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# Communications

## Asymmetric Total Synthesis of an A-Ring Precursor to Hormonally Active 1α,25-Dihydroxyvitamin $D_3$

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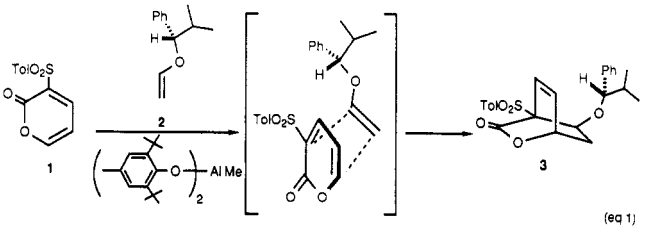
*Summary:* A new sulfinyl orthoester has been designed and used effectively in one-flask syntheses of dienoate esters from allylic alcohols; this new method as well as a highly stereocontrolled [2 + 4]-cycloaddition are applied to synthesis of 1α,25-dihydroxyvitamin $D_3$.

The Diels–Alder reaction certainly is one of the very best methods for controlling stereochemistry while forming two carbon–carbon bonds in one operation.[1] Attempts to use 2-pyrones and to isolate the initial Diels–Alder cycloadducts have regularly been thwarted because of facile cycloreversion involving spontaneous loss of $CO_2$ from the bicyclic lactone adducts.[2,3] We have discovered, however, that 3-sulfinyl-[4] and 3-sulfonyl-2-pyrones[5] react with enantiomerically pure vinyl ethers via exceptionally mild inverse-electron-demand Diels–Alder reactions and that the initial, bridged, bicyclic lactones can be isolated on gram scale in very high diastereomeric purity. To illustrate the synthetic potential of this methodology, we report now application of a significantly improved, Lewis acid mediated version of this [2 + 4]-cycloaddition to highly enantiocontrolled synthesis of an A-ring precursor of natural, hormonally active 1α,25-dihydroxyvitamin $D_3$; the entire reaction sequence starting with 3-(tolylsulfonyl)-2-pyrone[6] is short and high-yielding and includes design, preparation, and use of a new sulfinyl orthoester synthon for Claisen [3,3]-sigmatropic rearrangements of allylic alcohols.

Yamamoto's "MAD" Lewis acid[7] promoted very mild and highly stereocontrolled [2 + 4]-cycloaddition between pyrone sulfone 1[6] and enantiomerically pure vinyl ether (*S*)-2;[5a] after 12 h at −45 °C in 4:1 toluene/methylene chloride with 0.5 equiv of the catalyst and 2 equiv of vinyl ether (*S*)-2, cycloadducts were isolated on a 1.5-g scale in 93% yield as a 98:2 ratio of endo diastereomers with the major product being 3 as shown in eq 1. The absolute




(eq 1)

stereochemistry shown for cycloadduct 3 is consistent with

(1) (a) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1. (d) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (e) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: 1983. (f) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (g) Sauer, J.; Sustman, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

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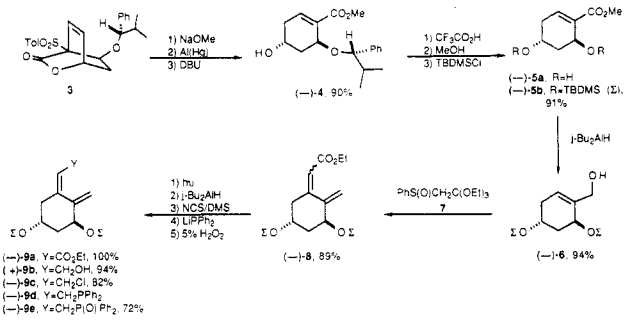
(5) (a) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. (b) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (c) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72.

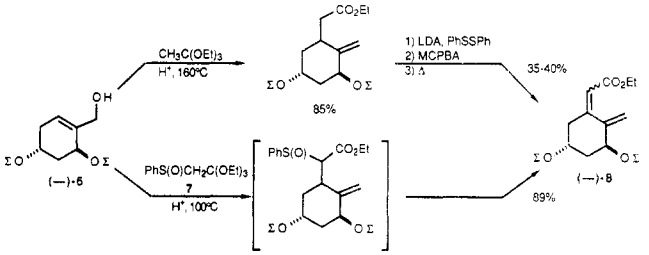
(6) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041. Pyrone sulfone 1 was prepared in five steps from commercially available 5,6-dihydro-2-pyrone.

(7) (a) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *Ibid.* **1988**, *110*, 3588.

**Scheme I**



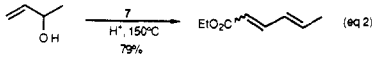
**Scheme II**



recent molecular orbital calculations,[8] indicating that the chiral, nonracemic vinyl ether (*S*)-**2** prefers to adopt an extended conformation in which the isopropyl and vinyl groups lie in the same plane as the ethereal oxygen atom; [2 + 4]-cycloaddition from this low energy conformation formed bicyclic lactone **3** with an outstanding 49:1 level of diastereoselectivity. This stereochemical result is noteworthy not only because of its extraordinary degree of asymmetric induction but also because spatial movement of the inducing chiral center in vinyl ether (*S*)-**2** is *not* restricted by the chiral center being bound rigidly to the reaction center. In the absence of "MAD", cycloaddition did occur but a considerable excess of the expensive vinyl ether **2** was needed and the cycloadduct was formed in only an 11.5:1.0 ratio of the endo diastereomers. Diastereomer **3** ($[\alpha]^{26}_D$ = −147° (*c* 0.5, $CHCl_3$); mp 147–9 °C), easily separated from the other endo diastereomer via short path chromatography, has a characteristic 400-MHz $^1H$ signal at δ 8.02 (d, *J* = 8.2 Hz, 2 H).

Methanolysis of the lactone bridge in bicycloadduct **3** (Scheme I, 28 equiv of NaOMe, 6:1 MeOH/$CH_2Cl_2$, −78 °C then 0 °C) followed by reductive desulfonylation (freshly prepared Al/Hg from Al foil exposed to mercuric chloride,[9] 8:1 THF/$H_2O$, 110 °C, 6 h) produced a mixture of α,β- and β,γ-unsaturated esters; double-bond isomerization (2 equiv of DBU, THF, 0 °C, 30 min, then 25 °C, 12 h) led to conjugated enoate ester (−)-**4** in 90% overall yield from bicycloadduct **3**. Sacrifice of the chiral auxiliary via trifluoroacetolysis[10] (40 equiv of $CF_3COOH$, $CH_2Cl_2$, 0 °C, 9 h) involved exclusive cleavage of the secondary *benzylic* carbon–oxygen bond and survival of the secondary *allylic* carbon–oxygen bond;[11] methanolic workup (MeOH, 25 °C, 10 h) produced diol (−)-**5a** and immediate O-silylation (*t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C, 14 h) produced enantiomerically pure bis-silyl ether (−)-**5b** as an oil ($[\alpha]^{25}_D$ = −43.1°, *c* 1.11, $CHCl_3$). Conjugated enoate ester (−)-**5b** had a characteristic $^1H$ NMR vinyl C–H signal at δ 6.88 (dd, *J* = 5.4 and 2.8 Hz). We envisioned introduction of the required additional two carbon atoms via a Claisen [3,3]-sigmatropic rearrangement[12] of the corresponding allylic alcohol (−)-**6**.[13]

Allylic alcohol (−)-**6**, $[[\alpha]^{26}D$ = −47.1° (*c* 1.13, $CHCl_3$) mp 57.0–58.5 °C], prepared in 94% yield by diisobutylaluminum hydride reduction (toluene, −78 °C, 1 h) of enoate (−)-**5**, was treated with ethyl orthoacetate ($CH_2Cl_2$, sealed tube, 150 °C, 2 h),[12,13] and the resulting γ,δ-unsaturated ester, formed in 85% yield, was sulfinylated (LDA, PhSSPh), oxidized (MCPBA), and pyrolyzed (150 °C, 2 h)[14] to form desired dienoate ester **8** in only 35–40% overall yield even after considerable experimentation (Scheme II). This unsatisfactory overall yield and the multistep nature of this linear sequence of transformations prompted us to design new sulfinyl orthoacetate **7**[15] that would undergo a Claisen [3,3]-sigmatropic rearrangement and subsequently an in situ sulfoxide pyrolytic 1,2-elimination.[16] Successful application of this convergent strategy to allylic alcohol (−)-**6** (1.6 equiv of sulfinyl orthoacetate **7**, trimethylbenzoic acid catalyst, $CH_2Cl_2$, sealed tube, 100 °C, 12 h) produced dienoate esters (−)-**8** as a 4:1 mixture of *E*/*Z* geometrical isomers in a gratifying 89% yield. Initial results suggest some generality for this type of tandem Claisen rearrangement–sulfoxide thermolysis to convert allylic alcohols *directly in one reaction vessel* into the corresponding 2-carbon extended dienoate esters (eq 2).[17]



Photochemical isomerization of dienoates **8** according to literature precedent[18a] gave the desired dienoate geometric isomer (−)-**9a** $[[\alpha]^{25}_D$ −39.5° (*c* 0.88, EtOH), lit.[18] $[\alpha]^{25}_D$ −36.9°] quantitatively. As described by the Hoffman-LaRoche researchers,[18a] dienoate ester (−)-**9a** was reduced to allylic alcohol (+)-**9b**; allylic chlorination, $S_N2$ displacement of chloride with lithium diphenylphosphide, and peroxide oxidation produced the key chiron phosphine oxide (−)-**9e** as the desired, enantiomerically pure A-ring unit $[[\alpha]^{24}_D$ = −2.3° (*c* 0.89, EtOH), lit.[18] $[\alpha]^{25}_D$ = −2.3°], spectroscopically identical with (−)-**9e** reported in the literature. Chiron (−)-**9e** has been converted previously

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(10) (a) Marsh, J. P., Jr.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491. (b) Beyerman, H. C.; Heiszwolf, G. J. *Recl. Trav. Chim. Pays-Bays* **1965**, *84*, 203. (c) Sleevi, P.; Glass, T. E.; Dorn, H. C. *Anal. Chem.* **1979**, *51*, 1931. (d) Hagen, A. P.; Miller, T. S.; Bynum, R. L.; Kapila, V. P. *Ibid.* **1982**, *47*, 1345.

(11) For a detailed verification of this outcome, see ref 5b, footnote 17.

(12) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (d) Ziegler, F. D. *Chem. Rev.* **1988**, *88*, 1423. (e) For examples of, and references to, amino-Claisen rearrangements and aza-oxa-Cope rearrangements, see: Blechert, S. *Synthesis* **1989**, 71.

(13) For a closely related recent example, see: Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1990**, *31*, 27.

(14) For a review, see: Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453.

(15) Prepared on gram scale by treating 2,2,2-trichloroethyl phenyl sulfoxide or 2,2-dichlorovinyl phenyl sulfoxide [Nagashima, E.; Suzuki, K.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1274] with sodium ethoxide.

(16) For Claisen rearrangements of sulfide-containing allylic vinylic ethers, see: (a) Lythgoe, B.; Milner, J. R.; Tideswell, J. *Tetrahedron Lett.* **1975**, 2593. (b) Ager, D. J.; Cookson, R. C. *Ibid.* **1982**, *23*, 3419. For Claisen rearrangements of sulfoxide-containing allylic vinylic ethers, see: (c) Nakai, T.; Tanaka, K.; Ogasawara, K.; Ishikawa, N. *Chem. Lett.* **1981**, 1289. (d) Vatele, J.-M. *Tetrahedron* **1986**, *42*, 4443.

(17) This experiment was performed in our labs by R. David Crouch; the scope and limitations of this procedure are being studied in detail and will be reported shortly.

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via Lythgoe coupling[19] into nature 1α,25-dihydroxyvitamin $D_3$.[18] Such vitamin $D_3$ hormonally active compounds are becoming popular as clinically useful regulators of such fundamental physiological processes as bone calcium mobilization (e.g., in chemotherapy of osteoporosis)[20] and cell proliferation and differentiation (e.g., in chemotherapy of psoriasis and leukemia).[20,21]

In summary, the overall reaction sequence from pyrone sulfone 1 to A-ring chiron (−)-**9e** required only 14 steps and proceeded in 34.6% overall yield, which compares very favorably indeed with other recent syntheses of the same[18] and similar[22] A-ring units as precursors to vitamin $D_3$ derivatives. Also of considerable potential is use of a new sulfinyl orthoacetate for efficient conversion of some allylic alcohols into the corresponding dienoate esters via consecutive Claisen rearrangements and sulfoxide β-eliminations occurring at 100 °C *all in one reaction flask*. We are actively pursuring this protocol for asymmetric synthesis of other A-ring units as precursors to analogues of 1α,25-dihydroxyvitamin $D_3$.

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**Supplementary Material Available:** Characterization data of compounds **3–9** (3 pages). Ordering information is given on any current masthead page.

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(20) (a) DeLuca, H. F.; Schnoes, H. K. *Ann. Rev. Biochem.* **1983**, *52*, 411. (b) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98. (c) *Calcium Regulation and Bone Metabolism: Basic and Chemical Aspects*; Cohn, D. V. Elsevier Science Publisher: B. V., 1987, and references therein. (d) "Vitamin D: Molecular, Cellular, and Chemical Endocrinology", proceedings of the Seventh Workshop on Vitamin D, Rancho Mirage, CA, Norman, A. W., Schaefer, K., Grigoleit, H.-G., Herrath, D. V., Eds.; Walter de Gruyter: Berlin, 1988, and references therein. (e) deCosta, B. R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc., Chem. Commun.* **1989**, 325.

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# 1,2-Addition of Sulfur Nucleophiles to the N-Acylated Imine Linkage. A Model Study for the Incorporation of Sulfur Nucleophiles during Metabolism of Acylated Aromatic Amines

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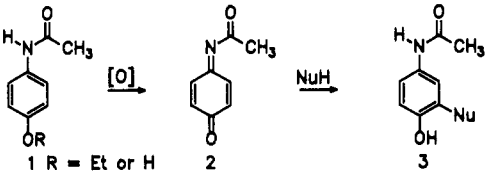
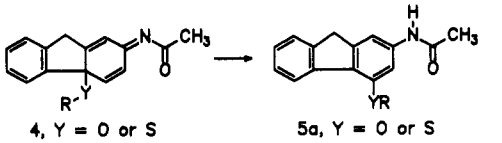
*Summary:* The imine linkage of an acylated quinone imine ketal reacts with ethanethiol to afford an isolable addition product which subsequently rearranges by a facile 1,2-shift to afford an ortho-substituted aromatic amide.

An understanding of the chemistry involved in the metabolism of acylated aromatic amines is central to establishing the mechanism of toxicity associated with drugs such as acetaminophen[1a-c] and phenacetin[1d-f] and the carcinogenicity of N-hydroxylated amides[2] (e.g., *N*-hydroxy-2-(acetylamino)fluorene). An important step in the metabolism of these compounds is oxidation of the amide nitrogen[1] with eventual production of aromatic substitution products of the parent amide. For example, metabolism of phenacetin (1, R = Et) gives amides[1d] such as **3**. The mechanism for formation of **3** is thought to involve 1,4-addition of a nucleophile to **2**, followed by aromatization. A second proposed mechanism[2a] for effecting aromatic substitution involves formation of a 4-substituted quinone imide intermediate such as **4**, followed by a 1,2-shift and aromatization.




However, the metabolism of (*N*-acetylamino)fluorene, **6**, in the rat affords glutathione conjugates at the 1- and

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