# 3-Deoxy-3-thia-1α,25-dihydroxyvitamin $D_3$ and Its 1β-Epimer: Synthesis and Biological Evaluation[1a,b]

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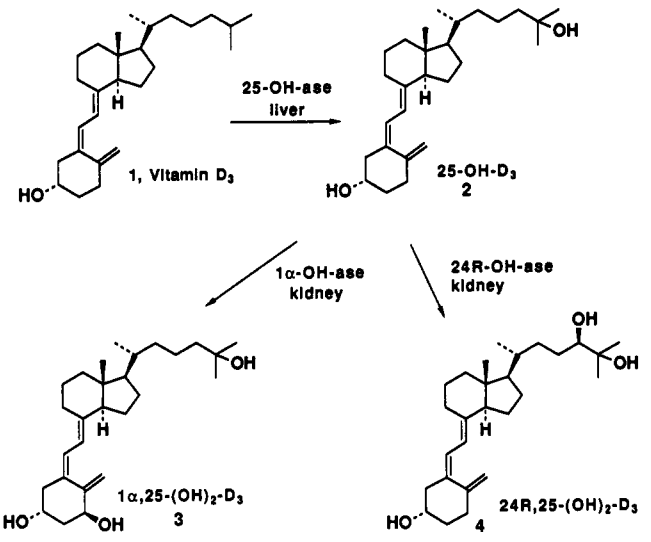
The syntheses of 3-deoxy-3-thia-1α,25-dihydroxyvitamin $D_3$ (**5a**) and its 1β-epimer **5b** have been achieved starting from CD-fragment **10** and the enantiomerically pure A-rings **11a** and **11b** prepared from thia 1,3-diketone **13**. For the preparation of **11a** and **11b**, the thia diketone **13** was converted in two steps to the trimethylsilyl enynone **18**. In the most effective route, the latter was asymmetrically reduced using (*R*)- or (*S*)-oxazaborolidine **24** and **25** and catecholborane to afford **19a** (87% ee) and **19b** (85% ee), respectively. Final enrichment to **11a** and **11b** was achieved via their crystalline carbamates **23a** and **22b** and then hydrolysis to the enantiomerically pure enynols **12a** and **12b** and silylated to the desired **11a** and **11b**. The absolute configuration at C-1 of the A-ring was examined in detail through four empirical correlation methods. The elution order of carbamates **22** and **23** by HPLC correlates with Pirkle's empirical rules. The specific rotations of enynols (−)-**12a** and (+)-**12b** correlate with Mills' rules for absolute configurations of chiral cyclohexenols. The enantiomeric sense of asymmetric reduction using the (*R*)- or (*S*)-oxazaborolidines and a complementary asymmetric reduction using $LiAlH_4$ and *N*-methylephedrine was exactly that predicted. The C-1 absolute configuration of (*S*,*S*)-carbamate **22b** was in fact fully confirmed by a single-crystal X-ray crystallographic study. Hence, the four empirically derived methods for establishing absolute configuration of the various enynols were mutually consistent. The analogues **5a** and **5b** were submitted for biological evaluation of their relative ability, in relation to the reference 1α,25-dihydroxyvitamin $D_3$ (**3**, 1α,25-$(OH)_2$-$D_3$), to stimulate intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) under in vivo conditions. Analogue **5a** was 20% and <10% while analogue **5b** was <20% and <10% as active as a 100 pmol dose of 1α,25-$(OH)_2$-$D_3$ for ICA and BCM, respectively. In addition, **5a** and **5b** were 14.5 ± 5.7% and 1.23 ± 0.38%, respectively, as effective as 1α,25-$(OH)_2$-$D_3$ in binding, under in vitro conditions, to a chick intestinal nuclear receptor.

## Introduction

A long-standing goal in this laboratory has been to understand the biological role of vitamin $D_3$ and its metabolites in its endocrine system at the molecular level.[2] As summarized in Scheme I, vitamin $D_3$ (**1**) formed in the skin or derived from the diet is initially transported to the liver where it is metabolized to 25-hydroxyvitamin $D_3$ (**2**, 25-OH-$D_3$). The final steps of this main metabolic pathway for activation of 25-OH-$D_3$ (**2**) involve the hydroxylation of 25-OH-$D_3$ (**2**) either to 1α,25-dihydroxyvitamin $D_3$ (**3**, 1α,25-$(OH)_2$-$D_3$) or to 24(*R*),25-dihydroxyvitamin $D_3$ (**4**) in the kidney. The steroid hormone 1α,25-$(OH)_2$-$D_3$ (**3**) increases intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) by inducing calcium-binding protein formation primarily through a genomic pathway, although alternative pathways have also been invoked. Besides exerting its classical calcitropic actions (ICA, BCM), 1α,25-$(OH)_2$-$D_3$ (**3**) also exerts other more newly uncovered biological actions. This same hormone is now recognized to be associated with normal cell proliferation and differentiation. Thus, it and its analogues may be useful clinically in cancer chemoprevention[3] or in the treatment of certain skin disorders.[4]

Scheme I




One of the specific aims of our vitamin D program has been to synthesize inhibitors of the enzyme 25-OH-$D_3$-1α-hydroxylase which is responsible for hydroxylation of 25-OH-$D_3$ (**2**) in the kidney to its biologically active form 1α,25-$(OH)_2$-$D_3$ (**3**).[2] Inhibitors of this enzyme are of interest because it might provide insight into its mechanism of action and help to elucidate the overall mechanism of action of 1α,25-$(OH)_2$-$D_3$ (**3**) itself. In light of the discovery of inhibitory properties of an oxa-A-ring vitamin D analogue from our laboratory,[5a–c] other heteroatom-containing

(1) (a) Paper 42 in the series Studies of Vitamin D (Calciferol) and Its Analogues. For paper 41 see: Maynard, D. F.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.*, in press. (b) This article was based in part on the Ph.D. dissertation submitted to the University of California, Riverside, by Adam S. Lee, December, 1991. (c) Department of Chemistry, University of California, Riverside. (d) The Division of Biomedical Sciences and the Department of Biochemistry, University of California, Riverside.

(2) (a) Norman, A. W., Bouillon, R., Thomasset, M., Eds. *Vitamin D: Gene Regulation , Structure-Function Analysis and Clinical Application*; Walter de Gruyter: Berlin, 1991. (b) Norman, A. W. *Vitamin D, the Calcium Homeostatic Steroid Homone*; Academic Press: New York, 1979. (c) Pardo, R.; Santelli, M. *Bull. Chim. Soc. Fr.* **1985**, 98. (d) Jones, G. (Guest Ed.) *Steroids* **1987**, *49*, 1. (e) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333.

(3) Differentiation of leukemia cells: (a) Honma, Y.; Hozumi, M.; Abe, E.; Konno, K.; Fukushima, M.; Hata, S.; Nishii, Y.; DeLuca, H. F.; Suda, T. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 201. (b) Koeffler, H. P.; Amatruda, T.; Ikekawa, N.; Kobayashi, Y.; DeLuca, H. F. *Cancer Res.* **1984**, *44*, 5624. (c) Munker, R.; Norman, A. W.; Koeffler, H. P. *J. Clinical Invest.* **1986**, *78*, 424.

(4) Such analogues are also potentially useful in the treatment of skin disorders such as psoriasis: (a) MacLaughlin, J. A.; Gange, W.; Taylor, D.; Smith, E.; Holick, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5409. (b) Morimoto, S.; Onishi, T.; Imanaka, S.; Yukawa, H.; Kosuka, T.; Kitano, Y.; Yoshikawa, Y. *Calcif. Tissue Int.* **1986**, *38*, 119. (c) Binderup, L.; Bramin, E. *Biochem. Pharmacology* **1988**, *37*, 889.

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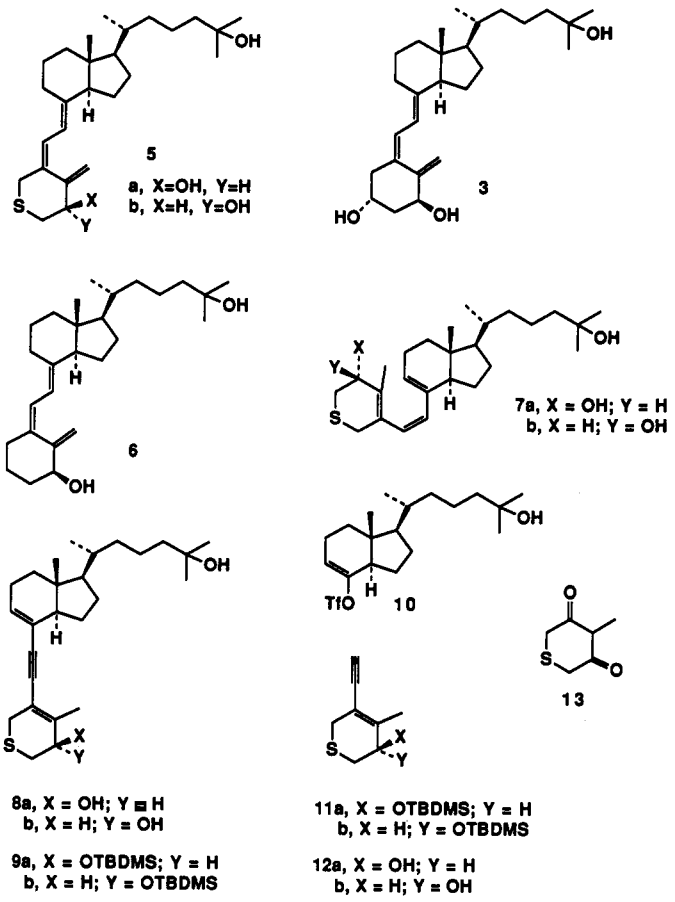
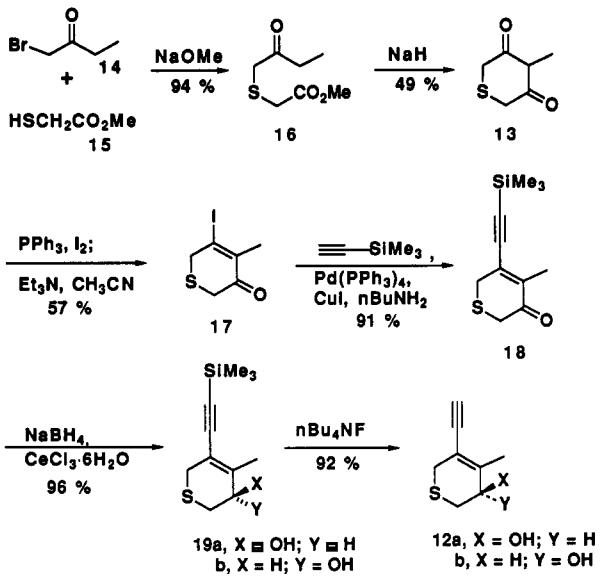
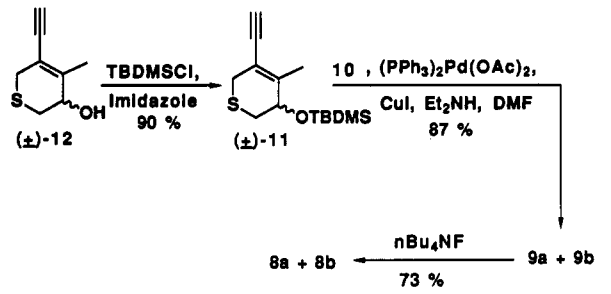
**Chart I**




**Scheme II**




**Scheme III**




analogues[5d] have emerged as desirable target molecules for synthesis and biological evaluation.

The purpose of this paper is to report the synthesis of 3-deoxy-3-thia-1α,25-dihydroxyvitamin $D_3$ (**5a**) and its 1β-epimer **5b** (Chart I). In an earlier paper,[5d] we reported the preparation of the 25-deoxy counterparts of **5**, but due to the lack of the side-chain hydroxyl, the interpretation of biological data was ambiguous. It has been established that the 25-hydroxy group is necessary for the biological function of the natural hormone **3**. Besides the possibility that **5a** or **5b** or their precursors might serve as enzyme inhibitors,[6] these analogues were also of interest as active agonists of the natural hormone 1α,25-$(OH)_2$-$D_3$ (**3**). Its relationship to the 3-deoxy analogue **6** is of some interest since the latter, synthesized and biologically evaluated previously by this laboratory,[7] has been shown to exhibit selective calcitropic action in the intestine.[7c]

## Results and Discussion

It was anticipated that 3-deoxy-3-thia-1α,25-$(OH)_2$-vitamin $D_3$ (**5a**) could be synthesized by thermally induced [1,7]-sigmatropic hydrogen shift of previtamin **7a** (Chart I),[8] which in turn could be obtained by catalytic semihydrogenation of dihydroxy dienyne **8a**. The latter would be anticipated to arise from the coupling of the known CD-triflate **10**[5a,9,10] and appropriate enynes **11** or **12**. A-ring enynes **11** or **12** were envisaged to be obtainable by modification of the known thia-1,3-diketone **13**.[5d,11]

The synthesis of the A-ring fragment began with the coupling of bromomethyl ethyl ketone **14** and thioglycolate **15** to afford keto ester **16** (Scheme II).[11] The latter underwent an intramolecular cyclization to produce thia 1,3-diketone **13** using sodium hydride to generate the

(5) (a) Barrack, S. A.; Gibbs, R. A.; Okamura, W. H. *J. Org. Chem.* **1988**, *53*, 1790. (b) Okamura, W. H.; Shen, G.-Y.; Barrack, S. A.; Henry, H. L. *Vitamin D: Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Gringoleit, H. G., Herrath, D. V., Eds.; Walter De Gruyter: Berlin, 1988; pp 12–21. (c) Henry, H. L.; Fried, S.; Shen, G-Y.; Barrack, S. A.; Okamura, W. H. *J. Steroid Biochem. Molec. Biol.* **1991**, *38*, 775. (d) Haces, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6105.

(6) Sulfur and sulfoxide containing analogues of a variety of biological substrates have been designed and prepared as potential inhibitors of oxidative enzymes. Mention was made in ref 5d of the 5,6-*trans*-sulfoxide analogues of molecules related to **5a** and **5b**, wherein the sulfoxide occupies a site topologically similar to the 1-OH of **5a** and **5b**. Thus, analogues of **5a** and **5b** are attractive targets as precursors to inhibitors or possibly even as inhibitors in their own right as heteroatom-containing A-ring analogues. For studies of other sulfur-containing analogues, see the following: (a) Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 713. (b) Corey, E. J.; d'Alarcao, M.; Matsuda, S. P. T. *Tetrahedron Lett.* **1986**, *27*, 3585. (c) Corey, E. J.; d'Alarcao, M.; Kyler, K. S. *Tetrahedron Lett.* **1985**, *26*, 3919. (d) Corey, E. J., Lansbury, Jr. P. T. *J. Am. Chem. Soc.* **1983**, *105*, 4093.

(7) (a) Okamura, W. H.; Mitra, M. N.; Procsal, D. A.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1975**, *65*, 24. (b) Procsal, D. A.; Okamura, W. H., Norman, A. W. *J. Biol. Chem.* **1975**, *250*, 8382. (c) Okamura, W. H.; Norman, A. W.; Mitra, M. N. U.S. Patent, 4,264,512, April 28, 1981.

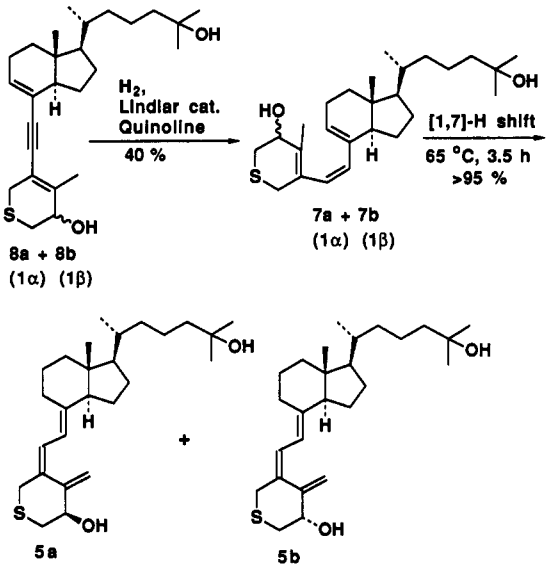
(8) (a) Enas, J. D.; Palenzuela, J. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 1355. (b) Enas, J. D.; Shen, G.-Y.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 3873. (c) Dauben, W. G.; Funhoff, D. J. H. *J. Org. Chem.* **1988**, *53*, 5376. (d) Dauben, W. G.; Funhoff, D. J. H. *J. Org. Chem.* **1988**, *53*, 5070. (e) Hoeger, C. A.; Johnston, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. (f) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268. (g) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (h) Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980.

(9) (a) Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449. (b) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *J. Chem. Soc., Perkin Trans.* 1 **1974**, 2654. (c) Dawson, T. M.; Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. C* **1971**, 2960.

(10) (a) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203. (b) Castedo, L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523.

(11) Terasawa, T.; Okada, T. *J. Org. Chem.* **1977**, *42*, 1163.

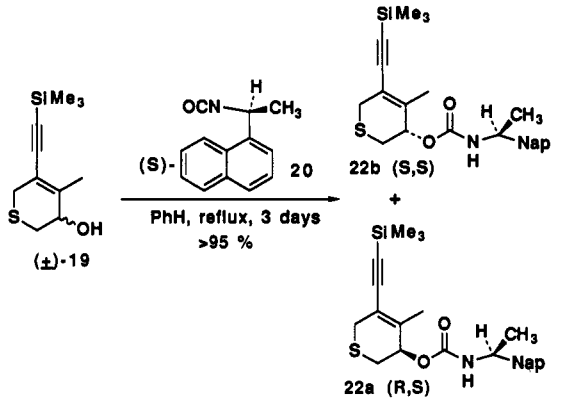
**Scheme IV**




enolate. The latter was then treated with triphenylphosphine, iodine, and triethylamine to produce iodo enone **17**,[12] which was coupled with trimethylsilyl acetylene using tetrakis(triphenylphosphine)palladium(0), copper iodide, and *n*-butylamine to give enone **18**.[13,14] The latter was reduced under Luche conditions with sodium borohydride and cerium(III) chloride heptahydrate to afford racemic trimethylsilyl enynol (±)-**19**.[15] This silylated enynol was then treated with tetrabutylammonium fluoride (TBAF) to afford racemic desilylated enynol (±)-**12**.[16,17]

Coupling of CD-enol triflate **10** and racemic enynol (±)-**12** using $(PPh_3)_2Pd(OAc)_2$, CuI, and $Et_2NH$ failed. The racemic enynol (±)-**12** could not be recovered upon workup, but CD-triflate **10** was readily recovered. The racemic enynol (±)-**12** was protected with *tert*-butyldimethylsilyl chloride and imidazole to give racemic silyloxyenyne (±)-**11** (Scheme III). The latter racemic material and CD-triflate **10** were successfully coupled using the same Pd-catalyzed procedure as above to produce the two diastereomers, 1α-(silyloxy) dienyne **9a** and its 1β-epimer **9b**.[14] These diastereomers could, however, not be separated by HPLC. This mixture was desilylated by treatment with TBAF to afford 1α-dihydroxy dienyne **8a** and 1β-**8b**, which could also not be separated by HPLC (Scheme IV). Hydrogenation of the mixture of dihydroxy

**Scheme V**




**Scheme VI**

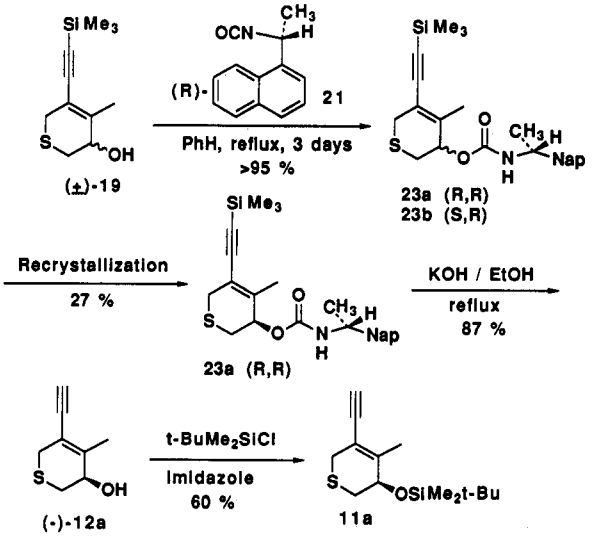
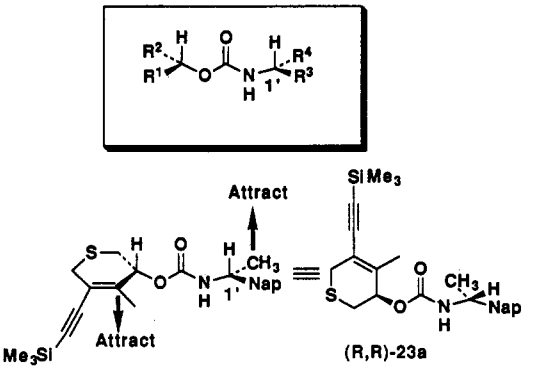



**Chart II**




dienynes **8a** and **8b** in the presence of Lindlar catalyst and quinoline poison afforded 3-thiaprevitamins $D_3$ **7a** and **7b** (Scheme IV),[18] which were transformed to vitamins **5a** and **5b** via a [1,7]-sigmatropic hydrogen shift upon mild heating.[8] Again, the two diastereomeric vitamins 1α-**5a** and 1β-**5b** could not be separated by HPLC. Thus, it was obvious from this series of experiments that an enantiom-

(12) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
(13) (a) Tsuji, J. *Synthesis* **1990**, 739. (b) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345. (d) Kwon, H. B.; Mckee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114. (e) Sonogashira, Y.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (f) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.
(14) (a) Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. (c) Hettrick, C. M.; Kling, J. K.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 1489. (d) Yang, Z.-Y.; Burton, D. J. *Tetrahedron Lett.* **1990**, *31*, 1369. (e) Chapdelaine, M. J.; Warwick, P. J.; Shaw, A. *J. Org. Chem.* **1989**, *54*, 1218. (f) King, A. O.; Okukado, N.; Negishi, E.-I. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (g) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (h) Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665.
(15) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) (a) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272. (b) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99. (c) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295. (d) Carpino, L. A.; Sau A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514. (e) Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35. (f) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.
(18) (a) Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, 1973; *Collect. Vol. 5*, p 880. (b) Rajaram, J.; Narula, A. P. S.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1983**, *39*, 2315. (c) McEwen, A. B.; Guttieri, M. J.; Maier, W. F.; Laine, R. M.; Shvo, Y. *J. Org. Chem.* **1983**, *48*, 4436. (d) Marvell, E. N.; Li, T. *Synthesis* **1973**, 457.

erically pure A-ring fragment needed to be accessed.

A method for resolution of secondary alcohols developed by Pirkle et al. was employed for obtaining the desired enantiomerically pure A-ring.[19] In the initial experiment, the racemic enynol (±)-**19** was reacted with (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate (**20**) to produce what ultimately proved to be (*S,S*)- and (*R,S*)-carbamates **22b** and **22a** (Scheme V). One of the diastereomers crystallized from 20% ethyl acetate/hexanes solution while the residue enriched in the other diastereomer was a viscous liquid which has as of yet not crystallized. The racemic enynyl alcohol (±)-**19** was also treated with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (**21**) to produce (*R,R*)- and (*S,R*)-carbamates **23a** and **23b** (Scheme VI), wherein one diastereomer crystallized.

In order to determine the absolute C-1 configuration of the carbamates, Pirkle's HPLC elution order empirical rule was initially employed.[20] Pirkle's studies using NMR and IR techniques indicate that the carbamates show more or less semirigid planar backbones. Enhanced population of the conformational model shown in Chart II is thought to occur due to the combination of steric effects, dipolar repulsion effects, etc. The retention times of the two diastereomeric carbamates are sensitive to the interactions between the substrate and stationary phase. When $R^1$ is more attractive (tighter binding to the stationary phase) than $R^2$ and $R^3$ is more attractive than $R^4$, the diastereomer having $R^1$ syn to $R^3$ will be the more strongly retained (i.e., longer retention time). Alternatively, if $R^2$ is more attractive than $R^1$ and $R^3$ is more attractive than $R^4$, the diastereomer having $R^2$ anti to $R^3$ will exhibit a shorter retention time. The stereochemistry of the carbamates correlates to the elution order by assuming these simple empirical relationships. As shown in Chart II, because the $R^1$ and $R^3$ of (*R,R*)-carbamate **23a** are anti to each other, it should elute faster than the other diasteromer, (*S,R*)-carbamate **23b**.

The liquid residue resulting after crystallization of the (*S,S*)-carbamate **22b** from the equimolar mixture of (*S,S*)- and (*R,S*)-carbamates was presumably enriched in the latter (**22a**). This **22a**-enriched mixture was subjected to HPLC separation (Whatman Partisil 10 Silica Magnum 9 column, 10% ethyl acetate/hexanes). The minor carbamate (the white crystalline **22b**) eluted first, and this was followed by major carbamate **22a**. The stereochemistry of these carbamates was assigned to be (*S,S*)-white crystalline **22b** and (*R,S*)-liquid **22a** by the predicted order of elution using Pirkle's empirical rule (Chart II).[19,20]

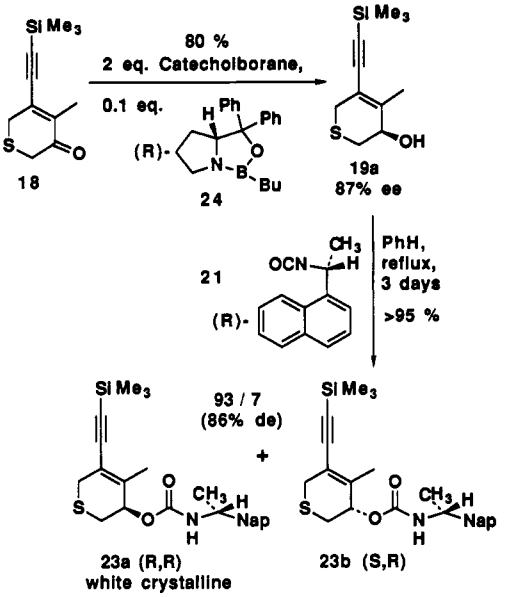
A complimentary result was obtained for the other pair of diastereomers. The mother liquor of the mixture of (*S,R*)- and (*R,R*)-carbamates **23b** and **23a**, respectively (enriched in the former), was also subjected to HPLC, and the order of elution was white crystalline (*R,R*)-**23a** first followed by liquid (*S,R*)-**23b** second.

It was proposed by Mills in 1952[21] that allylic chiral cyclohexenols having an (*S*)-configuration tended to be more levorotatory than its (*R*)-epimer. The observed specific rotations of the (1*R*)- and (1*S*)-enynols **12** were $[\alpha]^{23}_D$ −76.8 (*c* 1.0, $CHCl_3$) and $[\alpha]^{23}_D$ +74.4 (*c* 0.714, $CHCl_3$), respectively. It should be noted that our (1*R*)- and (1*S*)-enantiomers of **12** correspond to the (1*S*)- and (1*R*)-enantiomers in Mills' cyclohexenol sense. The Mills' rule based absolute configurations of the enynols **12** obtained by degradation of the corresponding carbamates correspond completely to the assignments based on Pirkle's empirical rule for the HPLC elution order of carbamates.

Finally, the C-1 configurational assignment of the crystalline (*S,S*)-carbamate **22b** from the coupling of enynol **19** and (*S*)-isocyanate **20** was fully confirmed by a single-crystal X-ray crystallographic study (the results are given in the supplementary material along with an ORTEP drawing of the structure).

In order to more efficiently prepare the (1*R*)-A-ring fragment, which leads to the natural 1α-OH vitamin analogue **5a**, the catalytic asymmetric reduction method recently developed by Corey and co-workers[22] was used to produce the (1*R*)-enynol **19a**. The enone **18** was treated with 0.1 equiv of (*R*)-oxazaborolidine **24** and 2 equiv of catecholborane (Scheme VII). The (1*R*)-enynol **19a** was produced in 80% yield with 87% enantiomeric purity (87% ee) as determined by $^1$H-NMR analysis using the chiral shift reagent (CSR) $Pr(hfc)_3$.[23] This 87% ee (1*R*)-enynol **19a** was treated with (*R*)-(−)-1-(1-naphthyl)-

**Scheme VII**




(19) (a) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143. (b) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. (c) Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197. (d) Mori, K.; Tamada, S.; Uchida, M.; Mizumachi, N.; Tachibana, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 1901. (e) Pirkle, W. H.; Sikkenga, D. L. *J. Chromatogr.* **1976**, *123*, 400. (f) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037. (g) Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957.

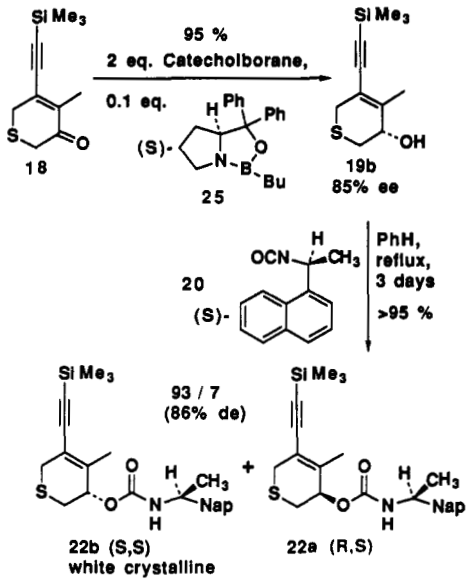
(20) (a) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839. (b) Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950. (c) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1979**, *44*, 1025. (d) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111.

(21) (a) Mills, J. A. *J. Chem. Soc.* **1952**, 4976. (b) Bose, A. K.; Chatterjee, B. G. *J. Org. Chem.* **1958**, *23*, 1425. (c) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5493.

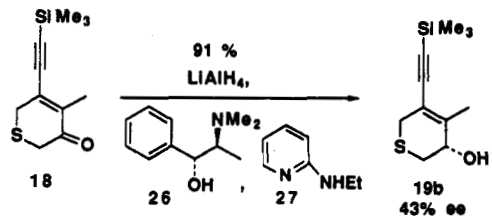
(22) (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J.; Da Silva Jardine, P.; Mohri, T. *Tetrahedron Lett.* **1988**, *29*, 6409. (e) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (f) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (g) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. (h) Jones, T. K.; Mohan J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski E. J. J. *J. Org. Chem.* **1991**, *56*, 763.

(23) (a) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038. (b) Hlubucek, J. R.; Shapiro, B. L. *Org. Magn. Reson.* **1972**, *4*, 825. (c) Fraser, R. R.; Petit, M. A.; Saunders, J. K. *J. Chem. Soc. Chem. Commun.* **1971**, 1450. (d) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913. (e) Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 5914. (f) Kalyanam, N.; Lightner, D. A. *Tetrahedron Lett.* **1979**, 415. (g) Sullivan, G. R.; Ciavarella, D.; Mosher, H. S. *J. Org. Chem.* **1974**, *39*, 2411. (h) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 1493. (i) Welti, D. H.; Linder, M.; Ernst, R. R. *J. Am. Chem. Soc.* **1978**, *100*, 403.

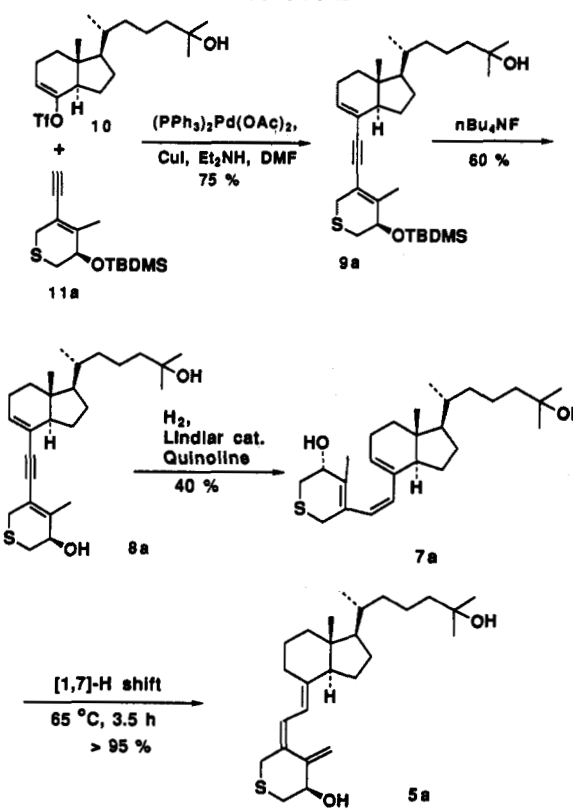
Scheme VIII




Scheme IX




Scheme X




ethyl isocyanate (**21**) to give the major crystalline (*R*,*R*)-carbamate **23a** and minor liquid (*S*,*R*)-**23b** (Scheme VII). The diastereomeric ratio (93:7) of these two carbamates **23a** and **23b** was determined on the crude material by $^1$H-NMR analysis, and the resulting diastereomeric purity (86% de) is consistent with the results based on the CSR $^1$H-NMR analysis of 87% ee (1*R*)-enynol **19a**. The (*R*,*R*)-carbamate **23a** was crystallized from 20% ethyl acetate/hexanes solution, and the crystalline material was treated with potassium hydroxide in ethanol as before to afford (1*R*)-enynol (−)-**12a** ([$\alpha$]$^{23}_D$ −76.8 (*c* 1.0, $CHCl_3$)). The optical purity of **12a** was determined by CSR studies using Pr(hfc)$_3$, and only one enantiomer could be detected by $^1$H-NMR analysis.

To obtain the unnatural 1$\beta$-OH-vitamin analogue **5b**, the enone **18** was treated with 0.1 equiv of (*S*)-oxazaborolidine **25** and 2 equiv of catecholborane to give a 95% yield with 85% ee of (1*S*)-enynol **19b** (Scheme VIII). The enantiomeric purity was also determined by an $^1$H-NMR experiment using the chiral shift reagent Pr(hfc)$_3$. The 85% ee enynol **19b** was treated with (*S*)-isocyanate **20** to produce major (*S*,*S*)-carbamate **22b** and minor (*R*,*S*)-carbamates **22a** in a diastereomeric ratio of 93:7 (86% de) by $^1$H-NMR analysis of the crude material. The white crystalline (*S*,*S*)-carbamate **22b** ([$\alpha$]$^{23}_D$ +67.0 (*c* 0.71, $CHCl_3$)) was treated with potassium hydroxide in ethanol as before to afford (1*S*)-enynol (+)-**12b** ([$\alpha$]$^{23}_D$ +74.4 (*c* 0.714, $CHCl_3$)). The optical purity of **12b** was determined by CSR studies using Pr(hfc)$_3$, and only one enantiomer could be detected by $^1$H-NMR analysis. The enantiomeric sense of asymmetric reduction is exactly that predictable by the empirical correlations of Corey.[22]

Another asymmetric reduction procedure was also applied to the enone **18** using lithium aluminum hydride which was partially decomposed with (1*R*,2*S*)-*N*-methylephedrine (**26**) and 2-(*N*-ethylamino)pyridine (**27**) (Scheme IX).[24] The (1*S*)-enynol **19b** was produced in 91% yield with 43% enantiomeric purity (43% ee) as determined by $^1$H-NMR CSR analysis using Pr(hfc)$_3$. This 43% ee pure (1*S*)-enynol **19b** was treated with (*S*)-(+)-1-(1-naphthyl)-ethyl isocyanate (**20**) to give the major (*S*,*S*)-carbamate **22b**. The diasteromeric ratio (72:28) of these two carbamates **22b** and **22a** was determined on the crude material by $^1$H-NMR analysis, and the result (44% de) was consistent with the results based on CSR $^1$H-NMR studies on the precursor (1*S*)-enynol **19b**. This asymmetric reduction was not as efficient as the method developed by Corey et al.,[22] but the enantiomeric sense of the asymmetric reduction is exactly that predicted by the empirical correlations developed by the earlier workers.[24]

To complete the synthesis of 3-deoxy-3-thia-1$\alpha$,25-(OH)$_2$-D$_3$ (**5a**) (Scheme X), CD-triflate **10** (CD-fragment) and the 1(*R*)-(silyloxy) enyne **11a** (A-ring component) were coupled using bis(triphenylphosphine)palladium(II) acetate, copper iodide, and diethylamine in dimethylformamide. The resulting 1(*R*)-(silyloxy) dienyne **9a** was treated with tetrabutylammonium fluoride (1.0 M in THF) to give (1*R*)-dihydroxy dienyne **8a**. Completion of the synthesis was achieved by hydrogenation of (1*R*)-dihydroxy dienyne **8a** in ethyl acetate in the presence of Lindlar catalyst and quinoline poison. The 3-thiaprevitamin **7a** was separated by HPLC, and thermolysis of previtamin **7a** at 65 °C for 3.5 h afforded the 3-deoxy-3-thia-1$\alpha$,25-(OH)$_2$-D$_3$ (**5a**) via a [1,7]-sigmatropic hydrogen shift. The synthesis of 3-deoxy-3-thia-1$\beta$,25-(OH)$_2$-D$_3$ (**5b**) was completed using the analogous procedure (**11b** plus **10** to **9b** and then **9b** to **8b** to **7b** to **5b**).

**Biological Evaluation.** With analogues **5a** and **5b** in hand, intestinal calcium absorption (ICA) and bone cal-

(24) (a) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* 1985, *33*, 52. (b) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* 1984, 239. (c) Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* 1980, 1026. (d) Terashima, S.; Tanno, N.; Koga, K. *Chem. Lett.* 1980, 981.

cium mobilization (BCM) were measured in vivo in comparison to vitamin $D_3$ (1) and 1α,25-$(OH)_2$-$D_3$ (3) in vitamin D deficient, rachitic chicks as previously described.[25] The results in this standard assay can be reported as the percentage of activity observed for both ICA and BCM in comparison to a standard dose of 100 pmol of 1α,25-$(OH)_2$-$D_3$. Analogue **5a** had 20% and <10% ICA and BCM values, respectively, while analogue **5b** had <20% and <10% ICA and BCM values, respectively. It is understandable that **5a** should exhibit somewhat greater ICA biological activity than **5b** since the former possesses a 1α-hydroxyl group (as in 1α,25-$(OH)_2$-$D_3$) whereas the latter does not. The analogue **5a** appears to be similar in biological activity to 3-deoxy-1α,25-$(OH)_2$-$D_3$ (**6**, Chart I), thus indicating that sulfur causes a minimal perturbation to the A-ring despite the presence of the slightly larger A-ring size due to the presence of bonds (two C–S bonds) longer than those in **6**. The analogues were also evaluated in vitro in terms of their ability to bind to the chick intestinal receptor in comparison to the natural hormone 1α,25-$(OH)_2$-$D_3$ (**3**). In this assay,[26] the analogues are scored in terms of relative competitive indices (RCIs) wherein the value for 1α,25-$(OH)_2$-$D_3$ is 100% by definition. The RCI values for **5a** and **5b** were 14.5 ± 5.7% and 1.23 ± 0.38%, respectively. These values are in qualitative agreement with the in vivo results described above. Indeed, the RCI value for **5a** is similar to that of **6** (RCI = 5.7%), in agreement with the in vivo data. In due course we will evaluate these and related analogues (e.g., their sulfoxides and sulfones[27]) as to their possible use as inhibitors of vitamin D metabolism.

## Experimental Section[28]

**(1*R*)-3-Deoxy-3-thia-1α,25-dihydroxyvitamin $D_3$ (1α-Isomer 5a).** A stirred mixture of (1*R*)-dihydroxy dienyne **8a** (5 mg, 0.014 mmol), Lindlar catalyst (100 mg), and quinoline (5 μL, 0.17 M hexane solution) in 4 mL of EtOAc was exposed to hydrogen gas at atmospheric pressure for 2.2 h. Filtration of the mixture through $SiO_2$ and concentration afforded a residual oil which was subjected to HPLC (Whatman Partisil 10 Silica Magnum 9, 35% ethyl acetate/hexanes) to afford 2.0 mg (40%) of previtamin $D_3$ **7a** and 1.0 mg of starting (1*R*)–dihydroxy dienyne **8a**. The pertinent $^1$H-NMR signals of the previtamin form already partially rearranged to vitamin include the following: δ 0.68 (3 H, $C_{18}$-$CH_3$, s), 0.95 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.3 Hz), 1.21 (6 H, $C_{26,27}$-$2CH_3$, s), 1.81 (3 H, $C_{19}$-$CH_3$, s), 2.77 (1 H, $H_2$, d with fine structure, $J$ = 13.9 Hz), 2.89 (1 H, $H_2$, dd, $J$ = 13.9 Hz, 2.4 Hz), 2.90 and 3.29 (2 H, $2H_4$, AB pattern, $J$ = 16.2 Hz), 3.90 (1 H, $H_1$, m), 5.56 (1 H, $H_9$, m), 5.78 and 5.89 (2 H, $H_{6,7}$, AB pattern, $J$ = 12.0 Hz). The previtamin $D_3$ (neat) was heated at 65 °C for 3.5 h, which induced its isomerization to vitamin **5a**. Purification of this material by HPLC as above afforded after vacuum drying 2 mg of **5a** as a colorless oil. $^1$H-NMR: δ 0.53 (3 H, $C_{18}$-$CH_3$, s), 0.93 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.3 Hz), 1.22 (6 H, $C_{26,27}$-$2CH_3$, s), 2.75–2.85 (2 H, $1H_2$ and $H_{9\beta}$, m), 3.06 (1 H, $H_2$, dd, $J$ = 13.4 Hz, 2.3 Hz), 3.12 and 3.33 (2 H, $2H_4$, AB pattern, $J$ = 12.9 Hz), 4.36 (1 H, $H_1$, m), 4.90 (1 H, $H_{19}$, s), 5.29 (1 H, $H_{19}$, s), 5.93 and 6.43 (2 H, $H_{6,7}$, AB pattern, $J$ = 11.2 Hz).

**(1*S*)-3-Deoxy-3-thia-1,25-dihydroxyvitamin $D_3$ (1β-Isomer 5b).** A stirred mixture of (1*S*)-dihydroxy dienyne **8b** (6 mg, 0.014 mmol), Lindlar catalyst (60 mg), and quinoline (6 μL, 0.16 M hexane solution) in 4 mL of EtOAc was exposed to hydrogen gas at atmospheric pressure for 1.5 h. Filtration of the reaction mixture through $SiO_2$ and concentration afforded a residual oil, which was subjected to HPLC (Whatman Partisil 10 Silica Magnum 9, 35% ethyl acetate/hexanes) to afford 2.0 mg (36%) of previtamin $D_3$ **7b** and 2.0 mg of starting (1*S*)-dihydroxy dienyne **8b**. The pertinent $^1$H-NMR signals of the previtamin form already partially rearranged to vitamin include the following: δ 0.68 (3 H, $C_{18}$-$CH_3$, s), 0.96 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.6 Hz), 1.22 (6 H, $C_{26,27}$-$2CH_3$, s), 1.81 (3 H, $C_{19}$-$CH_3$, s), 2.78 (1 H, $H_2$, d with fine structure, $J$ = 13.6 Hz), 2.88 (1 H, $H_2$, dd, $J$ = 13.6, 3.0 Hz), 2.93 and 3.30 (2 H, $2H_4$, AB pattern, $J$ = 17.2 Hz), 3.90 (1 H, $H_1$, m), 5.57 (1 H, $H_9$, m), 5.80 and 5.90 (2 H, $H_{6,7}$, AB pattern, $J$ = 12.0 Hz). The previtamin $D_3$ (neat) was heated at 60 °C for 10 h, which induced its isomerization to the vitamin **5b**. Purification of this material by HPLC as above afforded after vacuum drying 2 mg of **5b** as a colorless oil. $^1$H-NMR: δ 0.53 (3 H, $C_{18}$-$CH_3$, s), 0.93 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.0 Hz), 1.22 (6 H, $C_{26,27}$-$2CH_3$, s), 2.65–2.90 (3 H, $1H_2$, $H_{9\beta}$, m), 3.08 (1 H, $H_2$, dd, $J$ = 13.2, 2.1 Hz), 3.10 and 3.35 (2 H, $2H_4$, two d, AB pattern, $J$ = 12.9 Hz), 4.36 (1 H, $H_1$, m), 4.91 (1 H, $H_{19}$, br s), 5.30 (1 H, $H_{19}$, br s), 5.96 and 6.43 (2 H, $H_{6,7}$, two d, AB pattern, $H$ = 11.2 Hz).

**1(*R*),25-Dihydroxy-3-deoxy-3-thia-6,7-didehydroprevitamin $D_3$ (8a).** A 1.0 M tetrabutylammonium fluoride (TBAF) solution in THF (240 μL, 0.24 mmol) was added to a solution of 1(*R*)-(silyloxy) dienyne **9a** (32 mg, 0.06 mmol) at room temperature under argon. The reaction mixture was stirred at room temperature for 5.8 h and then passed through a short $SiO_2$ column (1 × 15 cm, EtOAc). The solution was concentrated and passed through a $SiO_2$ column (1 × 15 cm, ether) and then concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 30% ethyl acetate/hexanes) to afford after vacuum drying 15 mg (60%) of dihydroxy dienyne **8a** as a colorless oil, which was used for the next step as well as for spectral characterization. $^1$H-NMR: δ 0.69 (3 H, $C_{18}$-$CH_3$, s), 0.95 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.3 Hz), 1.21 (6 H, $C_{26,27}$-$2CH_3$, s), 2.77 and 2.89 (2 H, $2H_2$, AB pattern with fine structure, $J_{AB}$ = 13.7 Hz), 2.90 and 3.35 (2 H, $2H_4$, AB pattern, $J_{AB}$ = 17.3 Hz), 3.98 (1 H, $H_1$, m), 5.99 (1 H, $H_9$, narrow m).

**1(*S*),25-Dihydroxy-3-deoxy-3-thia-6,7-didehydroprevitamin $D_3$ (8b).** A 1.0 M tetrabutylammonium fluoride (TBAF) solution in THF (440 μL, 0.44 mmol) was added to a solution of 1(*S*)-(silyloxy) dienyne **9b** (60 mg, 0.11 mmol) at room temperature under argon. The reaction mixture was stirred at room temperature for 12.5 h and then passed through a short $SiO_2$ column (1 × 15 cm, ether). The solution was concentrated and passed through a $SiO_2$ column (1 × 15 cm, ether) and then concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 30% ethyl acetate/hexanes) to afford after vacuum drying 25 mg (54%) of (1*S*)-dihydroxy dienyne **8b** as a colorless oil, which was used for the next step as well as for spectral characterization. $^1$H-NMR: δ 0.69 (3 H, $C_{18}$-$CH_3$, s), 0.95 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.3 Hz), 1.21 (6 H, $C_{26,27}$-$2CH_3$, s), 2.77 and 2.89 (2 H, $2H_2$, AB pattern with fine structure, $J_{AB}$ = 13.7 Hz), 2.90 and 3.35 (2 H, $2H_4$, AB pattern, $J_{AB}$ = 17.0 Hz), 3.98 (1 H, $H_1$, m), 5.98 (1 H, $H_9$, narrow m).

**1(*R*)-(Silyloxy)-25-hydroxy-3-deoxy-3-thia-6,7-didehydroprevitamin $D_3$ (9a).** Diethylamine (17 μL, 0.16 mmol) was added to a solution of $(PPh_3)_2Pd(OAc)_2$ (6 mg, 0.008 mmol), CuI (3 mg, 0.016 mmol), 1(*R*)-(silyloxy) enyne **11a** (22 mg, 0.08 mmol), and CD-triflate **10** (37 mg, 0.09 mmol) in 2 mL of DMF at room temperature under argon. The reaction mixture was stirred at room temperature for 15 h, and then water (50 mL) was added. The solution was extracted with ether (4 × 10 mL), and then the organic layers were dried ($MgSO_4$) and then concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 30% ethyl acetate/hexanes) to afford after vacuum drying 32 mg (75%) of 1(*R*)-(silyloxy) dienyne **9a** as a

(25) (a) Hibberd, K. A.; Norman, A. W. *Biochem. Pharm.* **1969**, *18*, 2347. (b) Norman, A. W.; Wong, R. G. *J. Nutrition* **1972**, *102*, 1709. (c) For recent examples, see: Figadere, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452.

(26) (a) Procsal, D. A.; Okamura, W. H.; Norman, A. W. *Am. J. Clin. Nutrition* **1976**, *29*, 1271. (b) Wecksler, W. R.; Normal, A. W. *Methods Enzym.: Vitamins Co-Enzymes* **1980**, *67*, 488. (c) See also ref 7b.

(27) Besides ref 6, see: (a) Latham, J. A.; Walsh, C. *J. Am. Soc.* **1987**, *109*, 3421. (b) Branchaud, B. P.; Walsh, C. T. *J. Am. Chem. Soc.* **1985**, *107*, 2153. (c) Light, D. R.; Waxman, D. J.; Walsh, C. *Biochemistry* **1982**, *21*, 2490.

(28) Spectral and other analytical data are given in the supplementary material. Essential $^1$H-NMR spectral data are presented in the Experimental Section as well. General experimental procedures are also presented in the supplementary material, and the purities of all new compounds were judged by a combination of HPLC and $^1$H- and $^{13}$C-NMR analysis before mass spectral determination. For all new compounds, the level of purity is indicated by the inclusion of copies of $^1$H-NMR spectra and selected $^{13}$C-NMR spectra in the supplementary material.

colorless oil which was used for the next step and for spectral characterization. $^1$H-NMR: δ 0.10 (3 H, SiMe, s), 0.11 (3 H, SiMe, s), 0.69 (3 H, $C_{18}$-$CH_3$, s), 0.90 (9 H, Si-*t*-Bu, s), 0.95 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.6 Hz), 1.21 (6 H, $C_{26,27}$-2$CH_3$, s), 1.95 (3 H, $C_{19}$-$CH_3$, s), 2.6–2.8 (2 H, $2H_2$, m), 2.96 and 3.35 (2 H, $2H_4$, AB pattern, $J_{AB}$ = 16.7 Hz), 4.29 (1 H, $H_1$, m), 5.95 (1 H, $H_9$, narrow m).

**1(*S*)-(Silyloxy)-25-hydroxy-3-deoxy-3-thia-6,7-didehydroprevitamin $D_3$ (9b).** Diethylamine (39 μL, 0.38 mmol) was added to a solution of $(PPh_3)_2Pd(OAc)_2$ (7 mg, 0.0095 mmol), CuI (4 mg, 0.019 mmol), 1(*S*)-(silyloxy) enyne **11b** (47 mg, 0.17 mmol), and CD-triflate **10** (79 mg, 0.19 mmol) in 5 mL of DMF at room temperature under argon. The reaction mixture was stirred at room temperature after 12 h, and then water (40 mL) was added. The solution was extracted with ether (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 30% ethyl acetate/hexanes) to afford after vacuum drying 64 mg (71%) of 1(*S*)-(silyloxy) dienyne **9b** as a colorless oil, which was used for the next step as well as for spectral characterization. $^1$H-NMR: δ 0.10 (3 H, Si-Me, s), 0.11 (3 H, $SiCH_3$, s), 0.69 (3 H, $C_{18}$-$CH_3$, s), 0.90 (9 H, Si-*t*-Bu, s), 0.94 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.6 Hz), 1.21 (6 H, $C_{26,27}$-2$CH_3$, s), 1.95 (3 H, $C_{19}$-$CH_3$, s), 2.6–2.8 (2 H, $2H_2$, m), 2.96 and 3.34 (2 H, $2H_4$, AB pattern, $J_{AB}$ = 16.6 Hz), 4.29 (1 H, $H_1$, m), 5.95 (1 H, $H_9$, narrow m).

**25-Hydroxy-*de*-*A*,*B*-cholest-8-en-8-yl Trifluoromethanesulfonate (10).** This material was prepared as described previously.[5a,9,10] $^1$H-NMR: δ 0.75 (3 H, $C_{18}$-$CH_3$, s), 0.94 (3 H, $C_{21}$-$CH_3$, d, $J$ = 6.3 Hz), 1.20 (6 H, $C_{26,27}$-2$CH_3$, s), 1.65–1.85 (1 H, m), 1.9–2.1 (2 H, m), 2.2–2.4 (2 H, m), 2.4–2.5 (1 H, m), 5.55 (1 H, $H_9$, ddd, $J$ = 3.4, 3.4, 3.4 Hz).

**1(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-5-ethynyl-6-methyl-3-thiacyclohex-5-ene (11a).** Imidazole (272 mg, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (301 mg, 2.0 mmol) were added to a solution of (1*R*)-enynol **12a** (26 mg, 0.2 mmol) in 4 mL of $CH_2Cl_2$ at room temperature. The reaction mixture was stirred at room temperature for 4 h and then passed through a short $SiO_2$ column (1 × 15 cm, ether). The eluate was concentrated and passed through a short $SiO_2$ column (1 × 15 cm, hexanes) and then concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 2% ethyl acetate/hexanes) to afford 32 mg of 1(*R*)-(silyloxy) enyne **11a** (60%) which was used for the next step and spectral characterization. $^1$H-NMR: δ 0.11 (3 H, MeSi, s), 0.12 (3 H, MeSi, s), 0.90 (9 H, *t*-BuSi, s), 1.98 (3 H, $C_6$-$CH_3$, s), 2.60–2.80 (2 H, $C_2$-$CH_2$, m), 2.97 and 3.35 (2 H, $C_4$-$CH_2$, AB, $J_{AB}$ = 16.8 Hz), 3.17 (1 H, ethynyl, s), 4.28 (1 H, $H_1$, m).

**1(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-5-ethynyl-6-methyl-3-thiacyclohex-5-ene (11b).** Imidazole (429 mg, 6.2 mmol) and *tert*-butyldimethylsilyl chloride (475 mg, 3.1 mmol) were added to a solution of (1*S*)-enynol **12b** (41 mg, 0.31 mmol) in 8 mL of $CH_2Cl_2$ at room temperature under argon. The reaction mixture was stirred at room temperature for 6 h and then passed through a short $SiO_2$ column (1 × 15 cm, ether). The eluate was concentrated and passed through a short $SiO_2$ column (1 × 15 cm, hexane) and then concentrated again. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 2% ethyl acetate/hexanes) to afford 70 mg of 1(*S*)-(silyloxy) enyne **11b** (84%) which was used for the next step and for spectral characterization. $^1$H-NMR: δ 0.11 (3 H, MeSi, s), 0.12 (3 H, MeSi, s), 0.90 (9 H, *t*-BuSi, s), 1.98 (3 H, $C_6$-$CH_3$, s), 2.97 and 3.35 (2 H, $C_4$-$CH_2$, AB pattern, $J$ = 16.8 Hz), 3.17 (1 H, ethynyl, s), 4.28 (1 H, $H_1$, m).

**(±)-5-Ethynyl-6-methyl-3-thiacyclohex-5-en-ol (±)-12.** A $Bu_4NF$ solution (1.0 M in THF, 200 μL, 0.2 mmol) was added to a solution of enynol (±)-**19** (22 mg, 0.1 mmol) in 0.5 mL of THF at room temperature under argon. The reaction mixture was stirred at room temperature for 17 h, and then water (5 mL) was added. The mixture was extracted with ether (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (25% ethyl acetate/hexanes) to afford 12 mg (92%) of enynol (±)-**12**. The $^1$H-NMR spectral properties of this material were identical to the enantiomerically pure (1*R*)- and (1*S*)-isomers described below.

**(−)-(1*R*)-5-Ethynyl-6-methyl-3-thiacyclohex-5-en-1-ol ((−)-12a).** The (1*R*,1′*R*)-carbamate **23a** (100 mg, 0.23 mmol) and KOH (400 mg, 7.0 mmol) in 5 mL of EtOH were refluxed for 21 h. The reaction mixture was cooled to room temperature and passed through a $SiO_2$ column (1 × 15 cm, ether), and then the eluate was concentrated. The crude residue was passed through a $SiO_2$ column (1 × 15 cm, 20% ethyl acetate/hexanes), and the eluate was concentrated again. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 20% ethyl acetate/hexanes) to afford 26 mg (87%) of (1*R*)-enynol (−)-**12a** ($[\alpha]^{23}_D$ −76.8 (*c* 1.0, $CHCl_3$)) which was used for further spectral characterization and synthetic transformations. See below for studies related to assignment of absolute configuration as well as chiral LIS experiments. $^1$H-NMR: δ 2.06 (3 H, $C_6$-$CH_3$, s), 2.77 (1 H, $H_2$, ddd, $J$ = 13.8, 3.4, 1.2 Hz), 2.88 (1 H, $H_2$, dd, $J$ = 13.8, 2.7 Hz), 2.91 and 3.34 (2 H, $2H_4$, AB pattern, $J$ = 17.2 Hz), 3.22 (1 H, ethynyl, s), 3.98 (1 H, $H_1$, m).

**(+)-(1*S*)-5-Ethynyl-6-methyl-3-thiacyclohex-5-en-1-ol ((+)-12b).** The (1*S*,1′*S*)-carbamate **22b** (122 mg, 0.29 mmol) and KOH (323 mg, 5.8 mmol) in 10 mL of EtOH were refluxed under argon for 24 h. The reaction mixture was cooled to room temperature and passed through a $SiO_2$ column (1 × 15 cm, ether), and then the eluate was concentrated. The crude residue was passed through a $SiO_2$ column (1 × 15 cm, 20% ethyl acetate/hexanes) and concentrated. The crude residue was purified by HPLC (Whatman Partisil 10 Silica Magnum 9 column, 20% ethyl acetate/hexanes) to afford 35 mg (93%) of (1*S*)-enynol (+)-**12b** ($[\alpha]^{23}_D$ +74.4 (*c* 0.714, $CHCl_3$)), which was used for further spectral characterization and synthetic transformations. See below for studies related to assignment of absolute configuration as well as chiral LIS experiments. The NMR spectra data of this material were identical to that of (−)-**12a**.

**$^1$H-NMR Chiral Shift Reagent Studies of (1*R*)- and (1*S*)-5-Ethynyl-6-methyl-3-thiacyclohex-5-en-1-ol (12).** The enantiomeric purity of (1*R*)- and (1*S*)-enynols (−)-**12a** and (+)-**12b** together with the racemic material was determined by $^1$H-NMR analysis using the chiral shift reagent (CSR), tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]praseodymium-(III) derivative ($Pr(hfc)_3$). The $Pr(hfc)_3$ was added incrementally to the enynols (~2 mg in ~0.8 mL $CDCl_3$) in an NMR tube, recording the $^1$H-NMR spectrum after each addition. The ~1:1 ratio of alkynyl proton signals were base-line separated for the enantiomers of the racemic material in the $^1$H-NMR spectrum. The pure (1*R*)- and (1*S*)-enynols (−)-**12a** and (+)-**12b** exhibited only one shifted alkynyl signal. This attests to the essentially complete optical purity of the (−)-(1*R*)- and (+)-(1*S*)-enynols, (−)-**12a** and (+)-**12b**, respectively.

**6-Methyl-3-thiacyclohexane-1,5-dione (13).** A solution of keto ester **16** (22.8 g, 129 mmol) in 250 mL of THF was added dropwise over a period of 100 min to a stirred suspension of NaH (5.0 g, 129 mmol) in 150 mL of THF at room temperature (water bath) under argon. The reaction mixture was stirred at room temperature for 3 h and poured into ice–water (500 mL). The aqueous layer was extracted with ether (3 × 50 mL), and then the aqueous layer was acidified with 2 M aqueous HCl to a pH of 2–3. The resulting aqueous layer was extracted with $CHCl_3$ (5 × 100 mL), and the combined $CHCl_3$ extracts were washed with brine (100 mL) and dried ($Na_2SO_4$). The solvent was concentrated under reduced pressure, and then the crude residue was washed with ether several times to afford 9.08 g (49%) of thia diketone **13** which was used in the next step without further purification. The sample used for spectral characterization was recrystallized by $CH_2Cl_2$/ether (mp 133–134 °C (lit.[11] mp 132.5–133 °C)). $^1$H-NMR: δ 1.29 (3 H, $C_6$-$CH_3$, d, $J$ = 6.5 Hz), 3.35–3.55 (4 H, $H_{2,4}$, m), 3.73 (1 H, $H_6$, q, $J$ = 6.5 Hz).

**Methyl 2-[(3-Methylacetonyl)thio]acetate (16).** To a stirred, ice-cold solution of NaOMe, prepared from 2.76 g of sodium (120 mmol) and 55 mL of $CH_3OH$, was added (1 min) methyl thioglycolate (**15**, 11.2 mL, Aldrich, 119 mmol) followed by addition of 1-bromo-2-butanone (**14**, 20.0 g, 90%, Aldrich, 119 mmol) over a period of 15 min. The reaction mixture was stirred at room temperature for 25 min and at 57 °C for an additional 25 min. The mixture was filtered to remove precipitate (sodium bromide), the filtrate was poured into cold water (300 mL), and then the entire mixture was extracted with ether (3 × 70 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$),

and concentrated. The concentrate (19.8 g, 94%) was used for the next step without further purification. The sample for spectroscopic analysis was purified by HPLC (Whatman Partisil 10 Silica Magnum 9, 30% ethyl acetate/hexanes). $^1$H-NMR: δ 0.88 (3 H, $C_3$-$CH_3$, t, $J$ = 7.2 Hz), 2.43 (2 H, $C_3$-$CH_2$, q, $J$ = 7.2 Hz), 3.08 (2 H, $C_7$-$CH_2$, s), 3.25 (2 H, $C_1$-$CH_2$, s), 3.52 (3 H, $CO_2Me$, s).

**5-Iodo-6-methyl-3-thiacyclohex-5-en-1-one (17).** In a dry 25-mL round-bottom flask equipped with a condenser, magnetic stirring bar, septum, and argon inlet was placed triphenylphosphine (420 mg, 1.60 mmol), iodine (406 mg, 1.60 mmol), and acetonitrile (10 mL). After the mixture was stirred at room temperature for 3.5 h, triethylamine (225 μL, $d$ = 0.726, 1.6 mmol) and thia diketone **13** (144 mg, 1.00 mmol) were added. The reaction mixture was refluxed under argon for 24 h (followed by TLC). The crude material was passed through a dry silica gel column (10% ethyl acetate/hexanes) and then the eluate concentrated under reduced pressure. Purification of the crude residue by flash chromatography (silica gel, 2 × 25 cm, 10% ethyl acetate/hexanes) afforded 144 mg (57%) of iodo enone **17** as a light-sensitive, light brown oil. This material was used directly in the next step as well as for spectroscopic characterization without further purification. Extensive handling was avoided because of the tendency of this material to darken. $^1$H-NMR: δ 2.11 (3 H, 6-$CH_3$, t, $J$ = 1.9 Hz), 3.38 (2 H, br s), 3.90 (2 H, br s).

**5-[(Trimethylsilyl)ethynyl]-6-methyl-3-thiacyclohex-5-en-1-one (18).** Trimethylsilylacetylene (57 μL, 0.4 mmol) was added to a solution of iodoenone **17** (102 mg, 0.4 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), CuI (16 mg, 0.08 mmol), and $n$-$BuNH_2$ (60 μL, 0.6 mmol) in 5 mL of benzene at room temperature under argon. The reaction mixture was stirred at room temperature for 29 h and then quenched with water (20 mL). The aqueous layer was extracted with ether (3 × 6 mL), and the combined organic extracts were dried with $MgSO_4$. The crude solution was passed through a short $Al_2O_3$ column (ether), and then the eluate was concentrated. This material (82 mg, 91%) was used for the next step, and the sample for spectral characterization was obtained by HPLC (Whatman Partisil 10 Silica Magnum 9, 5% ethyl acetate/hexanes). $^1$H-NMR: δ 0.23 (9 H, $Me_3Si$, s), 2.03 (3 H, $C_6$-Me, s), 3.31 (2 H, $2H_4$, s), 3.41 (2 H, $2H_2$, s).

**(±)-5-[(Trimethylsilyl)ethynyl]-6-methyl-3-thiacyclohex-5-en-1-ol (±)-(19).** Sodium borohydride (9 mg, 0.24 mmol) was added slowly to a solution of enone **18** (52 mg, 0.23 mmol) and $CeCl_3 \cdot 6H_2O$ (86 mg, 0.23 mmol) in 5 mL of $CH_3OH$ at room temperature. The reaction mixture was stirred at room temperature for 10 min, and water (50 mL) was added. The solution was extracted with ether (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was passed through a silica gel column (1 × 15 cm, ether) to afford 50 mg (96%) enynol (±)-**19** which was used for the next step. The sample for spectroscopic characterization was purified by HPLC (Whatman Partisil 10 Silica Magnum 9 column, 20% ethyl acetate/hexanes). $^1$H-NMR: δ 0.19 (9 H, $SiMe_3$, s), 2.06 (3 H, 6-Me, narrow m), 2.77 (1 H, $H_2$, ddd, $J$ = 13.6, 3.3, 1.5 Hz), 2.87 (1 H, $H_2$, dd, $J$ = 13.6, 2.7 Hz), 2.90 and 3.34 (2 H, $2H_4$, AB pattern with fine structure, $J$ = 16.4 Hz), 3.97 (1 H, $H_1$, m).

**Asymmetric Reduction of Enone 18 by the CBS Procedure Using (*R*)-Oxazaborolidine 24 and Catecholborane: (*R*)-Enynol 19a.** To a solution of (*R*)-oxazaborolidine **24** (134 μL, 0.5 M toluene solution, 0.067 mmol) and enone **18** (150 mg, 0.668 mmol) in 6 mL of toluene at −78 °C under argon was added dropwise catecholborane (142 μL, 1.34 mmol). The reaction mixture was stirred at −78 °C for 20 h, and then water (5 mL) was added. The reaction mixture was warmed to room temperature and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, 20% ethyl acetate/hexanes) to afford 120 mg (80%) of (*R*)-enynol **19a** as a colorless oil. The enantiomeric purity was determined to be 86% ee by $^1$H-NMR analysis in conjunction with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]praseodymium(III) derivative ($Pr(hfc)_3$).

**Asymmetric Reduction of Enone 18 by the CBS Procedure Using (*S*)-Oxazaborolidene 25 and Catecholborane: (*S*)-Enynol 19b.** To a solution of (*S*)-oxazaborolidine **25** (100 μL, 0.5 M toluene solution, 0.05 mmol) and enone **18** (113 mg, 0.50 mmol) in 7 mL toluene at −78 °C under argon was added dropwise catecholborane (112 μL, 2.0 mmol). The reaction mixture was stirred at −78 °C for 6 h and kept in the freezer for 15 h. Water (30 mL) was added, and then the mixture was warmed to room temperature and extracted with ether (4 × 10 mL). The organic layer was washed with saturated $Na_2CO_3$ (20 mL) and saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), and then concentrated. The crude residue was flash chromatographed (silica gel, 20% ethyl acetate/hexanes) to afford 108 mg (95%) of enynol **19b** as a colorless oil. The enantiomeric purity was determined to be 85% ee by $^1$H-NMR analysis using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]praseodymium(III) derivative ($Pr(hfc)_3$).

**Asymmetric Reduction of Enone 18 Using $LiAlH_4$–*N*-Methylephedrine To Afford (*S*)-Enynol 19b.** A solution of (1*R*,2*S*)-*N*-methylephedrine **26** (538 mg, 3 mmol) in 6 mL of anhydrous ether was added dropwise over 30 min to a lithium aluminum hydride solution (1.0 M in ether, 3 mL, 3 mmol) at room temperature under argon. The reaction mixture was stirred at room temperature for 1.1 h, and then a solution of 2-(*N*-ethylamino)pyridine (**27**) (733 mg, 6 mmol) in 7 mL of ether was added dropwise over 35 min, and the mixture was stirred at room temperature for 1.5 h. The mixture was cooled to −78 °C, and a solution of enone **18** (225 mg, 1 mmol) in 5 mL of ether was added dropwise over 30 min. After being stirred at −78 °C for 2.6 h, the reaction was quenched with methanol (200 μL), and then water (10 mL) was added. The mixture was warmed to 0 °C, and 2 M aqueous NaOH (15 mL) was added. The mixture was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with saturated $Na_2CO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, 20% ethyl acetate/hexanes) to afford 206 mg (91%) of enynol **19b**. The enantiomeric purity was determined to be 43% ee by $^1$H-NMR analysis using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]praseodymium(III) derivative ($Pr(hfc)_3$).

**(+)-(1*S*,1′*S*)-5-[(Trimethylsilyl)ethynyl]-6-methyl-3-thiacyclohex-5-en-1-yl *N*-[1′-(1-Naphthyl)ethyl]carbamate (22b).** A solution of racemic enynol **19** (478 mg, 2.1 mmol), (*S*)-(+)-(1-naphthyl)ethyl isocyanate (370 μL, Aldrich, 2.1 mmol), and two drops of *N*,*N*-dimethylethanolamine in 20 mL of benzene was refluxed for 68 h. The reaction mixture was cooled to room temperature and passed through a $SiO_2$ column (3 × 5 cm, ether) and then concentrated. The crude residue was recrystallized from 20% ethyl acetate/hexanes to afford 320 mg (36%; 72% of theory) of white crystalline (1*S*,1′*S*)-carbamate **22b** [mp 176–177 °C; $[\alpha]^{23}_D$ +67.0 (*c* 0.71, $CHCl_3$)] which was used for the next step. $^1$H-NMR: δ 0.19 (9 H, $Me_3Si$, s), 1.66 (3 H, 2′-$CH_3$, d, $J$ = 6.6 Hz), 1.90 (3 H, 6-$CH_3$, s), 2.80–3.25 (4 H, $2H_2$, $2H_4$, m), 5.20 (1 H, –NH, br s), 5.31 (1 H, $H_1$, apparent, br s), 5.67 (1 H, $H_{1'}$, m), 7.80–8.20 (7 H, naphthyl-H, m). The mother liquors (~441 mg) were a mixture of (1*S*,1′*S*)- and (1*R*,1′*S*)-carbamates. This mixture was subjected to HPLC (Whatman Partisil 10 Silica Magnum 9, 10% ethyl acetate/hexanes), and elution order was (1*S*,1′*S*)-carbamate followed by the major (1*R*,1′*S*)-carbamate. HPLC comparisons attesting to configurational assignments and diastereomeric purities are described in the text.

In addition, a sample of the (1*S*,1′*S*)-enantiomer (recrystallized from $CHCl_3$/hexanes (1:1)) was submitted for single-crystal X-ray crystallographic determination to Dr. J. Ziller at the University of California, Irvine. The results confirm the assigned absolute configuration based on the configuration relative to the known absolute $C_1$-configuration of the starting isocyanate, and the details are presented in the supplementary material.

**(−)-(1*R*,1′*R*)-5-[(Trimethylsilyl)ethynyl]-6-methyl-3-thiacyclohex-5-en-1-yl *N*-[1′-(1-Naphthyl)ethyl]carbamate (23a).** Racemic enynol **19** (202 mg, 0.89 mmol), (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (177 μL, 0.98 mmol), and two drops of *N*,*N*-dimethylethanolamine in 20 mL of benzene were refluxed for 68 h. The reaction mixture was cooled to room temperature and passed through a $SiO_2$ column (3 × 5 cm, ether) and then concentrated. The crude material was recrystallized from 20% ethyl acetate/hexanes to afford 100 mg (27%; 54% of theory) of

white crystalline (1R,1'R)-carbamate **23a** [mp 177-178 °C, $[\alpha]^{23}_D$ -63.7 (c 0.49, $CHCl_3$)] which was used directly in the next step. $^1$H-NMR: δ 0.19 (9 H, $Me_3Si$, s), 1.66 (3 H, 2'-$CH_3$, d, $J$ = 6.6 Hz), 1.90 (3 H, $C_8$-$CH_3$, s), 2.80-3.25 (4 H, $2H_2$, $2H_4$, m), 5.20 (1 H, NH, br s), 5.31 (1 H, $H_1$, apparent br s), 5.67 (1 H, $H_{1'}$, m), 7.80-8.20 (7 H, naphthyl-H, m).

The mother liquors (~244 mg) contained a mixture of (1R,1'R) **23a** and (1S,1'R)-carbamates **23b** enriched in the latter. HPLC analysis (Whatman Partisil 10 Silica Magnum 9, 10% ethyl acetate/hexanes) led to elution of the minor (1R,1'R)-carbamate **23a** followed by the major (1S,1'R)-diastereomer **23b**. The HPLC elution profile is described in the text along with a discussion of studies attesting to configurational assignments and diastereomeric purities. Additional information is described elsewhere in the Experimental Section along with a description of the results of a single-crystal X-ray crystallographic study of the (1S,1'S)-enantiomer.

**Biological Evaluation: Intestinal Calcium Absorption and Bone Calcium Mobilization.** Intestinal calcium absorption (ICA) and bone calcium mobilization (BCM) were determined in vivo in vitamin D deficient chicks as described previously.[25] Twelve hours before assay, the chicks which had been placed on a zero-calcium diet 48 h before assay, were injected intramuscularly with vitamin D metabolite or analogue in 0.1 mL of ethanol/1,2-propanediol (1:1, v/v) or with vehicle. At the time of assay, 4.0 mg of $^{40}Ca^{2+}$ + 5 μCi of $^{45}Ca^{2+}$ (New England Nuclear) were placed in the duodenum of the animals which had been anesthetized with ether. After 30 min, the birds were decapitated and the blood collected. The radioactivity content of 0.2 mL of serum was measured in a liquid scintillation counter (Beckman LS8000) to determine the amount of $^{45}Ca^{2+}$ absorbed (which is a measure of ICA). BCM activity was estimated from the increase of total serum calcium as measured by atomic absorption spectrophotometry.

**1α,25-$(OH)_2$-$D_3$ Receptor Steroid Competition Assay.** A measure of competitive binding to the chick intestinal 1α,25-$(OH)_2$-$D_3$ receptor was performed by using the hydroxylapatite batch assay.[26] Increasing amounts of 1α,25-$(OH)_2$-$D_3$ or analogue were added to a standard amount of [$^3$H]-1α,25-$(OH)_2$-$D_3$ and incubated with chick intestinal cytosol. The relative competitive index (RCI) for the analogues was determined by plotting the percent maximum of 1α,25-$(OH)_2$-$D_3$ bound × 100 on the ordinate versus [competitor]/[1α,25-$(OH)_2$-[$^3$H]$D_3$] on the abscissa. The slope of the line obtained for a particular analogue is divided by the slope of the line obtained for 1α,25-$(OH)_2$-$D_3$; multiplication of this value by 100 gives the RCI value. By definition, the RCI for 1α,25-$(OH)_2$-$D_3$ is 100.

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**Supplementary Material Available:** Spectral and analytical data (34 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.

# Design, Synthesis, and Evaluation of an Improved Enantioselective Naproxen Selector

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The design, synthesis, and evaluation of an improved selector for the enantiomers of the nonsteroidal anti-inflammatory drug, naproxen, are described. So as to utilize the principle of reciprocity, two chiral stationary phases (CSPs) derived from (S)-naproxen were produced and HPLC techniques were used to screen candidate naproxen selectors. By determining how the structural features of the candidates influence enantioselective recognition by naproxen, a hypothetical chiral recognition mechanism for enantioselective recognition of naproxen was developed and used to design a selector which was incorporated into a new CSP. This comparatively simple CSP shows significant improvement in the separation of underivatized naproxen enantiomers relative to previous methods. Related compounds such as ibuprofen, ketoprofen, cicloprofen, fenoprofen, etc. are also resolved into their component enantiomers by this CSP.

## Introduction

Among the economically significant nonsteroidal anti-inflammatory drugs (NSAIDs), many of which are α-arylpropionic acids, only naproxen, **1**, is sold as a single enantiomer.[1] Consequently, there has been considerable interest in the asymmetric synthesis[2] and chromatographic resolution[3] of naproxen. Several rather complex synthetic receptors intended for enantioselective recognition of naproxen have been developed by Diederich and co-workers[4] In the best case seen to date, an enantioselectivity of 1.21 has been observed.[4d] In this paper, we describe a chromatographic approach which was used to develop a mechanistic rationale which, in turn, led to the design of an enantioselective selector for naproxen. This selector is straightforward in its preparation and shows enhanced

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(1) De Camp, W. H. *Chirality* **1989**, *1*, 2. In *Chiral Separations by HPLC, Applications to Pharmaceutical Compounds*; Krstulović, A., Ed.; John Wiley & Sons: New York, 1989.
(2) Haggin, J. *Chem. Eng. News* **1990**, May 7, 58.
(3) For a recent review of methods for the chromatographic separation of the enantiomers of naproxen and other NSAIDs see: Bojarski, J. *J. Liq. Chromatogr.* **1989**, *12*, 2685.
(4) (a) Rubin, Y.; Dick, K.; Diederich, F.; Georgiadis, T. *J. Org. Chem.* **1986**, *51*, 3270. (b) Dharanipragada, R.; Diederich, F. *Tetrahedron Lett.* **1987**, *28*, 2443. (c) Dharanipragada, R.; Ferguson, S., Diederich, F. *J. Am. Chem. Soc.* **1988**, *110*, 1679. (d) Castro, P.; Georgiadis, T.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835. (e) Georgiadis, P.; Georgiadis, T.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 3362. (f) Castro, P.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 6277.

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