ORGANIC LETTERS

2003
Vol. 5, No. 5
669−672

Synthesis of C-19-Functionalized 1α-Hydroxyvitamin D_2 Analogues via Ring-Closing Metathesis

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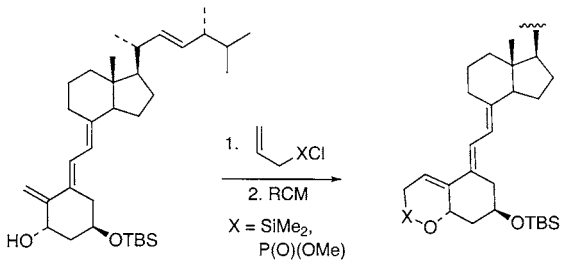
Received December 4, 2002

ABSTRACT



A heteroatom-tethered regioselective ring-closing metathesis reaction was used for the C-19 functionalization of 1α-hydroxy-5,6-*trans*-vitamin D_2 analogues. Applications of the reaction to form a range of analogues by manipulation of the tether using both organolithium reagents and Diels–Alder cycloadditions are described.

It has long been established that the hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 **1**, acts as a regulator in calcium and phosphate homeostasis.[1] More recent discoveries that the hormone can promote cell differentiation while inhibiting tumor cell proliferation led to the speculation that **1** could be used in the treatment of diseases such as leukemia and psoriasis.[2] However, at the doses of **1** required to produce therapeutically useful results, severe hypercalcemia is observed as a side effect.[3] Therefore, the synthesis of analogues that show the required discrimination between antiproliferation and calcemic activities has been the focus of much research. Structural changes in the A, C, and D rings as well as in the side chain region have led to analogues exhibiting the above discrimination.[3,4] Thus far, however,

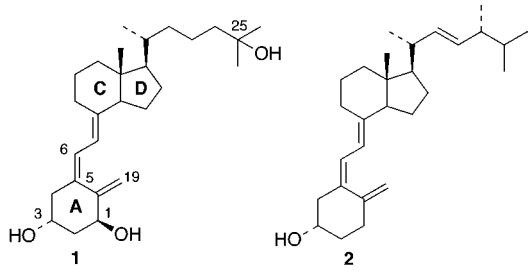


Figure 1. Structures of 1α,25-dihydroxyvitamin D_3 **1** and vitamin D_2 **2**.

(1) Norman, A. W. *Vitamin D the Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979.

(2) (a) Zhou, J. Y.; Norman, A. W.; Chen, D. L.; Sun, G. W.; Uskokovic, M.; Koeffler, H. P. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3929. (b) Anzano, M. A.; Smith, J. M.; Uskokovic, M. R.; Peer, C. W.; Mullen, L. T.; Letterio, J. J.; Welsh, M. C.; Shrader, M. W.; Logsdon, D. L.; Driver, C. L.; Brown, C. C.; Roberts, A. B.; Sporn, M. B. *Cancer Res.* **1994**, *54*, 1653. (c) Colston, K. W.; Chander, S. K.; Mackay, A. G.; Coombes, R. C. *Biochem. Pharmacol*. **1992**, *44*, 693.

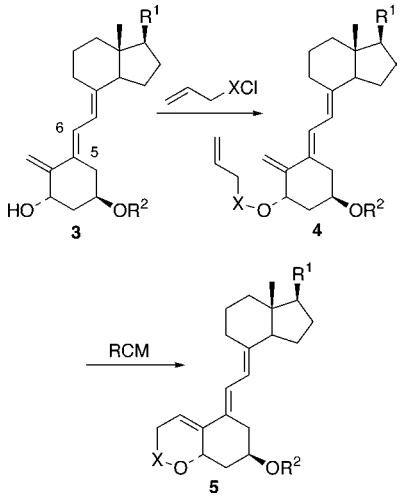
(3) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev*. **1995**, *16*, 200.

10.1021/ol027406w CCC: $25.00
Published on Web 02/01/2003

very few examples of C-19 functionalized analogues have been reported.[5]

The use of tethered heteroatoms such as silicon and boron in ring-closing metathesis (RCM) reactions has been shown to be synthetically very useful in the preparation of di- and trisubstituted alkenes.[6,7] We considered that this methodology could be applied to the regiospecific C-19 monosubstitution of 1α,25-dihydroxyvitamin D_3 **1**. The desired selectivity should be achieved due to the greater susceptibility of the terminal alkenes to RCM and the proximity of the tethered allylic substituent. Removal of the heteroatom tether following RCM should afford a range of functionalized C-19 alkenes. Herein we report preliminary studies of this strategy (Scheme 1) that are focused on the analogous 1α-hydroxy-

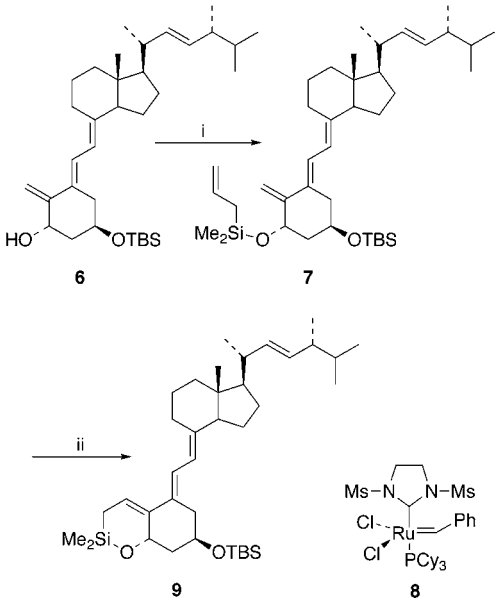
Scheme 1. Heteroatom Tethered RCM with 5,6-*trans*-vitamin D Derivatives



5,6-*trans*-vitamin D_2 **6**, which can be easily prepared from commercially available ergocalciferol **2**.[8]

Reaction of alcohol **6** with allylchlorodimethylsilane in the presence of triethylamine gave the silyl ether **7** in a 76% yield. Ring-closing metathesis was performed by heating a solution of **7** in dichloromethane at reflux with the ruthenium carbene **8** (20 mol %, Scheme 2). Gratifyingly, the only isolated product was the desired adduct **9** (82%) formed from reaction between the two terminal alkenes. It is noteworthy that the delicate triene system of the steroid survived the reaction without any significant decomposition or rearrangement reactions.

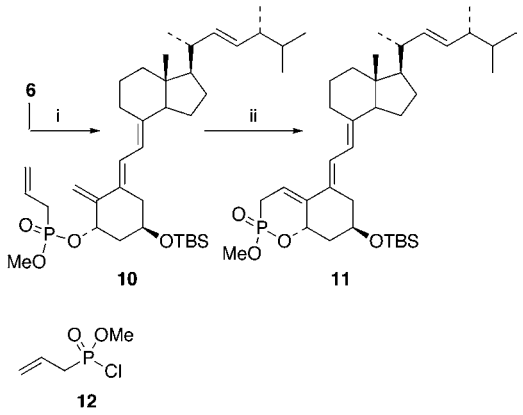
Scheme 2. RCM with a Silyl Ether Tether[a]



[a] Reagents and conditions: (i) $CH_2{=}CHCH_2SiMe_2Cl$, Et_3N, CH_2Cl_2, 25 °C 12 h, 76%; (ii) **8**, CH_2Cl_2, reflux, 3 h, 82%.

To show that the selective RCM was not limited to the use of silicon as a tether, the phosphorus analogue **10** was prepared by reaction of sterol **6** with the phosphonyl chloride **12** and triethylamine. Subsequent RCM afforded the cyclic phosphonate **11** in an excellent 79% yield (Scheme 3).

Scheme 3. RCM with a Phosphonate Ester Tether[a]



[a] Reagents and conditions: (i) **12**, Et_3N, CH_2Cl_2, 25 °C, 12 h, 60%; (ii) **8**, CH_2Cl_2, reflux, 3 h, 79%.

With the RCM product **9** in hand, several methods were used to transform the product to afford a variety of C-19 functionalized analogues. We expected that on Tamao oxidation[9] the diol **13** should be formed as the major product

(4) (a) Muralidharan, K. R.; De Lera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1993**, *58*, 1895. (b) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823. (c) Kanzler, S.; Halkes, S.; van de Velde, J. P.; Reischl, W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1865.

(5) (a) Yamada, S.; Suzuki, T.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 3085. (b) Yamada, S.; Nakayama, K.; Takayama, H.; Itai, A.; Iitaka, Y. *J. Org. Chem.* **1983**, *48*, 3477. (c) Addo, J. K.; Ray, R. *Steroids* **1998**, *63*, 218. (d) Swamy, N.; Addo, J. K.; Ray, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 361. (e) Addo, J. K.; Swamy, N.; Ray, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 279.

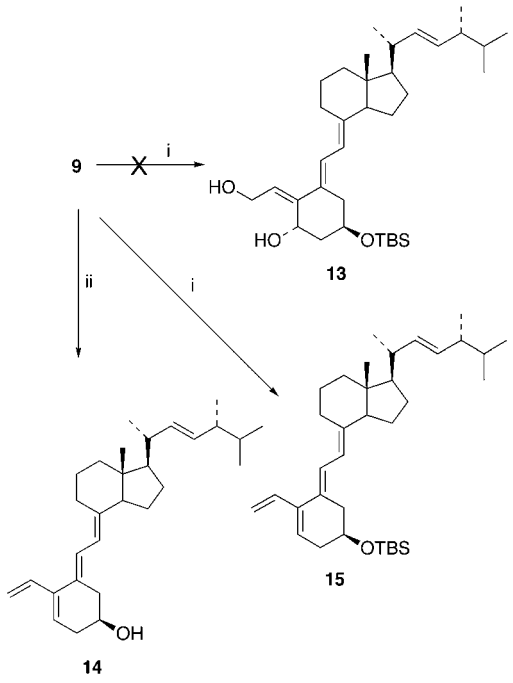
(6) (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861.

(7) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152.

(8) (a) Andrews, D. R.; Barton, D. H. R.; Cheng, K. P.; Finet, J. P.; Hesse, R. H.; Johnson, G.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 1635. (b) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609.

(Scheme 4). However, when **9** was allowed to react with hydrogen peroxide and a fluoride source in a variety of

Scheme 4. Tetraene Synthesis via Peterson Olefination[a]

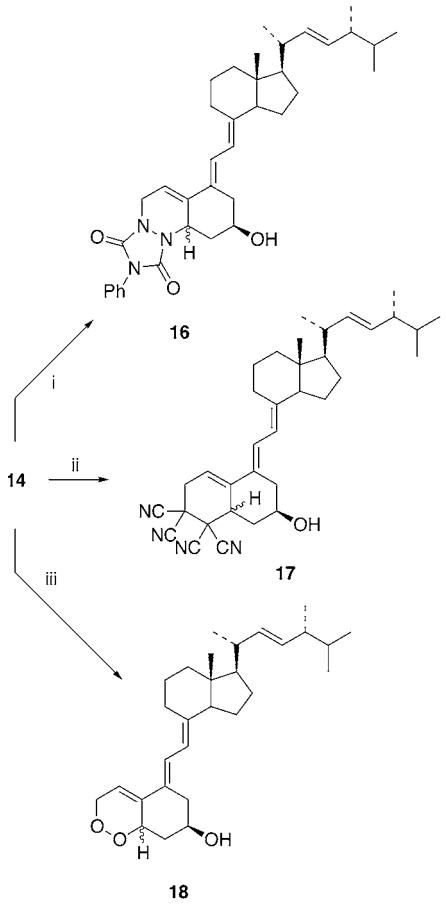


[a] Reagents and conditions: (i) H_2O_2, KF, DMF, 25 °C, 3 h, 50%; (ii) Bu_4NF, THF, 25 °C, 15 h, 64%.

solvents, none of the expected product **13** was isolated. Instead, in DMF as solvent, the tetraene **15** (50%) was formed, presumably by a vinylogous Peterson olefination reaction.[10] Consistent with this hypothesis, reaction of the cyclic adduct with tetrabutylammonium fluoride in THF gave the deprotected tetraene **14** in 64% yield.

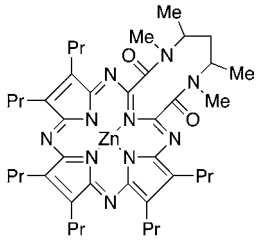
While the outcome of the oxidation reaction was not the expected one, the tetraene **14** could still be used to form C-19-functionalized derivatives via Diels−Alder reactions. A variety of dienophilies were examined; however, only highly electron-deficient dienophiles were effective (Scheme 5). Both Cookson's dienophile[11] and tetracyanoethylene **19** afforded the Diels−Alder cycloadducts **16** and **17** in good yields. In both cases, no significant diastereoselectivity of reaction was observed and both C-1 isomers were formed in a 1:1 ratio (Scheme 5). Singlet oxygen, generated using the *seco*-porphyrazine sensitizer[12] **20** (Figure 2), was allowed to react with the tetraene **14** to form the endoperoxide **18**, although due to the instability of the product, the isolated

Scheme 5. Diels−Alder Cycloadditions of Tetraene **14**[a]



[a] Reagents and conditions: (i) Cookson's reagent, EtOAc, 0 °C, 30 min, 75%; (ii) $(NC)_2C{=}C(CN)_2$ **19**, $CDCl_3$, 25 °C, 24 h, 67%; (iii) air, *seco*-porphyrazine **20**, $CDCl_3$, 25 °C, 8 h, 8%.

yield was low on chromatographic purification. The reactions to produce adducts **17** and **18** were carried out in deuteriochloroform to facilitate monitoring by NMR spectroscopy.



20

Figure 2. *seco*-Porphyrazine sensitizer **20**.

The manipulation of the silicon tether was also achieved using organolithium reagents. Reaction of silyl ether **9** with phenyl- and methyllithium gave, after hydrolytic workup, the adducts **21** and **22** (Scheme 6).

In summary, we have shown that heteroatom-tethered regioselective ring-closing metathesis reactions can be used

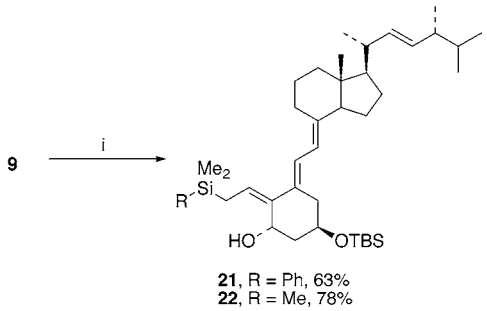
(9) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

(10) (a) Takano, S.; Otaki, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1985**, 485. (b) Angell, R.; Parsons, P. J.; Naylor, A.; Tyrrell, E. *Synlett* **1992**, 599.

(11) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett*. **1962**, *3*, 615.

(12) Baum, S. M.; Trabanco, A.-A.; Garrido Montalban, A.; Micallef, A. S.; Zhong, C.; Meunier, H. G.; Suhling, K.; Phillips, D.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem*. **2003**, *68*, in press.

Scheme 6. Ring Cleavage of Silyl Ether **9** Using PhLi and MeLi[a]



21, R = Ph, 63%
22, R = Me, 78%

[a] Reagents and Conditions: (i) RLi, PhMe, −30 °C, 2 h.

for the C-19 functionalization of 1α-hydroxy-*trans*-vitamin D_2 analogues.[13] Using this method, both silicon- and phosphorus-tethered systems have been successfully prepared. Application of the process to form a range of analogues has been shown by the manipulation of the silicon tether using both substitution with phenyllithium and methyllithium or by elimination and subsequent Diels−Alder cycloaddition reactions.

(13) All new compounds were characterized by spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, UV, and LRMS) and HRMS except for **11** ((^{1}H NMR, ^{13}C NMR, UV, LRMS .and HRMS), **18** (^{1}H NMR, ^{13}C NMR, IR, and UV), and **17** for which ^{1}H NMR, ^{13}C NMR, and LRMS were obtained, due to instabilities of the products.

Acknowledgment. We thank the EPSRC for their support of this research, Glaxo SmithKline for the generous endowment (to A.G.M.B.) and for support of our research on alkene metathesis, the Royal Society and Wolfson Foundation for a Royal Society-Wolfson Research Merit Award (to A.G.M.B.), the Ramsay Memorial Fellowship Trust for postdoctoral support (to C.E.A.), and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College. We also thank Sven Baum (Imperial College) for providing a sample of *seco*-porphyrazine **20**.

Supporting Information Available: All experimental procedures, and characterization of all novel compounds **7**, **9**−**11**, **14**, **15**, **16** (both isomers), **17**, **18**, **21**, and **22** including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027406W