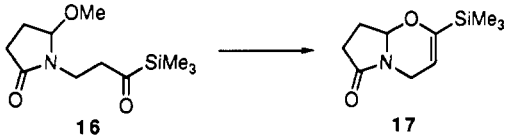
The cyclization is not limited to the formation of dihydropyrans. Dihydrofuran 11[9] (entry 19) could also be obtained. We found that 11 was more sensitive to the hydrogen halides and that a higher reaction temperature resulted in a lower yield. Therefore, using more potassium iodide to shorten the reaction time was crucial to ensure a better yield. Unfortunately, this method was not useful for seven-membered ring formation (entry 20). In another experiment, using modified Finkelstein reaction conditions,[10] acylsilane 14 gave only α,β-unsaturated acylsilane 15 (entry 21).

It is not necessary to use (haloacyl)silane in this type of cyclization. When an acyliminium ion was generated from 16[11] (eq 2), it could be trapped by the acylsilane to



(2)

16 17

conditions:	% yield
CH_3CN, rt, CSA (cat), 7 h	81
THF, rt, CSA (cat), 11 h	77
CH_2Cl_2, rt, CSA (cat), 8 h	62

*CSA: camphorsulfonic acid

give the interesting heterocycle 17 in good yields under very mild conditions.

We have also synthesized δ,ϵ-unsaturated acylsilane 19 (Scheme II) via alkylation of 18[12] (85%) followed by hydrolysis (70%) with ceric ammonium nitrate (CAN).[13-15] Treatment of 19 with phenylselenyl bromide at room temperature gave dihydropyran 20 in 72% yield. This cyclization reaction is a new addition to the family of olefin-initiated cyclization processes.[16]

In summary, this new cyclization method provides easy access to 2-silyldihydropyrans and 2-silyldihydrofurans from acylsilanes.[17] Previously, these types of compounds were prepared by lithiation of dihydropyrans or dihydrofurans followed by silylation.[8,9] Our method provides a versatile alternative through which compounds bearing a variety of substituents, such as 17 and 20, can be prepared. The special substitution pattern at C-2 and C-3 in the cyclization products affords a handle for further manipulations that may be useful in the synthesis of polyether antibiotics.[18]

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Supplementary Material Available: Experimental procedures for the cyclizations, preparation of compounds 4, 6, 8, 10, 12, 14, 19, and 20, and spectroscopic data for new compounds 1-4, 6-17, 19 and 20 (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A New and Efficient Asymmetric Synthesis of an A-Ring Precursor to Physiologically Active 1α-Hydroxyvitamin D_3 Steroids

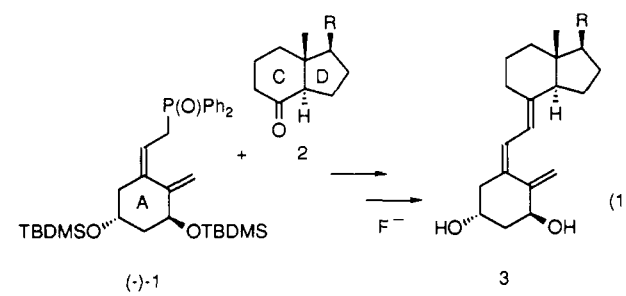
Gary H. Posner,* Jean-Christophe Carry,[1] Tizah E. N. Anjeh, and Andrew N. French

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received September 17, 1992

Summary: A highly stereocontrolled and mild Diels-Alder cycloaddition involving stereochemically matched pyrone (*S*)-lactate 4 and Lewis acid (−)-Pr(hfc)$_3$ produced bicyclic lactone *endo*-5 via a double stereodifferentiation process. Bicyclic lactone 5 was then transformed smoothly and in high yield into phosphine oxide (−)-1, an important A-ring precursor to various physiologically active 1α-hydroxyvitamin D_3 steroids.

Lythgoe-type (i.e., Horner–Wittig)[2] coupling of the conjugate base of the A-ring phosphine oxide (−)-1 with C,D-ring units 2 carrying various side-chain groups R (eq 1) is one of the most popular and reliable methods currently used to prepare 1α-hydroxyvitamin D_3 compounds having desirable medicinal properties, such as separation



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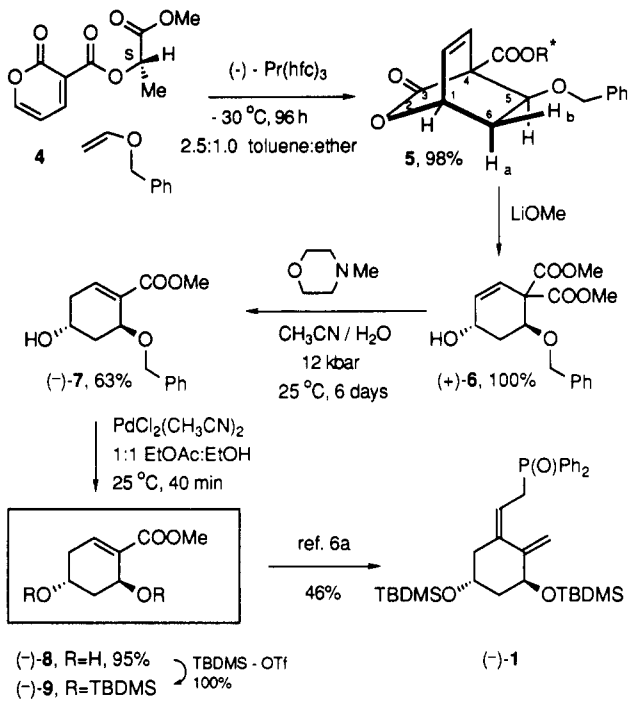
Scheme I



of calcemic from cell growth activities.[3,4] Phosphine oxide (-)-1 has been prepared from chiral pool (e.g., terpene) precursors[5] and via asymmetric synthesis.[3,4] Pursuing our interest in 2 + 4 cycloadditions of 2-pyrones[6] and in the organic and medicinal chemistry of vitamin D_3 steroids,[3a] we have designed and executed a new asymmetric approach to phosphine oxide (-)-1. This approach complements our recent efforts using enantiomerically pure vinylic ethers[6a] and features a highly stereocontrolled and high-yielding Diels–Alder cycloaddition of easily-prepared,[7] enantiomerically pure 2-pyrone (*S*)-lactate 4 with the appropriately matched enantiomeric form of the NMR shift reagent $Pr(hfc)_3$[8] to produce bicyclic lactone endo diastereomer 5 on a 0.5-g scale under mild conditions; this very high level of molecular recognition has led synergistically to a very high level of asymmetric induction (Scheme I).

As expected based on our recent experience with similar 2 + 4 cycloadditions of 2-pyrones,[6] only two endo bicycloadducts were formed (in quantitative yield) as established by high-field ^1H NMR spectroscopy including decoupling experiments on HPLC-purified products;[6] the ratio of these two endo diastereomers was 98:2 (i.e., 96% diastereomeric excess). Characteristic ^1H NMR data for bicyclic lactone endo-diastereomer 5 are as follows: 5.24 δ (H_1, $J_{1,6a}$ = 3.6 Hz, $J_{1,6b}$ = 1.6 Hz), 4.54 δ (H_5, $J_{5,6a}$ = 7.6 Hz, $J_{5,6b}$ = 1.6 Hz), 2.53 δ (H_{6a}), 1.71 δ (H_{6b}); $[\alpha]^{25}_D$ = -22° (*c* = 1.3, $CHCl_3$). The absolute stereochemistry of the major diastereomer 5 was established ultimately via correlation with A-ring synthon (-)-9 of known absolute configuration.[6a] Detailed study of the formation of bicycloadduct 5 has led to the following observations: (1) using the same NMR shift reagent (-)-$Pr(hfc)_3$ but the enantiomeric pyrone (*R*)-(+)-lactate starting material slowed the *rate* of the cycloaddition by a factor of 3–5 and diminished the *diastereoselectivity* significantly (96% → 89%); (2) using the original pyrone (*S*)-(-)-lactate 4 but the *achiral* NMR-shift reagent $Pr(fod)_3$ gave significantly lower diastereoselectivity (96% → 88%); (3) using *achiral* 2-pyrone-3-carboxylate esters (e.g., methyl or glycolyl) with the enantiopure NMR shift reagent (-)-$Pr(hfc)_3$ also gave lower diastereoselectivity (96% → 23%); (4) using ^1H NMR spectroscopy, the doublet due to the lactate methyl group of pyrone (*S*)-lactate 4 was shown to undergo a larger upfield shift (by about 1 ppm) in the presence of 1–2 equiv of (-)-$Pr(hfc)_3$ than in the presence of 1–2 equiv of enantiomeric (+)-$Pf(hfc)_3$; and (5) a deeper red color (due to stronger complexation) appeared upon mixing pyrone (*S*)-lactate 4 with its stereochemically matched Lewis acid (-)-$Pr(hfc)_3$. Taken together, these observations indicate that the 2 + 4 cycloaddition leading to bicyclic lactone 5 proceeded with double stereodifferentiation[9] in which the absolute stereochemistry of the chiral diene and the absolute stereochemistry of the chiral Lewis acid were mutually compatible.

Methanolysis of the bicyclic lactone endo diastereomers produced enantiomerically pure cyclohexene malonate (+)-6. After considerable experimentation, optimized conditions were found using *N*-methylmorpholine under pressure[10] for decarboxylation and double-bond conjugation forming cyclohexenol benzyl ether (-)-7. Palladium-promoted debenzylation[11] proceeded smoothly and rapidly giving diol (-)-8 that was easily silylated into A-ring chiron (-)-9 of 96% enantiomeric purity ($[\alpha]_D$ = -41.0° (*c* = 3.47, $CHCl_3$) (lit.[6a] $[\alpha]_D$ = -43.1°)). We have previously converted chiron (-)-9 in seven steps and in 46% overall yield into phosphine oxide (-)-1.[6a] Thus, the five chemical operations and the 59% overall yield in Scheme I for conversion of cheap and easily obtained 2-pyrone lactate 4 into highly enantiomerically enriched A-ring chiron (-)-9 rep-

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(7) Commercial (Aldrich) methyl 2-pyrone-3-carboxylate was transformed into 2-pyrone-3-carboxylic acid using trimethylsilyl iodide, converted into the acid chloride using oxalyl chloride, and esterified with cheap, commerical methyl (*S*)-(-)-lactate. 2-Pyrone (*S*)-(-)-lactate 4 had $[\alpha]^{25}_D$ = -7.4° (*c* = 11.4, $CHCl_3$).

(8) For previous examples of chiral NMR shift reagents used as Lewis acids in Diels–Alder cycloadditions, see: (a) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (c) For reviews with leading references, see: Danishefsky, S. *Chemtracts* **1989**, *2*, 273. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

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resent a new and efficient asymmetric synthetic approach to various physiologically active 1α-hydroxyvitamin D_3 steroids via Lythgoe-type coupling (eq 1).[12]

Finally, the successful stereochemical outcome and the mildness of the 2 + 4 cycloaddition in Scheme I producing stable bicyclic lactone endo diastereomer **5** almost exclusively represent another valuable example of how electronically matched electron-poor pyrone dienes and electron-rich vinyl ether dienophiles can be useful in effective synthesis of complex organic molecules.[6] We are working to make Scheme I even more efficient (e.g., by use of a catalytic amount of a cheap Lewis acid).

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Supplementary Material Available: Full experimental details and spectral data for compounds **4-9** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Articles

Addition of Phenols to Perfluorovinyl Ethers. Protonation and Halogenation of Carbanionic Intermediates†,‡

Andrew E. Feiring* and Edward R. Wonchoba

Du Pont Central Research & Development, Experimental Station, P.O. Box 80328, Wilmington, Delaware 19880-0328

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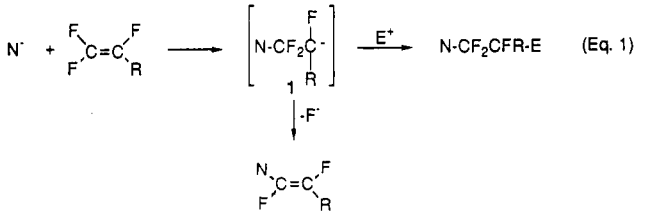
Fluorinated ethers $ArOCF_2CFHOR_f$ are obtained in good yield by base-catalyzed addition of phenols to perfluoroalkyl vinyl ethers, $CF_2{=}CFOR_f$ (R_f = C_3F_7, $C_3F_7OCF(CF_3)CF_2$, $CH_3O_2CCF_2CF_2OCF(CF_3)CF_2$). Reaction of sodium phenoxides with fluorinated vinyl ethers and hexachloroethane affords chlorinated ethers $ArOCF_2CFClOR_f$. Treatment of $BrCF_2CFBrOC_3F_7$ with sodium phenoxide in the presence of $CF_2{=}CFOC_3F_7$ gives $PhOCF_2CFBrOC_3F_7$ in high yield at room temperature, probably by an anionic chain mechanism. Sodium phenoxide reacts cleanly with $CF_2{=}CFOC_3F_7$ in the absence of an electrophile to give a 1:1 cis-trans mixture of olefins $PhOCF{=}CFOC_3F_7$. NMR chemical shifts of the OCF_2CFHOR_f group proton shows an unusually large solvent dependence.

Introduction

Additions of nucleophiles to fluorinated olefins are among the best known reactions in organofluorine chemistry.[1] The initially formed carbanion[2] **1** (eq 1) can be



(Eq. 1)

trapped by electrophiles or isolated as the substituted fluoroolefin after loss of fluoride ion. The product mixture depends on the fluoroolefin, nucleophile and the reaction conditions, and complex mixtures are often formed especially since the product fluoroolefin may also react with the nucleophile. The electrophile is typically a proton, although a variety of other trapping agents, such as carbon dioxide,[3] dimethyl carbonate,[4] and positive halogen sources[5,6] have been employed.

Nucleophilic additions to tetrafluoroethylene, chlorotrifluoroethylene, and larger perfluorinated olefins have been widely investigated, but relatively little has been reported[7] on additions to the perfluorinated vinyl ethers **2**. In the course of developing synthetic approaches to novel fluorinated monomers and polymers,[8] we have in-

† Contribution No. 6316.

‡ Presented in part at the 13th International Symposium on Fluorine Chemistry, Bochum, Germany, Sept 1991.

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