reduction, and Swern oxidation[9] to give the *all-(E)*-tetraenal **A15**. Our initial cyclization of this sensitive intermediate with Me_2AlCl in CH_2Cl_2 at ca.–10 to –15 °C for 28 h gave rise to a complex mixture containing two major products, dienal **A17** and the tricyclic alcohol **A18**.[10] Cyclization at –78 to –30 °C for 4.5 h, on the other hand, afforded a 1:1 mixture of the expected carbinyl epimers **A16** and **A17** in nearly 80% yield.[11,12] Pure samples could be obtained via chromatography on silica gel. Detailed ^1H NMR analysis and comparison with the spectrum of a kijanolide derivative (Table I) supports the structure assignments.[2a] The epimeric hydronaphthalenes **A16** and **A17** showed little contamination by other diastereoisomers as judged by the high-field ^1H NMR spectra. When allowances are made for impurities in enal **A15** (C-4 epimer and 10-*Z* isomer), the yield of cyclic products **A16** and **A17** approaches 90%.

Conceivably the unwanted 8α epimer **A17** could be inverted via deprotection, oxidation and reduction to the desired 8β epimer **A16**.[13] However, a more satisfactory solution would entail synthesis of an acyclic precursor (**A15**) with the correct absolute configuration at C-4, C-6, and C-7 for direct cyclization to optically active **A16**.[15] The efficient transformation of the epimers **A15** to a 1:1 mixture of **A16** and **A17** demonstrates the feasibility of this approach. Work along these lines is currently in progress.

Acknowledgment. Support for this work was provided by a research grant from the National Cancer Institute of the NIH (CA 34243). We thank the South Carolina NSF Regional NMR Center for cooperation in obtaining high-field spectra.

(9) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(10) The structure assignment is based upon high-field ^1H NMR analysis. Although the product is an apparent mixture of epimeric centers in the five-membered ring, the benzyloxy carbinyl proton is clearly axial. Thus only the equatorial benzyloxy epimer **A16** undergoes this ene-type cyclization.

(11) Typically a 0.1 M solution of enal was cooled to –78 °C, and an equimolar quantity of 1 M Me_2AlCl in hexanes was added dropwise. Our previous experience suggests that the *Z* isomer contaminant of **A15** will not cyclize under these conditions. The minor contaminants present in **A16** and **A17** are therefore most likely related to the ca. 5% cis-dimethyl isomer of **A15**.

(12) The C-11 unsubstituted analogue of **A15** was found to cyclize under comparable conditions to a 1:1 epimeric mixture analogous to **A16** and **A17**. The stereochemistry of these cyclizations is consistent with a product-like transition state with the tether ring in a chair and the Diels–Alder ring in a boat conformation. Diastereoselectivity stems from the preferred equatorial orientation of the C-5-methyl grouping in this boat-chair conformation. Relative energies of the diastereomeric boat-chair conformers, calculated via Still's Model program,[14] can be used to predict the major cyclization product.[1c,13] For recent ab initio calculations in support of such a picture, see: Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609.

(13) Audia, J. E. Ph.D. Thesis, University of South Carolina, **1985**, pp 59–62, 75–87.

(14) Cf.: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(15) *trans*-2,4-Dimethylglutaric acid has been resolved and both enantiomers are known. Möeller, E. *Lunds Univ. Arsskr. Avd. 2* **1919**, *15*, 56; *Chem. Abstr.* **1920**, *14*, 942. Grunfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277. For a review on asymmetric reductions of acyclic ketones leading to chiral alcohols of predictable configuration, see: Midland, M. M.; Grandbois, E. R.; Howard, S. I.; Morrison, J. D. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 2, Chapters 2 and 3, pp 45–89.

James A. Marshall,* Jonathan Grote, Barry Shearer

Department of Chemistry
University of South Carolina
Columbia, South Carolina 29208

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A Direct, Regio- and Stereoselective 1α-Hydroxylation of (5*E*)-Calciferol Derivatives

Summary: Selenium-IV reagents, particularly buffered selenious acid, afford a regio- and stereoselective 1α-hydroxylation of the trialkylsilyl ethers of (5*E*)-calciferols leading to a convenient synthesis of 1α-hydroxycholecalciferol, 1α-hydroxycalciferol, and 1α,25-dihydroxycholecalciferol.

Sir: While the high potency and striking effects of 1α-hydroxylated vitamin D derivatives on calcium metabolism have stimulated many efforts to prepare such compounds, even the best syntheses are relatively inefficient and/or indirect.[1] Simple allylic hydroxylation of a triene such as **1** or its isomer **5** (Chart I) has been an obvious and beguiling possibility, but to quote from a pertinent paper,[2] "Direct allylic oxidation of Vitamin D is feasible but, because of difficulty in controlling the site, extent and stereochemistry of hydroxylation it is not (at least as yet) an efficient process." We now report an efficient process for the regio- and stereoselective 1α-hydroxylation of (5*E*,7*E*)-trienes such as **5**–**8**. This procedure permits a simple, rather direct synthesis of 1α-hydroxylated vitamin D derivatives.

We noted that while either cholecalciferol (**1**) or its 5*E* isomer (**5**) [available in high yield from the former through electrocyclic addition of SO_2 ($SO_2/C_6H_6/H_2O$) followed by stereospecific thermal elimination of SO_2 (EtOH, $NaHCO_3$) from adducts[3] **9a** and **9b**] gave unpromising mixtures of products upon reaction with SeO_2 in most solvents, a cleaner reaction took place in methanol or solvent mixtures containing methanol and afforded variable amounts of four isomeric 1-hydroxylated products (**10**, **11**, **12**, and **13**), together with a rich mixture of byproducts, several of which contained selenium. While addition of standard reoxidants, e.g., H_2O_2 or $(CH_3)_3CO_2H$,[4] did not improve the reaction, addition of periodate salts [$NaIO_4$, $(C_4H_9)_4NIO_4$] (4 equiv) suppressed formation of selenium-bearing byproducts and increased the yield of **10**, **11**, **12**, and **13** (30% combined). Use of bulky ester blocking groups at 3 (for instance **6**), by suppressing the fortuitous equilibration about the 5,6 bond which accompanied the hydroxylation of **1** or **5**, revealed that while the 5*E* isomer **6** was quickly hydroxylated to afford only 5*E* products (**14** and **15**), the 5*Z* isomer **2** reacted sluggishly to afford both 5*E* and 5*Z* products in poor yield. Throughout this communication

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(2) Paaren, H. E.; Hammer, D. E.; Schnoes, H. K.; DeLuca, H. F. *Proc. Natl. Acad. Sci.* **1978**, *75*, 2080.

(3) (a) Yamada, S.; Takayama, H. *Chem. Lett.* **1979**, 583. (b) Reischl, W.; Zbiral, E. *Helv. Chim. Acta* **1979**, *62*, 1763. Reischl, W.; Zbiral, E. *Monatsh. Chem.* **1979**, *110*, 1463. (c) Yamada, S.; Suzuki, T.; Takayama, H.; Miyamoto, K.; Matsunaga, I.; Nawata, Y. *J. Org. Chem.*, **1983**, *48*, 3483.

(4) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

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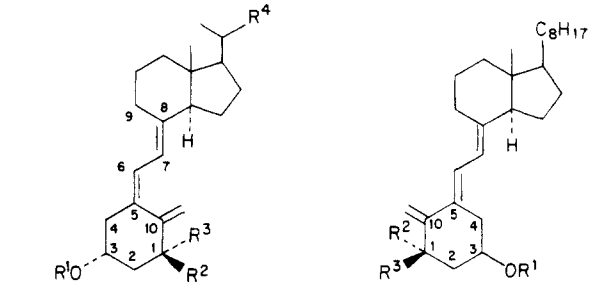
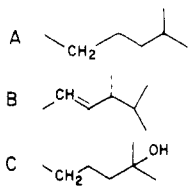
Chart I

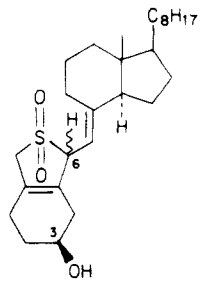


1, $R^1=R^2=R^3=H$; R^4="A"
2, R^1=t-BuCO; $R^2=R^3=H$; R^4="A"
3, $R^1=R^2=R^3=H$; R^4="B"
4, $R^1=R^2=R^3=H$; R^4="C"
10, $R^1=R^3=H$; R^2=OH; R^4="A"
11, $R^1=R^2=H$; R^3=OH; R^4="A"
20, $R^1=R^3=H$; R^2=OH; R^4="B"
21, $R^1=R^3=H$; R^2=OH; R^4="C"

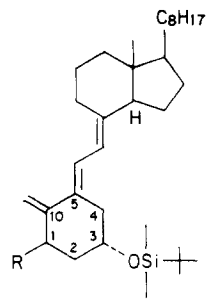
side chains



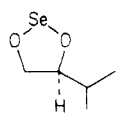
5, $R^1=R^2=R^3=H$
6, R^1=t-BuCO; $R^2=R^3=H$
7, R^1=t-BuMe$_2$Si; $R^2=R^3=H$
8, R^1=t-BuMe$_2$Si; $R^2=R^3=H$
12, $R^1=R^3=H$; R^2=OH
13, $R^1=R^2=H$; R^3=OH
14, R^1=t-BuCO; R^2=OH; $R^3=H$
15, R^1=t-BuCO; $R^2=H$; R^3=OH
16, R^1=t-BuMe$_2$Si; R^2=OH; $R^3=H$
17, R^1=t-BuMe$_2$Si; $R^2=H$; R^3=OH



9a, 6*R*
9b 6*S*



18, R=H
19, R=OH

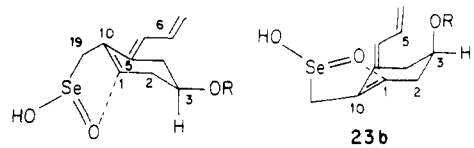


22

all reactions of hydroxylation were carried out under reflux.

The superiority of methanol as solvent at first suggested involvement of selenite esters in the hydroxylation. Indeed we found that dimethyl selenite, diethyl selenite, or ethylene selenite (0.5–1 equiv) accomplished a similar, smooth hydroxylation in *nonalcoholic solvents* when accompanied by a suitable reoxidant (4–5 equiv) such as a periodate salt, $(CH_3)_3CO_2H$, or *N*-methylmorpholine *N*-oxide (NMO). The last of these reoxidants, which proved superior in our hands, has not, to our knowledge, been previously used for this purpose.

While the hydroxylation of **6** now afforded **14** and **15** in good yield (48%) the stereoselectively, all-be-it in the correct sense (1α:1β, 3:1), was unsatisfactory. Use of the chiral selenite **22** produced little change in the 1α/1β ratio but altering the protecting group at 3 to a silyl ether, i.e., **7** or **8**, produced a dramatically favorable change (1α-(**16**):1β(**17**), 20:1). The improved stereoselectivity surely results from an enforcement of conformation **23a** upon the putative selenoxide intermediate[5] rather than **23b**. This



23a **23b**

is dictated by a strong predisposition for an equatorial conformation of the 3-silyloxy group.[6] In keeping with this we found that the 3-epi compound **18** was smoothly and stereoselectively converted into the corresponding 1β-hydroxy isomer **19** (characterised as the 1-*m*-dinitrobenzoate).

A simple conversion of calciferol derivatives into 1α-hydroxylated analogues was thus at hand. For instance, cholecalciferol was treated with SO_2 in benzene/water and the resulting mixture of adducts[3] (**9a** and **9b**) was heated in ethanolic $NaHCO_3$ to afford (5*E*)-cholecalciferol (**5**) (90%). Silylation (chloro-*tert*-butyldimethylsilane, imidazole, dimethylformamide) of **5** gave **8** (95%), which on oxidation [SeO_2 (0.7 equiv), NMO (4 equiv) in methanol–CH_2Cl_2] gave the 1α-hydroxy-(5*E*)-vitamin derivative **16** (58%). The later, upon illumination in the presence of acridine,[7] isomerized cleanly to the 5*Z* configuration (82%). Removal of the silyl group [$(C_4H_9)_4N^+F^-$, THF, (87%)] gave crystalline[1a] 1α-hydroxycholecalciferol (**10**) [yield (from **1**), 35%]. In an analogous fashion ergocalciferol (**3**) and 25-hydroxycholecalciferol (**4**) were converted into crystalline 1α-hydroxyergocalciferol[1i] (**20**) (31%) and 1α,25-dihydroxycholecalciferol[1a] (**21**) (32%), respectively.[8]

We knew of no convincing report of involvement of selenite esters in allylic hydroxylation and we had reason to doubt a *direct* participation. First, phenylseleninic anhydride[9] (a reagent which could, in principle, hydroxylate at 1 via the accepted mechanism[4]) reacts with calciferol derivatives to afford completely different products.[10] Second, the reactions we observed were substantially, but unpredictably, promoted by traces of water. Subsequently we found that partially "hydrated" SeO_2 (0.7 equiv) in mixtures of CH_3CN/chlorinated hydrocarbon accompanied by NMO (4 equiv.) as the reoxidant accomplished the same smooth, regio- and stereoselective hydroxylation of **8** as was achieved with selenite esters (yield of **16** (68%)). Although selenous acid, itself, brought about extremely rapid degradation of the substrate under the above conditions, selenous acid (0.7 equiv) buffered with 0.5–1 equiv of *N*-methylmorpholine afforded, by contrast, smooth hydroxylation of **8** into **16**.[11] Although these observations do not clearly reveal the exact nature of the functioning oxidant, we speculate that selenous acid, slowly liberated

(5) Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jesen, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 7917.

(6) Schneider, H. J.; Hopper, V. *J. Org. Chem.* **1978**, *43*, 3866.

(7) Gielen, J. W. J.; Koolstra, R. B.; Jacob, H. J. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 306.

(8) 1-Hydroxyergocalciferol (**20**) had mp 141–143 °C (lit.[1i] mp 138–140 °C). Other physical constants were as reported.[1i] 1α,25-Dihydroxycholecalciferol (**21**) was characterised as the crystalline chloroform solvate identical in all respects with that previously reported.[1a]

(9) Barton, D. H. R.; Ley, S. V.; Magnus, P. D.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans 1* **1977**, 567. Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130.

(10) The major products were apparently derived from attack at the 5,6-double bond and from phenyl selenenylation at C-19.

(11) A solution of NMO (monohydrate, 660 mg) in CH_2Cl_2 (5 mL) was stirred with anhydrous $MgSO_4$ for 30 min and then filtered into a solution of **8** (545 mg) in 1,2-dichloroethane (5 mL). The mixture was warmed to reflux and quickly treated with a solution of selenious acid (140 mg) and *N*-methylmorpholine (110 mg) in acetonitrile (5 mL). After 25 min at reflux (TLC control) the mixture was diluted with CH_2Cl_2 and then washed with saturated aqueous $NaHCO_3$ followed by brine. The organic phase was dried (Na_2SO_4), concentrated in vacuo, and purified by preparative TLC to afford **16** (360 mg, 64%).

or well-buffered, produces in a controlled fashion *monomeric* SeO_2 which then serves as the active oxidant.[12]

Whatever the mechanism it is clear that this system can accomplish efficient, selective hydroxylation of sensitive and heretofore intractible substrates.

(12) Preliminary studies of the effects of "pH" and of water are consistent with this interpretation.

David R. Andrews, Derek H. R. Barton
Kwok P. Cheng, Jean-Pierre Finet, Robert H. Hesse*
Graham Johnson, Maurice M. Pechet
Research Institute for
Medicine and Chemistry
Cambridge, Massachusetts 02142
Received February 14, 1985

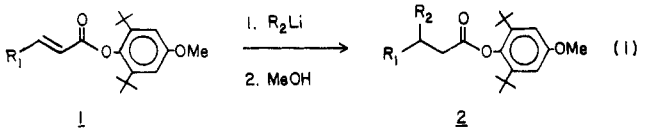
Sterically Directed Conjugate Addition Reactions of Unsaturated Esters

Summary: Unsaturated esters of 2,6-di-*tert*-butyl-4-methoxyphenol undergo conjugate addition reactions with a variety of organolithium reagents. Oxidation of adducts with ceric ammonium nitrate provides substituted carboxylic acids.

Sir: The reaction of strong nucleophiles with α,β-unsaturated esters usually results in the formation of products resulting from carbonyl addition.[1] Products resulting from the alternate 1,4 or conjugate addition mode generally require the use of organocopper reagents derived from reactive nucleophiles.[2] Recent reports suggest that lithium enolates of some esters also reliably undergo conjugate addition reactions with unsaturated acyclic esters.[3]

It was observed some time ago that conjugate addition reactions of unsaturated ketones can be promoted by steric interference with the 1,2-addition process. DeMeester and Fuson[4] found that Grignard reagents undergo predominantly 1,4-addition reactions with mesityl vinyl ketone and more recently Seebach and co-workers have demonstrated similar selectivity for 1,4-addition with organolithium reagents and unsaturated trityl ketones as well as amide acceptors derived from a highly hindered amine.[5]

While occassional reports of conjugate addition reactions of organometallic reagents to unsaturated *sec*-butyl[1c,6] and *tert*-butyl esters[7] have appeared, no general method for the steric suppression of carboxyl reactivity in unsaturated esters has been reported. A recent report by Seebach[8] noting the resistance of 2,6-di-*tert*-butyl-4-methylphenyl esters (BHT esters) to carboxyl attack by alkyllithium reagents suggested that conjugate addition reactions might be favored in unsaturated acceptors having this type of carbonyl steric protection. We now report that α,β-unsaturated esters of 2,6-di-*tert*-butylphenol derivatives cleanly undergo conjugate addition reactions with a range of organolithium reagents (eq 1). Results of nucleophilic

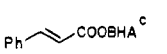
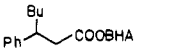
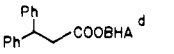
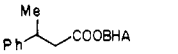
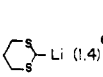
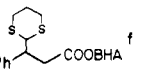
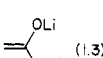
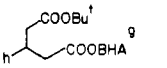
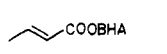
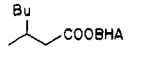
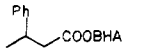
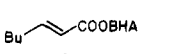
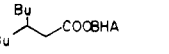
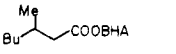


1 2 (1)

additions to unsaturated esters of 2,6-di-*tert*-butyl-4-methoxyphenol (BHA esters, **1**) chosen for their ease of oxidative hydrolysis (vide infra) are shown in Table I.[9]

Typical unsaturated BHA esters (**3**, **9**, and **12**), prepared from the corresponding acid chlorides and lithium 2,6-di-*tert*-butyl-4-methoxyphenoxide in the manner previously described for the preparation of saturated BHA esters[10] undergo exceptionally clean 1,4-addition reaction reactions with lithium reagents in THF at −78 °C over the course of several minutes giving enolates which, when

Table I. Addition of Lithium Reagents to Unsaturated BHA Esters[a,b]

entry	acceptor	RLi (equiv)	product	yield (%)
1	 3	n-BuLi (1.1)	 4	99
2		PhLi (1.3)	 5	87
3		MeLi (1.3)	 6	96
4		 (1.4)[e]	 7	91
5		 (1.3)[e]	 8	93
6	 9	n-BuLi (1.2)	 10	75
7		PhLi (1.2)	 11	91
8	 12	n-BuLi (1.2)	 13	95
9		MeLi (1.1)	 14	92

[a] All structures are supported by spectral and analytical data. [b] See ref 11 for a typical procedure. [c] mp 120–121 °C. [d] mp 145.5–147.0 °C. [e] Inverse addition. [f] mp 149.0–150.5 °C. [g] mp 84.5–85.5 °C.

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