19] which was converted to iodide **17** by treatment with triphenylphosphine, imidazole, and iodide. Iodide **17** was reacted with the kinetic enolate of **3b** (formed by reaction with potassium hexamethyldisilazide in 1:1 DMF/toluene at −80 °C).[20] Subsequent desilylation with TBAF followed by allylation of the ketone group furnished dienyne **12a** in 53% yield (three steps) as an inseparable 1:1 diastereomeric mixture. In this case, dienyne RCM of **12a** with 15% of ruthenium carbene **8a** did indeed take place to render the desired tetracyclic system **1** (48%), showing the feasibility of this new tandem process.

In conclusion we have shown for the first time that [6.4.0] systems can be constructed by tandem ring-closing metathesis of dienynes, in which formation of the all-carbon cyclooctane ring by enyne RCM is followed by closure of the six-membered ring by olefin RCM. It is envisaged that this approach should allow access to general linear 6−8−*n* fused systems starting from conformationally locked *n*-membered cycloalkanones. We are currently extending it to the synthesis of potential haptens **I** with a view to their use to elicit catalytic antibodies.

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Supporting Information Available: Experimental procedure and ^1H and ^{13}C NMR spectra of compounds **11a**, **11d**, **11e**, **17**, **12a**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) These reaction conditions were kindly suggested by Prof. Claudio Palomo (Univ. País Vasco), who developed them in his studies of asymmetric alkylations.