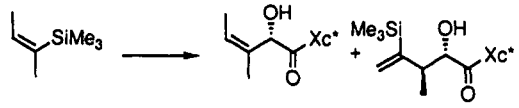
logical and synthetic importance.[3]

From a mechanistic point of view, the reaction with vinylsilane provides valuable insight into the continuum of mechanisms ranging from cationic substitution to the pericyclic ene pathway, depending critically on both the particular Lewis acid[5] used and the vinylsilane geometry (eq 3). In sharp contrast to the exclusive formation of



(3)

(Z)-1a $TiCl_4$ (quant) 1 : 1
$SnCl_4$ (quant) 0 : 100 (>99% *anti*)

substitution product with (*E*)-vinylsilane, (*Z*)-vinylsilane provides not only the substitution product[11] but also the ene product.[13] More significantly, the use of $SnCl_4$ provides only the ene product.[13,14] Thus, vinylsilane may represent a novel mechanistic probe for Lewis acid promoted ene reactions.[15]

Supplementary Material Available: Experimental details of the substitution reactions and physical data of the products (7 pages). Ordering information is given on any current masthead page.

(13) ^1H NMR 0.00 (s, 9 H), 5.30 (d, J = 2.2 Hz, 1 H), 5.55 (d, J = 2.2 Hz, 1 H) ppm.

(14) The $SnCl_4$-promoted ene reaction provides a high enantiomeric purity (>99% de) along with enhanced anti diastereoselectivity[4] (>99%) as compared with (*E*)-2-butene without the silyl group (94% anti).[10]

(15) For a mechanistic probe based on primary kinetic isotope effect: Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160. Song, Z.; Beak, P. *Ibid.* **1990**, *112*, 8126 and references.

Stereocontrolled Synthesis of a Trihydroxylated A Ring as an Immediate Precursor to 1α,2α,25-Trihydroxyvitamin D_3

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Summary: 3-Bromo-2-pyrone (1) was coaxed into inverse-electron-demand Diels–Alder cycloaddition with dioxole 2 under sufficiently mild thermal conditions to allow isolation of functionally and stereochemically rich bicycloadduct *endo*-3 that was transformed into trihydroxylated A-ring allylic phosphine oxide as an immediate precursor to 1α,2α,25-trihydroxyvitamin D_3.

Metabolic hydroxylation of vitamin D_3 produces 1α,25-dihydroxyvitamin D_3 (calcitriol)[1] that is a potent regulator of cell differentiation and proliferation[2] as well as intestinal calcium and phosphorus absorption and bone calcium mobilization. Calcitriol is used currently for clinical treatment of osteoporosis and for chemotherapy of certain metabolism disorders such as neonatal hypocalcemia, chronic renal failure, and hypoparathyroidism.[3] Various calcitriol analogues having modified D-ring side chains are being developed internationally for chemotherapy of psoriasis, a disease characterized by hyperproliferation of skin cells.[4] In comparison, relatively little effort, however, has been devoted to preparing ring-A modified vitamin D_3 derivatives.[5] Herein we report an efficient, practical, and stereocontrolled synthesis of a trihydroxylated A ring as an immediate precursor to 1α,2α,25-trihydroxyvitamin D_3, a new vitamin D_3 analogue.

We have recently shown that electron-deficient 3-sulfinyl- and 3-sulfonyl-2-pyrones undergo inverse-electron-demand Diels–Alder cycloadditions with various electron-rich dienophiles under sufficiently mild conditions to allow isolation of the initial rigid, bridged, bicyclic adducts without loss of CO_2 by cycloreversion and without subsequent aromatization.[6] We have now discovered that even 3-bromo-2-pyrone (1), readily prepared on multigram scale from 5,6-dihydro-2-pyrone[7a] and at least 20 times *less* reactive than 3-(*p*-tolylsulfonyl)-2-pyrone (as determined by a competition experiment), also cycloadds as an electron-deficient diene under carefully controlled thermal conditions.[8] For example, heating 3-bromo-2-pyrone (1) and 2,2-dimethyl-1,3-dioxole (2)[6b,9] along with a small

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(2) (a) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Science (Washington, D.C.)* **1984**, *224*, 1438. (b) Provvedini, D. M.; Tsoukas, C. D.; Deftos, L. J.; Manolagas, S. C. *Science (Washington, D.C.)* **1983**, *221*, 1181.

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(4) For example, see: Calverley, M. J. In *Vitamin D: Molecular, Cellular, and Clinical Endocrinology*; Norman, A. W., Ed.; de Gruyter: Berlin, 1988; p. 51. Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609.

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(6) (a) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967. (b) Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573. (c) Posner, G. H. *Pure Appl. Chem.* **1990**, *62*, 1949.

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(8) For normal-electron-demand cycloaddition using 3-bromo-2-pyrone involving as the major reaction pathway thermal extrusion of CO_2 from the initial bicycloadducts, see: Nesterova, T. L.; Shusherina, N. P.; Shulishov, E. V. *Zh. Org. Khim.* **1985**, *21*, 427 (*J. Org. Chem. U.S.S.R.* **1985**, *21*, 387) and references therein. For an extensive listing of cycloadditions with other pyrones, see: *Dienes in the Diels-Alder Reaction*; Fringuelli, F., Taticchi, A., Eds.; John Wiley, Inc.: New York, 1990.

(9) Mattay, J.; Thünker, W.; Scharf, H.-D. *Synthesis* **1983**, 208.

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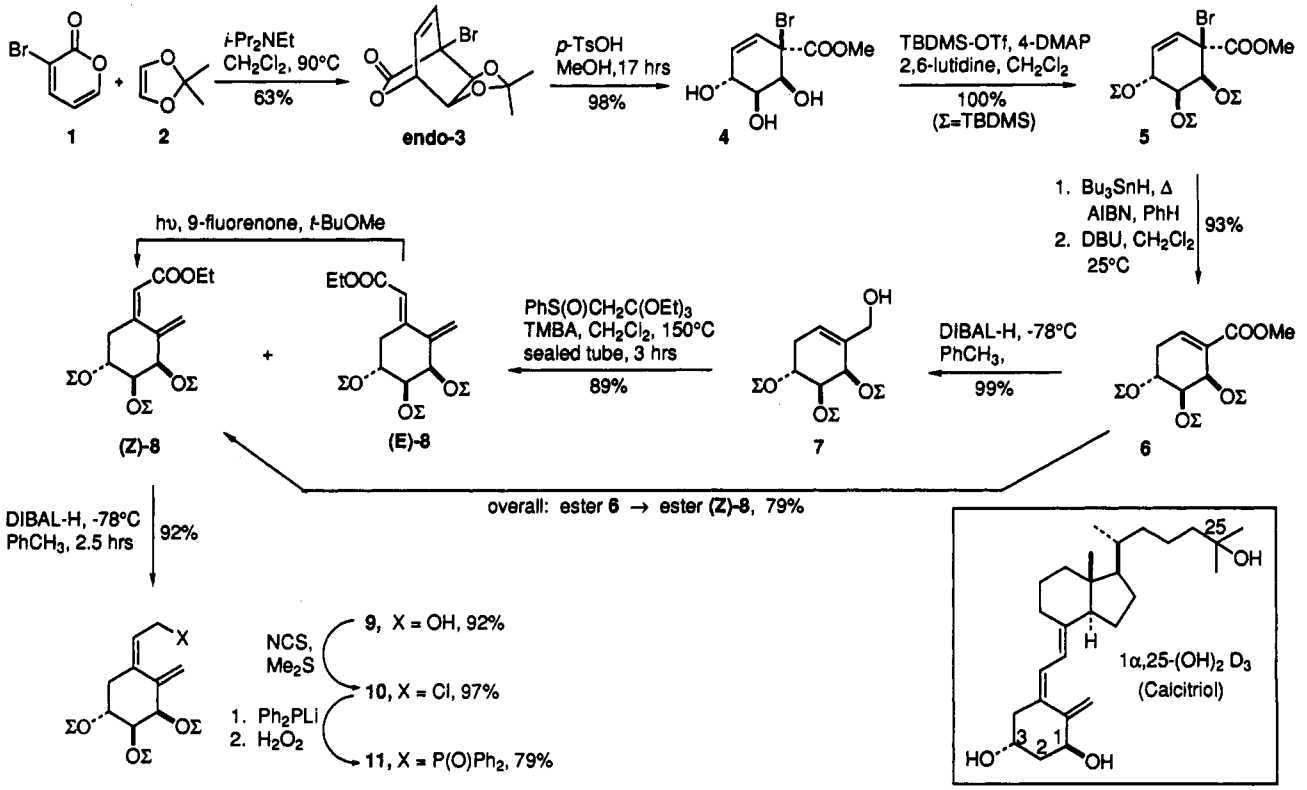
Scheme I



amount of ethyldiisopropylamine in a sealed tube at 90 °C for 4 days gave cycloadduct **3** as a 4:1 mixture of endo:exo isomers in good yield (Scheme I). Even slightly higher temperatures (e.g. ≥100 °C), however, caused formation of substantial amounts of side products. Bicycloadducts **3** were obtained also in good yield as a mixture of endo and exo isomers via high-pressure (~11 kbar) cycloaddition at room temperature. Use of Lewis acid catalysts, however, caused rapid decomposition of dioxole **2**.[10] Purification of bromine-containing cycloadducts **3** was tricky because of their instability when in prolonged contact with silica gel; rapid (i.e. <3 min) flash column chromatography followed by crystallization, however, gave the desired isomer *endo*-**3** in 63% yield. The endo stereochemistry of this cycloadduct was assigned in analogy with previous work by us[6] and by others[11] as well as by chemical correlation with chorismic acid[6b] and with shikimic acid.[7b]

Acidic methanolysis of the lactone bridge and of the acetonide functionality in *endo*-**3** produced crystalline, pentasubstituted cyclohexene **4** as a stable, single diastereomer. Triple silylation of the hydroxyl groups in triol **4** formed *tert*-butyldimethylsilyl (TBDMS) ether **5** that underwent smooth radical debromination and double bond isomerization to give conjugated enoate ester **6**. Carbonyl reduction with diisobutylaluminum hydride (DIBAL-H) gave allylic alcohol **7** cleanly. Trioxygenated allylic cyclohexenol **7** reacted at 145 °C with 1-(phenylsulfinyl)-2,2,2-triethoxyethane[6a] in the presence of 2,4,6-trimethylbenzoic acid (TMBA) as catalyst via a one-flask, four-step sequence, as follows: (1) allylic alcohol–ortho ester exchange; (2) elimination of ethanol to form a mixed ketene acetal that is also an allylic vinylic ether; (3) thermal [3,3]sigmatropic Claisen rearrangement[12] to produce a γ,δ-olefinic α-sulfinyl ester; and finally (4) in situ β-elimination of benzenesulfenic acid[13] to produce a 4:3 mixture of *E*:*Z* dienoate esters **8** in 89% yield. The operational simplicity of this convenient, efficient, and regiospecific ethoxycarbonylmethylenation procedure is a highlight of this paper; a complete report will soon delineate the full potential of this one-flask protocol.[14]

Dye-sensitized photoisomerization[15] of *E*- and *Z*-**8** produced the desired dienoate ester *Z*-**8** as expected. Reduction of the ester carbonyl group with DIBAL-H yielded allylic alcohol **9** cleanly. It is noteworthy that the nature of the hydroxyl-protecting groups in triol *Z*-**8** was critical for the successful preparation of allylic alcohol **9**; when DIBAL-H was used with *cis*-diol *acetonide* corresponding to *cis*-diol silyl ether *Z*-**8** much *conjugate* reduction occurred presumably due to complexation between DIBAL-H and the acetonide unit.[16] Thus the successful carbonyl reduction of the ester group in *cis*-diol silyl ether *Z*-**8** is one dramatic example of the considerably lower ability of alkyl silyl ethers vs dialkyl ethers to coordinate with Lewis acids.[16]

(10) For BF_3·OEt_2-promoted polymerization of dioxole **2** see: Akkapeddi, M. K.; Reimschuessel, H. K. *Macromolecules* **1979**, *12*, 827.

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Allylic chlorination gave Z-dienyl chloride 10 that reacted with lithium diphenylphosphide[15] and then with hydrogen peroxide to form allylic phosphine oxide 11. Thus in 11 steps and in 32% overall yield, easily prepared 3-bromo-2-pyrone has been transformed into an immediate precursor of 1α,2α,25-trihydroxyvitamin D_3, a new analogue of vitamin D_3.

Important aspects of this report include the following: (1) discovery that 3-bromo-2-pyrone can be coaxed into effective inverse-electron-demand cycloaddition with an electron-rich dienophile under sufficiently mild thermal conditions to prevent loss of CO_2 from the initial bicycloadduct; (2) use of easily prepared 3-bromo-2-pyrone instead of less easily prepared 3-(tolylsulfonyl)-2-pyrone as an important practical improvement of this cycloaddition methodology;[6] (3) use of a new sulfinyl ortho ester for one-flask, regiospecific conversion of complex allylic alcohol 7 into 2-carbon-extended conjugated dienoate ester 8; and (4) demonstration that silyl ether protection in contrast to alkyl ether protection can effectively prevent ether oxygen–Lewis acid coordination (e.g. Z-8 → 9).

Continuing efforts are being directed at (1) preparation of enantiomerically pure allylic phosphine oxide 11; (2) conversion of 11 into 1α,2α,25-trihydroxyvitamin D_3 via Lythgoe coupling;[14,16] and (3) biological evaluation of this new vitamin D_3 derivative. Results of these efforts will be reported in due course.

Acknowledgment. We thank the NIH (GM-30052) for generous financial support and Professor Jacqueline Seyden-Penne (Orsay, France) for first bringing to our attention the difference in Lewis acid coordinating ability of silyl vs alkyl ethers.

Supplementary Material Available: Characterization of compounds 3–11 (5 pages). Ordering information is given on any current masthead page.

Decarboxylative Cyclization of Allylic Cyclic Carbamates: Applications to the Total Synthesis of (−)-Codonopsine[1]

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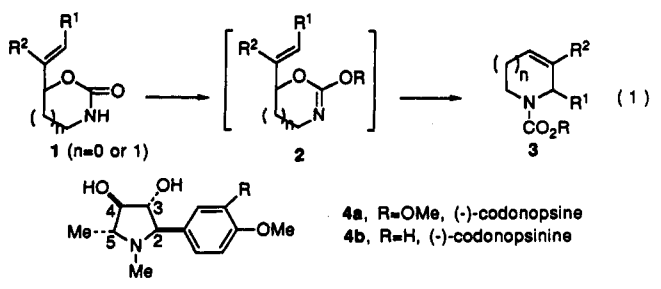
Received April 8, 1991

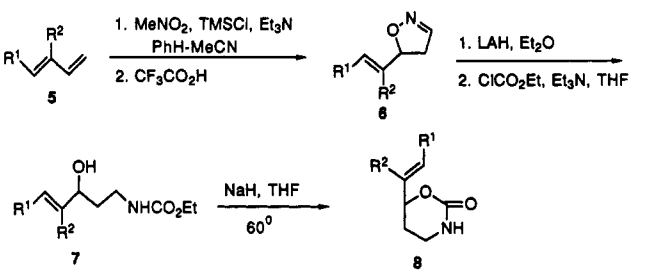
Summary: Decarboxylative cyclization of allylic cyclic carbamates 1 leading to 2-substituted Δ³-piperidines and -pyrrolidines, as well as its application to the total synthesis of (−)-codonopsine, is described.

2-Alkyl-Δ³-piperidines and -pyrrolidines are useful intermediates in the synthesis of various alkaloids.[2] None of the methods for synthesis of these compounds, however, are suitable for the synthesis of 2-aryl-Δ³-pyrrolidines. In a project directed toward the synthesis of (−)-codonopsine (**4a**), a natural product[3] that possesses hypotensive activity with no effect on the central nervous system,[4] we needed a 2-aryl-Δ³-pyrrolidine as a key intermediate. A general entry to both 2-aryl- or alkyl-substituted Δ³-pyrrolidines and -piperidines was desired for the synthesis not only of (−)-codonopsine but also of other alkaloids such as pumiliotoxin C.[5] Since the Claisen rearrangements of lactonic (silyl) enolates[6] and acyclic allylic imidates[7] to functionalized cycloalkenes and amides have been fruitful areas of organic synthesis, we initiated a program to study whether allylic cyclic carbamates 1 undergo similar rearrangement to 3 through intermediate 2 (eq 1). Herein we report our preliminary results and an application to the first total synthesis of natural (−)-codonopsine.

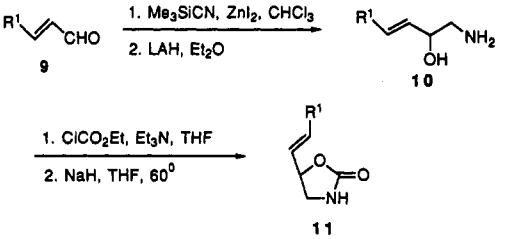


†Du Pont Merck Pharmaceutical Co.
‡Du Pont Co.

Scheme I



Scheme II



The synthesis of compounds 1 (n = 1) is shown in Scheme I. Addition of trimethylsilyl ester of *aci*-nitro-

(1) Contribution No. 91-P9 from Du Pont Merck Pharmaceutical Co.
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