Taxol Total Synthesis: Preparation of a Chiral Ring A Moiety via Biomimetic Cyclization and Evaluation of a Tandem Nitrile Oxide Strategy for Rings B/C[1]

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A fully functionalized taxol ring A moiety **7** was efficiently prepared via biomimetic cation–olefin cyclization of chiral geraniol epoxide **2b** using $SnCl_4$ in toluene. Fractional crystallization provided *endo*-**3** (50% yield from **2b**) that was converted to aldehyde **5** by stereospecific epoxidation, secondary alcohol protection, and PCC oxidation. NaOMe-mediated ring opening secured enal **6**. Addition of lithium dithiane to **6** at low temperature provided **7** as the sole product in good yield. A tandem nitrile oxide cycloaddition strategy for creating the remaining B/C carbocycles as well as key functionality present in both rings was validated, in part, by cyclization of **14** to tricyclic isoxazoline **15**.

Introduction

The promising clinical performance[2] and unique molecular architecture of taxol (**1**) have evoked a vast array of synthetic options[3] for its total synthesis.[4] The most efficient of these exploit a convergent strategy utilizing a functionalized ring A equivalent upon which the remaining carbon skeleton is appended. Notable examples include ring A constructs arising from chiral terpenoids,[5] carbohydrates,[6] Diels–Alder adducts,[7] isoprenoids,[8] aldol products,[9] and other inventive annulation strategies.[10] Our approach to **1**, outlined retrosynthetically in Scheme 1, relies upon tandem nitrile oxide cycloadditions to elaborate the basic taxol ring system starting from a protected ring A synthon. Herein, we describe the concise, stereocontrolled preparation of a suitable ring A intermediate utilizing a readily accessible and inexpensive chiral precursor[11] and report on our progress toward an asymmetric total synthesis of **1** exploiting [3 + 2]-cycloaddition methodology.

Despite the appeal of biomimetic, cation–olefin cyclizations of polyisoprenoids,[12,13] such annulations have not proven to be broadly useful on a preparative scale, especially when initiated by Brönsted- or Lewis acid-catalyzed oxirane openings. Pinacol rearrangement to the corresponding carbonyl and/or halohydrin formation are often competitive compared to cyclization at car-

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(1) Presented in part at the 4th Tohwa University International Symposiun "Chemistry on Biologically- and Physiologically-Active Natural Products", Minami-Ku, Fukuoka, Japan; Nov 19–22, 1994.

(2) Clinical reviews: Rothenbery, M. *Curr. Opin. Invest. Drugs* **1993**, *2*, 1269–1277. *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1994.

(3) Reviews: Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Natl. Prod.* **1993**, *61*, 1–192. Nicolaou, K. C.; Dai W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47–75.

(4) Total syntheses of taxol: Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Susuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598; 1599–1600. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud J.; Couladourous, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653–659.

(5) Kitagawa, I; Shibuya, H.; Fujioka, H.; Kajiwara, A.; Tsujii, S.; Yamamoto, Y.; Takagi, A. *Chem. Lett.* **1980**, 1001–1004. Wender, P.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878–5879. Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Munoz Dorado, M.; Toromanoff, E.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 1137–1140. Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. *Tetrahedron Lett.* **1993**, *34*, 55–58. Wender, P.; Floreancig, P. E.; Glass, T. E.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C. *Tetrahedron Lett.* **1995**, *36*, 4939–4942.

(6) Pettersson, L.; Magnusson, G.; Frejd, T. *Acta Chem. Scand.* **1993**, *47*, 196–207 and earlier references. Ermolenko, M. S.; Shekharam, T.; Lukacs, G.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2461–2464.

(7) (a) Nicolaou, K. C.; Hwang, C. K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117–1118. (b) Benchikh le-Hocine, M.; Do Khac, D.; Fetizon, M.; Guir, F.; Guo, Y.; Prange, T. *Tetrahedron Lett.* **1992**, *33*, 1433–1446. (c) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843–4846. (d) Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745–3752. (e) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043–4047. (f) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989–4992. Wong, T.; Romero, M. A.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 5527–5529.

(8) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1991**, *39*, 1359–1364. Parsons, P. J.; Stevinovic, M. *Synlett* **1993**, 931–932. Chai, K.-B.; Sampson, P. *J. Org. Chem.* **1993**, *58*, 6807–6813. Crich, D.; Crich, J. Z. *Tetrahedron Lett.* **1994**, *35*, 2469–2472.

(9) Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165–3174. Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014–6017.

(10) Snider, B. B.; Allentoff, A. J. *J. Org. Chem.* **1991**, *56*, 321–328. Oh, J.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1992**, *57*, 6664–6667.

(11) For an alternative, but achiral approach to ring A using geraniol, see: Doi, T.; Roberton, J.; Stork, G.; Yamashita, A. *Tetrahedron Lett.* **1994**, *35*, 1481–1484.

(12) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295–3296. Van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937–5938. Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1–8. van Tamelen, E. E.; McCormick, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 1847–1848. Sharpless, K. B.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1969**, *91*, 1848–1949. van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152–158. van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061–2062. van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259–1270. Taylor, S. K.; *Org. Prep. Proc. Int.* **1992**, *24*, 247–284.

(13) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111–120.

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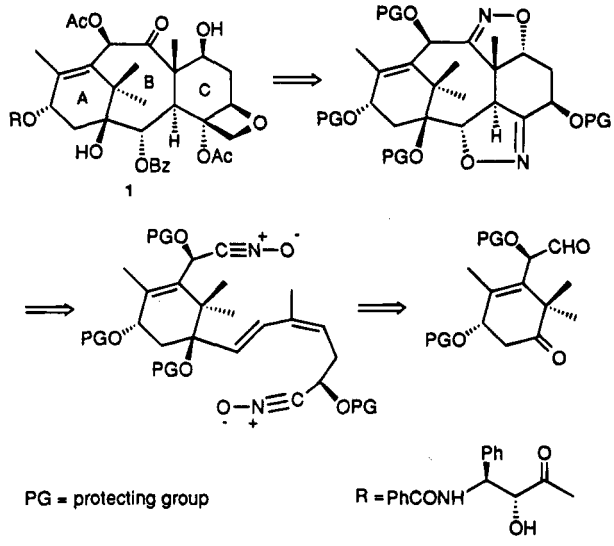
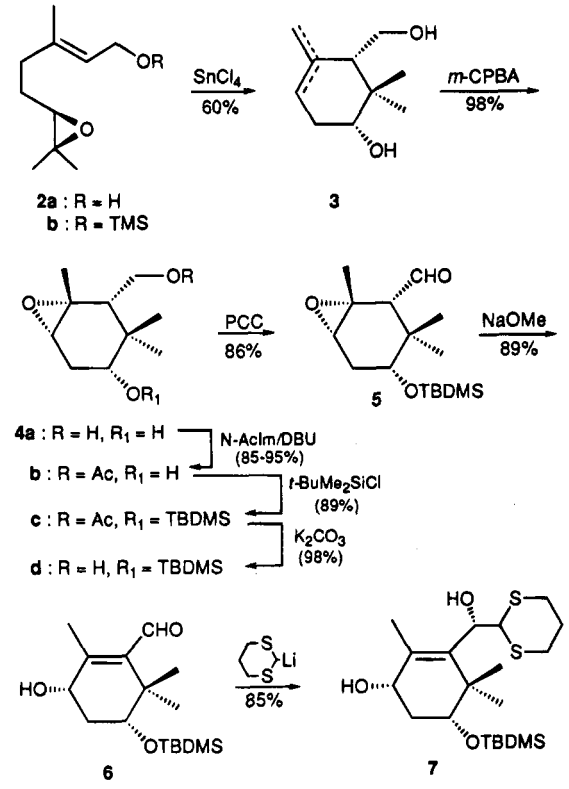
Scheme 1

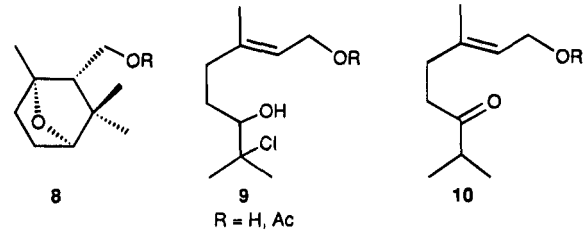


bon.[14,15] Ring closures which are terminated by deprotonation are further complicated by the accumulation of protic acids during the reaction as well as a general lack of positional control resulting in unproductive mixtures of regioisomeric olefins.[16]

In the case of geraniol epoxide **2a**, a review of the literature suggests that, among other parameters, the nature of the C(1)-alcohol substituent and the choice of catalyst play significant roles in determining the product distribution.[13,15,17] Accordingly, a systematic examination was conducted to optimize the yield of monocyclic diol **3** from chiral **2** which was derived from geranyl acetate by Sharpless asymmetric dihydroxylation (AD-mix-α, 90% ee), selective mesylation, and closure to the oxirane as described by Vidari *et al.*[18] The best cyclization conditions utilized a 0.17 M solution of TMS ether **2b** and $SnCl_4$ (0.5 equiv) in toluene at 0 °C for 0.5 h (Scheme 2). Chromatographic purification on SiO_2 gave **3** as an *ca.* 85:15 *endo/exo*-olefin mixture. Fractional crystallization of the mixture conveniently afforded the pure *endo*-isomer (50% from **2b**). In practice, the cyclization could be conducted on a multigram scale without appreciable loss of efficiency. Under the above conditions, **2a** and its acyl esters generated complex product mixtures including cyclic ether **8**, chlorohydrin **9**, and ketone **10** in varying amounts. Alternative catalysts, *inter alia*, $BF_3{\cdot}Et_2O$, $TiCl_4$, $MeAlCl_2$, Me_2AlCl, and H_3PO_4, proved inferior. Interestingly, the *tert*-$BuMe_2Si$ analog of **2b** gave rise to **3** using $SnCl_4$ in almost the same yield as **2b**. This is consonant with the observations of Corey *et al.*[19] and suggests that the R_3Si group may be widely beneficial in cation–olefin cyclizations of this type.

Scheme 2





Oxidation of **3** (*endo*-isomer) with 3-chloroperbenzoic acid in CH_2Cl_2 gave a single epoxide **4a** in excellent yield. Analogous epoxidations of the primary acetate or TBDMS ether, secondary TBDMS ether, or bis-acetate of **3** resulted in mixtures of α/β-epoxides[20] and cogently demonstrated the role of both alcohols in directing the approach of the reagent. A series of conventional protection/deprotection steps converted **4a** to **4d** in good yield via acetate **4b** (>99% ee via NMR analysis of Mosher's ester), silylation to **4c**, and deacetylation using K_2CO_3. Pyridinium chlorochromate (PCC) oxidation of **4d**, moderated by NaOAc, furnished aldehyde **5** as a white solid

(14) Goldsmith, D. J. *J. Org. Chem.* **1962**, *84*, 3913–1918. Kishi, M.; Kato,T.; Kitahara, Y. *Chem. Pharm. Bull.* **1967**, *7*, 1071–1073. Goldsmith, D. J.; Phillips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862–5870. Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265–280. Taylor, S. K.; May, S. A.; Hopkins, J. A. *Tetrahedron Lett.* **1993**, *34*, 1283–1286.

(15) Mousseron-Canet, M.; Vedel, M. M. *Bull. Chem. Soc. Fr.* **1961**, 443–444.

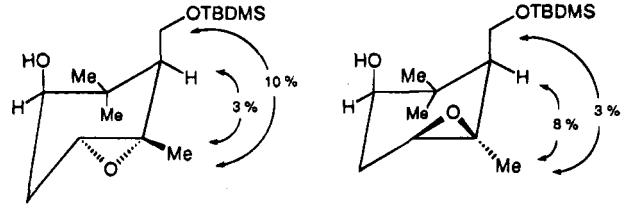
(16) For examples providing acceptable yields, see: Tanis, S. P.; Chuang, Y. H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929–4938. Yee, N. K. N.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4598–4608. Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873–8874. Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849–7852.

(17) Coates, R. M.; Melvin, L. S. *Tetrahedron*, **1970**, *26*, 5699–5706. Yamada, Y.; Sanjoh, H.; Iguchi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 997. Rouessac, F.; Aziz, M. *Tetrahedron* **1988**, *44*, 101–110. Gut, S.; Wolleb, H.; Pfander, H. *Helv. Chem. Acta* **1989**, *72*, 496–501.

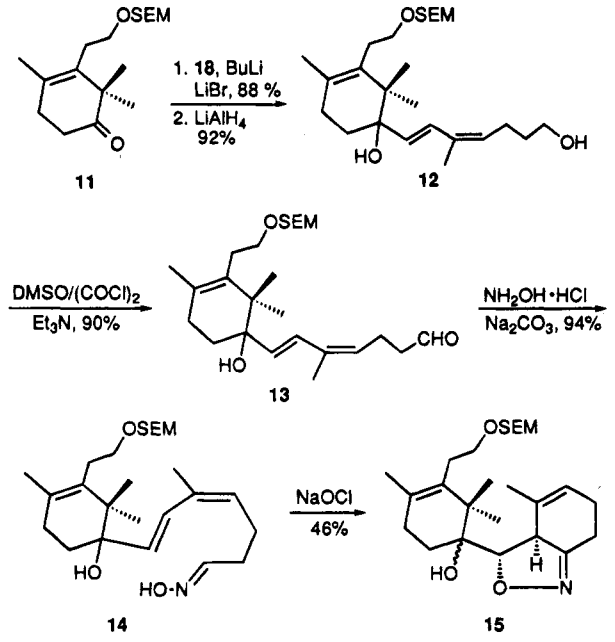
(18) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.

(19) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005–7008.

(20) Stereochemical assignments were based on nOe studies. Some representative data are shown in the figure:



Scheme 3



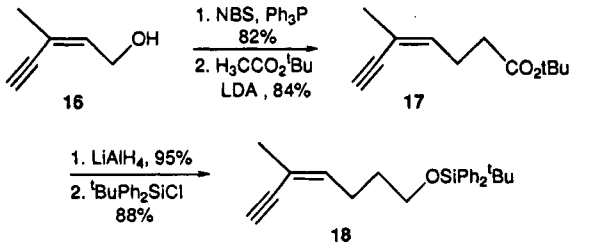
from which γ-hydroxy enal **6** was obtained by facile epoxide opening mediated by NaOMe. Low-temperature addition of lithium dithiane to **6** provided adduct **7** as the sole product which was provisionally assigned the *S* stereochemistry at C(10) (taxol numbering) on the basis of the CD of the corresponding *p*-bromobenzoate[21] and is consistent with attack from the less hindered carbonyl face (Cram addition). This result was unexpected in light of the poor stereospecificity observed during addition of a closely related cyclohexenyl anion to aldehydes.[7f]

To partially validate the global strategy embodied in Scheme 1, the readily available ring A model compound **11**[7e] was combined with the lithium anion of *O*-(*tert*-butyldiphenylsilyl)-*cis*-5-methyl-4-hepten-6-yn-1-ol (**18**) in the presence of LiBr[22] at −78 °C (Scheme 3). LAH reduction of the adduct in refluxing THF generated the *trans,cis*-diene and simultaneously desilylated the primary alcohol affording diol **12**. Aldehyde **13**, obtained from **12** by Swern oxidation, was converted to oxime **14** by standard treatment with hydroxylamine hydrochloride. Subsequent sodium hypochlorite oxidation of **14** and *in situ* [3 + 2]-cycloaddition of the intermediate nitrile oxide resulted in closure of ring C furnishing tricyclic isoxazoline **15** as a chromatographically separable 4:1 mixture of diastereomers in 46% combined yield.

Access to acetylene **18** was easily gained from commercial *cis*-3-methyl-2-penten-4-yn-1-ol (**16**) via ester **17** by alcohol/bromide interchange and displacement with the lithium salt of *tert*-butyl acetate (Scheme 4). $LiAlH_4$ reduction of **17** in Et_2O and silylation completed the sequence in *ca.* 58% overall yield from **16**.

In summary, we have established an efficient route to a fully functionalized, chiral taxol ring A precursor based on a biomimetic cation−olefin cyclization of an inexpensive geraniol silyl ether derivative. Additionally, we have described the foundation for a tandem nitrile oxide

Scheme 4



cyclization strategy for the further elaboration[23] of both the carbon skeleton and key functionalities present in the remainder of the target molecule.

Experimental Section

General. Chromatography, elemental analyses, and routine laboratory manipulations were as previously described.[24] Melting points are uncorrected. The Midwest Center for Mass Spectrometry provided high-resolution mass spectra. All reactions were conducted under an inert atmosphere.

(*R*)-6,7-Epoxygeranyl Trimethylsilyl Ether (2b). Chlorotrimethylsilane (19.14 g, 176.2 mmol) was added dropwise to a solution of **2a**[13](20 g, 117.5 mmol) and triethylamine (65.4 mL, 470.0 mmol) in Et_2O (600 mL) at 0 °C. After 3 h at room temperature, the precipitated salt was removed by filtration through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was distilled (58 °C, 0.03 mmHg) to afford **2b** (27.9 g, 98%) as a colorless liquid: $[\alpha]^{23}_D$ +2.3 (*c* 2.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.24 and 1.28 (2 s, 6H), 1.69 (s, 3H), 1.57−1.72 (m, 2H), 2.13 (q, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 1H), 4.13 (d, *J* = 6.5 Hz, 2H), 5.34 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.6, 16.0, 16.5, 24.6, 26.9, 35.9, 58.0, 59.1, 63.7, 124.2, 136.4; IR (neat) 2959, 2926, 2871, 1671, 1456, 1378, 1250, 1063, 877, 840 cm^{-1}; MS (CI/NH_3) *m/z* (rel %) 260 [$(M + NH_4)^+$, 45], 204 (16), 169 (15), 153 (100), 135 (12).

3(*S*)-(Hydroxymethyl)-2,2,4-trimethylcyclohex-3-en-1(*R*)-ol (*endo*-3). A solution of tin(IV) chloride (1 M in dichloromethane, 10.3 mL, 10.3 mmol; Aldrich Chem. Co.) was diluted with toluene (20 mL) and then added dropwise over 30 min to a vigorously stirring, 0 °C solution of **2b** (5 g, 20.6 mmol) in toluene (120 mL). After 1 h at 0 °C, a saturated solution of NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with saturated brine (50 mL) and dried over $MgSO_4$. The residue was purified by silica gel chromatography to give the relatively nonpolar bicyclic ether **8** (526 mg, 15%) as a colorless oil and the more polar diol **3** (2.3 g, 66%; 85/15 *endo/exo*-olefin mixture) as a colorless, viscous oil. Fractional crystallization (hexane/ether, 1:1) afforded pure *endo*-**3** (1.75 g, 50% overall yield) as a white solid (mp 113−114 °C): $[\alpha]^{23}_D$ +45.8° (*c* 1.93, $CHCl_3$); TLC (SiO_2) $R_f \sim 0.28$ (hexane/AcOEt, 2:3); ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 and 1.10 (2 s, 6H), 1.75 (s, 3H), 1.70−1.80 (m, 1H), 2.00−2.22 (m, 1H), 2.28−2.52 (m, 1H), 3.39 (d, *J* = 4.5 Hz, 1H), 3.75 (d, *J* = 2.6 Hz, 2H), 5.45−5.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 24.2, 28.4, 31.9, 36.9, 50.8, 58.4, 70.9, 120.0, 131.4; IR (KBr) 3228, 2959, 2912, 2885, 1471, 1450, 1385, 1079, 908 cm^{-1}; MS (CI/NH_3) *m/z* (rel %) 188 [$(M + NH_4)^+$, 19], 171 (100), 153 (69), 135 (19). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.72; H, 10.41.

3(*R*)-(Hydroxymethyl)-4(*R*),5(*S*)-oxido-2,2,4-trimethylcyclohexan-1(*R*)-ol (4a). To a solution of diol **3** (3.00 g, 17.62 mmol) in dichloromethane (30 mL) was added 3-chloroperoxybenzoic acid (4.78 g, 19.38 mmol; 75% grade) in one portion. After the mixture was stirred for 2 h, saturated aqueous

(21) Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775−3776. Also see, Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.* **1994**, *59*, 7227−7237.

(22) Brandsma, L.; Verkruijsse, H. D. In *Synthesis of Acetylenes, Allenes, and Cumulenes: A Laboratory Manual;* Elsevier: New York, 1981; pp 75−76.

(23) An intramolecular nitrile oxide cycloaddition leading to an eight-membered bridged structure analogous to ring B of taxol has been reported: Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z. B. *J. Am. Chem. Soc.* **1984**, *106*, 1845−1847.

(24) Bhatt, R. K.; Chauhan, K.; Wheelan, P.; Murphy, R. C. Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050−5056.

$NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated to give epoxide **4a** (3.22 g, 98%) as a colorless oil: $[\alpha]^{23}_D$ −5.0° (*c* 1.6, $CHCl_3$); TLC (SiO_2) R_f = 0.41 (AcOEt); ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 and 1.10 (2 s, 6H), 1.75 (s, 3H), 1.70−1.80 (m, 1H), 2.00−2.22 (m, 1H), 2.28−2.52 (m, 1H), 3.39 (d, *J* = 4.75 Hz, 1H), 3.75 (d, *J* = 2.6 Hz, 2H), 5.45−5.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 24.2, 28.4, 31.9, 36.9, 50.8, 58.4, 70.9, 120.0, 131.4; IR (neat) 3386, 2966, 2932, 2881, 1654, 1446, 1382, 1098, 1051, 1000 cm^{-1}; MS (CI/NH_3) *m*/*z* (rel %) 204 [(M + NH_4)$^+$, 100], 186 (67), 174 (23), 169 (85), 156 (99). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.34; H, 9.49.

3(*R*)-[(Acetyloxy)methyl]-4(*R*),5(*S*)-oxido-2,2,4-trimethylcyclohexan-1(*R*)-ol (4b). To a room temperature solution of epoxide **4a** (2.0 g, 10.73 mmol) and DBU (408 mg, 2.70 mmol) in dry benzene (20 mL) was added *N*-acetylimidazole (1.3 g, 11.81 mmol) by portions over a period of 30 min. All volatiles were removed *in vacuo* and the residue was purified by silica gel chromatography (hexane/EtOAc, 1:1) to give acetate **4b** (85−95%) as a white solid (mp 29−31 °C): $[\alpha]^{23}_D$ +41.8° (*c* 3.3, $CHCl_3$), TLC (SiO_2) R_f = 0.47 (hexane/AcOEt, 2:3); ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.06 (s, 3H), 2.05 (s, 1H), 1.90 (part X of an ABX system, t, *J* = 6.1 Hz, 1H), 2.05 (s, 3H), 2.15−2.19 (m, 2H), 3.10−3.22 (m, 2H), 4.34 (part B of an ABX system, J_{AB} = 11.4 Hz, J_{BX} = 7.2 Hz, 1H), 4.47 (part A of an ABX system, J_{AB} = 11.4 Hz, J_{AX} = 5.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 22.9, 24.9, 28.2, 28.7, 35.7, 46.2, 59.6, 60.4, 63.8, 73.9, 170.6; IR (KBr) 3510, 2968, 2934, 1739, 1437, 1386, 1367, 1240, 1047 cm^{-1}; MS (CI/NH_3) *m*/*z* (rel %) 246 [(M + NH_4)$^+$, 100], 229 (94), 211 (13), 186 (15), 169 (24), 168 (19), 151 (16). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.34; H, 8.84. The optical purity of **4b** was determined to be >99% by ^1H NMR analysis of the (*R*)-(+)-MTPA (Mosher) ester of the C(1)-alcohol which displayed a triplet at δ 4.70 and a singlet at 3.47; racemic **4b** showed triplets at δ 4.60 and 4.70 ppm (−COOC*H*−) and singlets at 3.47 and 3.65 (*Me*O−).

1(*R*)-[[(1′,1′-Dimethylethyl)dimethylsilyl]oxy]-3(*R*)-[(acetyloxy)methyl]-4(*R*),5(*S*)-oxido-2,2,4-trimethylcyclohexane (4c). A solution of **4b** (1.2 g, 5.23 mmol), diisopropylethylamine (1.30 mL, 15.26 mmol) and 4-(dimethylamino)-pyridine (64 mg, 0.52 mmol) in DMF (2 mL) was mixed with *tert*-butyldimethylsilyl chloride (1.02 g, 6.80 mmol) at room temperature. After 24 h at 45 °C, saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc, 7:3) to give **4c** (1.59 g, 89%) as a colorless oil: $[\alpha]^{23}_D$ +9.8° (*c* 1.6, $CHCl_3$); TLC (SiO_2) R_f = 0.74 (hexane/AcOEt, 1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.06 (s, 3H), 0.90 and 0.92 (2 s, 15 H), 1.38 (s, 3H), 1.80 (t, *J* = 7.4 Hz, 1H), 2.02 (dd, *J* = 6.3 and 4.5 Hz, 2H), 2.07 (s, 3H), 2.83−2.86 (m, 1H), 3.30 (t, *J* = 5.5 Hz, 1H), 4.43 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 73.6, 64.3, 58.8, 58.0, 46.6, 36.6, 30.3, 27.3, 25.7 (3 C), 24.9, 21.2, 20.4, 17.9, −4.3, −5.0; IR (neat) 2957, 2930, 2885, 2857, 1741, 1472, 1388, 1364, 1252, 1115, 1081, 1018, 884, 838, 775 cm^{-1}; MS (CI/NH_3) *m*/*z* (rel %) 360 [(M + NH_4)$^+$, 100], 343 (89), 283 (45), 168 (17), 151 (12). Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.0. Found: C, 63.24; H, 9.93.

1(*R*)-[[(1′,1′-Dimethylethyl)dimethylsilyl]oxy]-3(*R*)-(hydroxymethyl)-4(*R*),5(*S*)-oxido-2,2,4-trimethylcyclohexane (4d). To a solution of **4c** (500 mg, 1.46 mmol) in anhydrous methanol (5 mL) was added K_2CO_3 (303 mg, 2.19 mmol). After 1 h , water (5 mL) was added and the methanol was removed *in vacuo*. The aqueous solution was extracted with AcOEt (3 × 7 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc, 1:1; R_f = 0.56) to give **4d** (453 mg, 98%) as a colorless oil: $[\alpha]^{23}_D$ −11.3° (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.93 (s, 3H), 0.97 (s, 3H), 1.43 (s, 3H), 1.69 (part X of a ABX system, dd, *J* = 5.7 and 3.6 Hz, 1H), 2.10−2.00 (m, 2H), 2.95−2.90 (m, 1H), 3.32 (t, *J* = 5.2 Hz, 1H), 3.96 (part B of an ABX system, J_{AB} = 11.2 Hz, J_{BX} = 5.7 Hz, 1H), 4.05 (part A of a ABX system, J_{AB} = 11.2 Hz, J_{AX} = 5.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0, −4.3, 15.5, 21.0, 24.6, 28.8 (3C), 28.4, 30.2, 36.8, 49.1, 61.0, 73.8; IR (neat) 3414, 2958, 2929, 2883, 2857, 1472, 1387, 1362, 1257, 1099, 1005, 885, 836, 775 cm^{-1}; MS (CI/NH_3) *m*/*z* (rel %) 318 [(M + NH_4)$^+$, 16], 301 (100), 283 (20), 270 (28), 253 (33), 186 (20); HRMS calcd for $C_{16}H_{32}O_3Si$ *m*/*z* 300.2121, found *m*/*z* 300.2133.

3(*R*)-[[(1′,1′-Dimethylethyl)dimethylsilyl]oxy]-5(*R*),6(*S*)-oxido-2,2,6-trimethylcyclohexan-1(*R*)-carboxaldehyde (5). PCC (545 mg, 2.53 mmol) and NaOAc (31 mg, 0.38 mmol) were suspended in anhydrous dichloromethane (5 mL). After 5 min, a solution of alcohol **4d** (400 mg, 1.26 mmol) in dichloromethane (1 mL) was added in one portion. After 3 h at room temperature, Et_2O (20 mL) was added and the solution stirred vigorously for 1 h. The salts were removed by filtration through a pad of Celite/florisil and the solvent concentrated under vacuum. The residue was purified by silica gel chromatography (hexane/EtOAc, 7:3; R_f = 0.43] to give aldehyde **5** (323 mg, 86%) as a white solid (mp 74−76 °C); $[\alpha]^{23}_D$ +52.1° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 and 0.08 (2 s, 6H), 0.88 (s, 9H), 0.94 and 0.98 (2 s, 6H), 1.32 (s, 3H), 2.10 (dd, *J* = 2.6, 5.5 Hz, 1H), 2.18 (d, *J* = 4.4 Hz, 1H), 3.02 (t, = 2.6 Hz, 1H), 3.36 (t, *J* = 5.5 Hz, 1H), 9.91 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0, −4.5, 17.7, 20.3, 24.0, 25.6 (3C), 26.7, 30.0, 37.7, 56.1(2C), 59.8, 72.6, 205.0; IR (KBr) 2957, 2930, 2857, 1713, 1473, 1389, 1365, 1255, 1111, 1074, 1010, 882, 838, 776 cm^{-1}; MS (DCI/NH_3) *m*/*z* (%) 316 [(M + NH_4)$^+$, 53] 299 (31), 270 (46), 254 (25), 253 (100). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.46; H, 10.13.

5(*R*)-[[(1′,1′-Dimethylethyl)dimethylsilyl]oxy]-3(*S*)-hydroxy-2,6,6-trimethylcyclohexen-1-carboxaldehyde (6). To a 0 °C solution of **5** (100 mg, 0.34 mmol) in THF (2 mL) was added NaOMe (22 mg, 0.42 mmol) in one portion. After 15 min, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3; R_f = 0.35) to give enal **6** (90 mg, 89%) as a white solid (mp 132−135 °C): $[\alpha]^{23}_D$ −36.4° (*c* 1.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.16 (s, 3H), 0.90 (s, 3H), 1.14 (s, 3H), 1.24 (s, 3H), 2.10−2.00 (m, 2H), 2.25 (s, 3H), 3.63 (t, *J* = 3.3 Hz, 1H), 3.90 (t, *J* = 3.5 Hz, 1H), 10.2 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ −4.9, −4.2, 16.0, 17.9, 22.8, 25.8 (3C), 26.1, 33.1, 38.7, 69.8, 76.7, 137.6, 152.6, 193.6; IR (KBr) 3425, 2956, 2930, 2884, 2858, 1679, 1605, 1472, 1371, 1255, 1122, 1070, 873, 839, 775, 734 cm^{-1}; MS (CI/NH_3) *m*/*z* (rel %) 316 [(M + NH_4)$^+$, 100], 299 (46), 298 (47), 281 (46), 253 (100). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.33; H, 10.28.

Dithiane Adduct 7. *n*-Butyllithium (1.25 mL of a 1.6 M solution in hexanes, 2 mmol) was added to a solution of 1,3-dithiane (242 mg, 2 mmol) in THF (8 mL) at −78 °C. After 30 min at −30 °C, this solution was added dropwise to a solution of **6** (200 mg, 0.67 mmol) in THF (3 mL) at −50 °C. The resulting mixture was allowed to warm to 0 °C and was maintained at this temperature for 3h. The reaction was quenched with saturated aqueous NH_4Cl solution (7 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a residue that was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1; R_f = 0.35] to give **7** (238 mg, 85%) as a white solid (mp 117−120 °C); $[\alpha]^{23}_D$ +6.0° (*c* 2.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.09 (s, 3H), 1.16 (s, 3H), 2.03 (s, 3H), 1.80−2.15 (m, 4H), 3.85−3.95 (m, 1H), 3.61 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.40 (part A of ABX system, J_{AB} = 9.8 Hz, 1H), 4.53 (part B of ABX system, J_{AB} = 9.8 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ −4.9, −4.2, 16.0, 17.9, 22.8, 25.8 (3 C), 26.1, 33.1, 38.7, 69.8, 76.7, 137.6, 152.6, 193.6; IR (KBr) 3425, 2956, 2930, 2884, 2858, 1679, 1605, 1472, 1371, 1255, 1122, 1070, 873, 839, 775, 734 cm^{-1}; MS (CI/NH_3) *m*/*z* (%) 436 [(M + NH_4)$^+$, 100], 299

(46), 298 (47), 281 (46), 253 (100). Anal. Calcd for $C_{20}H_{38}O_3S_2Si$: C, 57.37; H, 9.15. Found: C, 57.42; H, 9.17.

Stereochemical Analysis of 7. A sample of **7** (10 mg, 0.024 mmol) was selectively acetylated at C(13) (taxol numbering) by stirring overnight at room temperature in benzene (0.3 mL) with DBU (5 μL) and *N*-acetylimidazole (3 mg, 10.027 mmol). SiO_2 chromatography (hexane/EtOAc 4:1) of the residue remaining after evaporation of all volatiles *in vacuo* gave the acetate of **7** (9.7 mg, 89%) as a colorless oil: TLC (SiO_2, hexane/EtOAc 7:3) $R_f \sim 0.36$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.35 (t, J = 9.5 Hz, 1H), 4.48 (bs, 2H), 3.61 (dd, J = 7.2, 2.4 Hz, 1H), 2.65−3.05 (m, 4H), 2.09 (s, 3H), 1.75−2.15 (m, 4H), 1.77 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). To a solution of the preceding acetate (19 mg, 0.02 mmol) and DMAP (0.1 mg) in dry pyridine (0.2 mL) was added *p*-bromobenzoyl chloride (22 mg) in one portion. After 24 h, the solvent was evaporated and the residue purified by PTLC (hexane/Et_2O 7:3; $R_f \sim 0.64$) to give the bromobenzoate (11 mg, 85%) as a white solid: $[\alpha]^{23}_D$ +25° (*c* 0.006, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.50−2.25 (m overlapping two singlets at 1.96 and 2.08, 13H), 2.68−3.05 (m, 4H), 3.54 (dd, J = 7.2, 2.4 Hz, 1H), 4.59 (d, J = 7 Hz, 1H), 5.40 (t, J = 9.5 Hz, 1H), 6.24 (d, J = 7 Hz, 1H), 7.60 (d, J = 6.5 Hz, 2H), 7.93 (d, J = 6.5 Hz, 2H); ^{13}C NMR (50 MHz, $CHCl_3$) δ −4.97, −4.04, 16.81, 17.99, 21.19, 25.30, 25.78 (3C), 29.67, 30.91, 33.68, 72.08, 72.68 (2C), 128.33, 128.75, 131.36, 131.85, 134.01 (2C), 164.65, 170.89; CD (MeOH) λ 251 nm, $\Delta\epsilon$ −4.40.

Preparation of 12. *n*-BuLi (6.96 mmol; 1.6 M solution in hexanes) was added dropwise to a −78 °C solution of acetylene **18** (2.69 g, 7.42 mmol) in dry THF (20 mL). The mixture was kept for 1 h, warmed to −40 °C for 15 min, and then recooled to −78 °C. A solution of anhydrous LiBr (201 mg, 2.31 mmol) in THF (10 mL) was introduced followed by ketone **11** (1.45 g, 4.64 mmol) in THF (10 mL). After complete addition, the reaction mixture was slowly warmed to 0 °C over 12 h, quenched with H_2O and extracted with Et_2O. Chromatographic purification [SiO_2: hexane/Et_2O (9:1), $R_f \sim 0.6$] of the residue obtained upon evaporation of the combined ethereal extracts afforded the adduct (2.76 g, 88%) as a colorless oil: ^{1}H NMR (250 MHz, C_6D_6) δ 0.01 (s, 9H), 0.98 (t, J = 8.0 Hz, 2H), 1.05−1.45 (complex m, 14H), 1.50−1.82 (m, 7H), 1.97 (br t, J = 4.5 Hz, 4H), 2.36−2.60 (m, 4H), 3.26 (q, J = 7.0 Hz, 1H), 3.58−3.77 (m, 8H), 4.66 (s, 2H), 5.46 (t, J = 7.0 Hz, 1H), 7.21−7.38 (m, 6H), 7.72−7.85 (m, 4H); ^{13}C NMR (63 MHz, C_6D_6) δ -1.28, 15.55, 18.36, 19.46, 19.83, 22.61, 23.31, 25.30, 27.12, 27.56, 29.78, 30.01, 32.57, 43.34, 63.91, 64.99, 67.59, 73.68, 83.77, 95.02, 97.09, 118.37, 129.91, 131.66, 134.66, 134.32, 136.00, 137.31. Anal. Calcd for $C_{41}H_{62}O_4Si_2$: C, 72.94; H, 9.26. Found: C, 72.83; H, 8.99.

The above adduct (1.97 g, 2.92 mmol) and $LiAlH_4$ (332 mg, 8.75 mmol) in THF (35 mL) were heated at 45 °C for 6 h. The reaction mixture was cooled to 0 °C and carefully quenched with H_2O and extracted with Et_2O (3 × 20 mL). The combined ethereal extacts were washed with brine, dried, and evaporated, and the residue was purified by SiO_2 chromatography [hexane/Et_2O (7:1), $R_f \sim 0.19$] to give diol **12** (1.18 g, 92%) as a colorless oil: ^{1}H NMR (250 MHz, C_6D_6) δ 0.01 (s, 9H), 0.98 (t, J = 8.0 Hz, 2H), 1.04−1.22 (m, 8H), 1.24−2.05 (complex m, 11H), 2.28 (q, J = 7.5 Hz, 2H), 2.44−2.64 (m, 2H), 3.26 (q, J = 7.0 Hz, 1H), 3.34 (t, J = 6.0 Hz, 2H), 3.58−3.78 (m, 4H), 4.65 (s, 2H), 5.32 (t, J = 7.5 Hz, 1H), 5.95 (d, J = 16.0 Hz, 1H), 7.15 (d, J = 16.0 Hz, 1H); ^{13}C NMR (63 MHz, C_6D_6) δ -1.24, 14.22, 18.22, 20.32, 21.02, 22.33, 24.35, 24.91, 29.70, 30.32, 32.92, 43.00, 60.26, 62.26, 65.02, 67.21, 75.79, 94.99, 125.72, 129.51, 132.49, 132.61, 134.77; HRMS calcd for $C_{25}H_{46}O_4Si$ *m*/*z* 438.3165, found 438.3162.

7-[1-Hydroxy-2,2,4-trimethyl-3-[2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]cyclohex-3-enyl]-5-methylhepta-*cis*-4-*trans*-6-dienal (13). A solution of DMSO (69 mg, 0.88 mmol) in dry CH_2Cl_2 (2 mL) was added to a −78 °C solution of freshly distilled oxalyl chloride (56 mg, 0.44 mmol) in CH_2Cl_2 (5 mL). After 5 min, **12** (130 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added dropwise and the whole maintained for 35 min. To this was added Et_3N (180 mg, 1.77 mmol) and the mixture was allowed to warm to ambient temperature over 4 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 10mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated, and the residue was purified by flash SiO_2 chromatography (hexane/EtOAc, 2:1; $R_f \sim 0.47$) to give aldehyde **13** (115 mg, 90%) as a colorless oil: ^{1}H NMR (250 MHz, C_6D_6) δ 0.01 (s, 9H), 0.98 (t, J = 8.0 Hz, 2H), 1.08−1.42 (m, 8H), 1.64 (s, 3H), 1.80 (s, 3H), 1.82−2.21 (m, 5H), 2.40 (q, J = 7.5 Hz, 2H), 2.58−2.65 (m, 2H), 3.72 (q, J = 8.0 Hz, 4H), 4.70 (s, 2H), 5.15 (t, J = 7.5 Hz, 1H), 6.18 (d, J = 16 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 9.32 (t, J = 2.1 Hz, 1H); HRMS calcd for $C_{25}H_{44}O_4Si$ *m*/*z* 436.3008, found 436.3020.

7-[1-Hydroxy-2,2,4-trimethyl-3-[2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]cyclohex-3-enyl]-5-methylhepta-*cis*-4-*trans*-6-dienal Oxime (14). To a stirring solution of aldehyde **13** (60 mg, 0.137 mmol) in Et_2O (6 mL) was added a solution of hydroxylamine hydrochloride (95 mg, 1.137 mmol) and Na_2CO_3 (145 mg, 1.37 mmol) in H_2O (3 mL). After 26 h, brine was added and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 × 4 mL) and the combined organic extracts were dried and concentrated *in vacuo*, and the residue was purified by chromatography [PTLC: SiO_2, hexane/Et_2O (1:1), $R_f \sim 0.53$ and 0.64] affording oxime **14** (59 mg, 94%) that was used directly in the next step.

2,2,4-trimethyl-1-(4-methyl-3,3a,6,7-tetrahydrobenzo-[*c*]isoxazol-3-yl)-3-[2-[[2-(trimethylsilyl)ethoxy]methoxy]-ethyl]cyclohex-3-en-1-ol (15). To a vigorously stirring, 0 °C solution of oxime **14** (34 mg, 0.075 mmol) in CH_2Cl_2 (2 mL) was added dropwise a 0.67 M aqueous NaOCl (0.255 mL, 0.15 mmol). After 12 h, the reaction mixture was extracted with CH_2Cl_2 (2 × 2 mL), and the combined organic phases were dried and evaporated *in vacuo*, and the residue was chromatographed [PTLC: SiO_2, hexane/Et_2O (4:1), two elutions] to give cycloadduct **15** (15.5 mg, 46%) as a 4:1 diastereomeric mixture ($R_f \sim 0.58$ and 0.38).

Major (more polar) isomer: ^{1}H NMR (250 MHz, C_6D_6) δ 0.01 (s, 9H), 0.95 (t, J = 6 Hz, 2H), 1.07(s, 3H), 1.20−1.98 (complex m, 13H), 2.34−2.65 (m, 6H), 3.58−3.84 (multiplet overlapping triplet at 3.72, J = 8.0 Hz, 6H), 4.44 (d, J = 8.0 Hz, 1H), 4.71 (s, 2H), 5.08 (br s, 1H); ^{13}C NMR (63 MHz, C_6D_6) δ −1.29, 18.37, 20.27, 21.47, 21.66, 21.98, 25.23, 27.22, 28.27, 28.39, 29.98, 30.18, 44.04, 52.82, 64.98, 68.01, 75.29, 87.84, 95.02, 123.45, 132.76, 133.71, 158.92; HRMS calcd for $C_{25}H_{43}NO_4Si$ *m*/*z* 449.2961, found 449.2969.

Minor (less polar) isomer: ^{1}H NMR (250 MHz, C_6D_6) δ 0.01 (s, 9H), 0.98−2.64 (complex multiplet with methyl singlets at 1.00, 1.14, 1.52, 1.76, 25H), 3.52 (t, J = 8.0Hz, 2H), 3.68 (d, J = 8 Hz, 2H), 3.88 (br d, J = 8 Hz, 1H), 4.58 (d, J = 9 Hz, 1H), 4.67 (s, 2H), 5.20 (br s, 1H); ^{13}C NMR (63 MHz, C_6D_6) δ −1.32, 18.38, 20.01, 20.19, 21.74, 21.93, 23.16, 26.11, 27.39, 27.80, 29.76, 30.18, 43.82, 53.16, 65.06, 67.62, 75.64, 84.10, 95.0, 122.10, 129.10, 132.76, 135.48, 158.20; HRMS calcd for $C_{25}H_{43}NO_4Si$ *m*/*z* 449.2961, found 449.2950.

***tert*-Butyl 5-methylhept-*cis*-4-en-6-ynoate (17).** To a −30 °C solution of *cis*-3-methyl-2-penten-4-yn-1-ol (**16**) (10 g, 104 mmol; Aldrich Chem. Co.) in anhydrous CH_2Cl_2 (100 mL) was added Ph_3P (32.73 g, 124.8 mmol) followed by freshly recrystallized *N*-bromosuccinimide (22.2 g, 124.8 mmol). After 3.5 h, the reaction mixture was diluted with ether (300 mL), warmed to room temperature, and washed with saturated aqueous Na_2CO_3 solution (2 × 200 mL) and then brine (200 mL). The residue obtained after drying and evaporation *in vacuo* was triturated in petroleum ether (200 mL), filtered to remove precipitated triphenylphosphine oxide and succinimide, concentrated under reduced pressure, and chromatographed (SiO_2: petroleum ether, $R_f \sim 0.56$) to furnish 5-bromo-3-methylpent-*cis*-3-en-1-yne (13.56 g, 82%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95 (s, 3H), 3.32 (s, 1H), 4.18 (dd, J = 0.6, 8.2 Hz, 2H), 6.00 (t, J = 8.2 Hz, 1H). Anal. Calcd for C_6H_7Br: C, 45.32; H, 4.44. Found: C, 45.40; H, 4.46.

To a −78 °C solution of diisopropylamine (9.49 g, 93.8 mmol) in anhydrous THF (140 mL) was added *n*-BuLi (53.3 mL of 1.6 M solution in hexane, 85.26 mmol). The mixture was warmed to 0 °C, then re-cooled to −78 °C after 1.5 h. To this was added dropwise a solution *tert*-butyl acetate (9.90 g, 85.26

mmol) in THF (10 mL). After 1.5 h, the above bromide (13.56 g, 85.26 mmol) in THF (40 mL) was introduced and the mixture was maintained at −78 °C for 10 h. The solution was diluted with hexanes (100 mL), washed with H_2O (3 × 200 mL), dried, and evaporated *in vacuo*. Purification of the residue by chromatography [SiO_2: hexane/Et_2O (39:1), $R_f \approx 0.14$] afforded the homologated ester **17** (13.8 g, 84%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.84 (s, 3H), 2.27 (t, J = 7.9 Hz, 2H), 2.52 (dt, J = 7.2, 7.2 Hz, 2H), 3.18 (s, 1H), 5.73 (t, J = 7.2 Hz, 1H). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.45.

Acetylene 18. To a 0 °C solution of $LiAlH_4$ (8.65 g, 228.05 mmol) in Et_2O (200 mL) was added the *tert*-butyl ester **17** (13.84 g, 71.27 mmol) in Et_2O (30 mL). The mixture was stirred at room temperature overnight, cautiously quenched at 0 °C with H_2O, and extracted with Et_2O (5 × 30 mL). The combined ethereal extracts were washed with brine, dried, and concentrated *in vacuo* to give 5-methylhept-*cis*-4-en-6-yn-1-ol (8.85 g, >95%) as a colorless oil which could be used in the next reaction without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (apparent pent, J = 6.5 Hz, 2H), 1.88 (s, 3H), 2.36 (dt, J = 6.5, 7.2 Hz, 2H), 3.10 (s, 1H), 3.68 (t, J = 6.5 Hz, 2H), 5.73 (t, J = 7.2 Hz, 1H); TLC (SiO_2) hexane/EtOAc (1:1), $R_f \sim 0.58$. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.71.

To a solution of the above alcohol (8.79 g, 70.8 mmol) in dry DMF (180 mL) was added imidazole (6.27 g, 92.1 mmol) and *tert*-butylchlorodiphenylsilane (25.32 g, 92.12 mmol). The mixture was maintained at 45 °C for 12 h, and then the solvent and all volatiles were removed *in vacuo*. The residue was partitioned between H_2O and Et_2O. Evaporation of the ether phase and chromatographic purification [SiO_2: hexane/Et_2O (39:1), $R_f \sim 0.37$] of the residue furnished the corresponding silyl ether **18** (22.60 g, 88%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.57−1.68 (m, 2H), 1.82 (dd, J = 1.5, 6.5 Hz, 2H), 2.34 (q, J = 6.5 Hz, 2H), 3.03 (s, 1H), 3.56 (t, J = 6.5 Hz, 2H), 5.70 (t, J = 7.4 Hz, 1H), 7.32−7.44 (m, 6H), 7.60−7.70 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.19, 22.86, 26.86, 27.12, 31.98, 63.39, 80,59, 80.61, 83.01, 117.11, 127.57, 129.49, 134.00, 135.57, 139.37. Anal. Calcd for $C_{21}H_{30}OSi$: C, 79.51; H, 8.34. Found: C, 79.29; H, 8.27.

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Supporting Information Available: $^1H/^{13}C$ NMR spectra for **2b**, **4d**, and both diastereomers of **15** and the CD of **7** acetate *p*-bromobenzoate (9 pages). This material is contained in 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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