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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone, and eleutherobin, which operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach to the elucidation of the pharmacophore common to these structurally dissimilar substances, using a combination of synthetic and computational studies. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.

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TABLE OF CONTENTS

INTRODUCTION

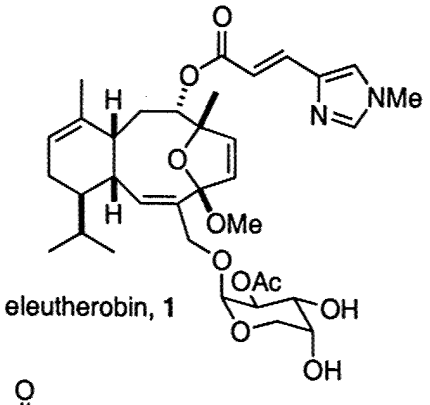
This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone, and eleutherobin, which operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach to the elucidation of the pharmacophore common to these structurally dissimilar substances, using a combination of synthetic and computational studies. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.

BODY

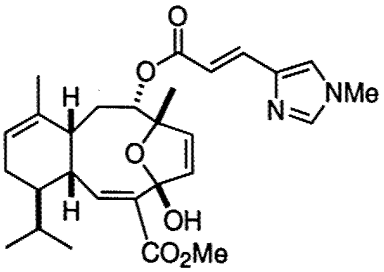
Significant progress has been achieved in Task 4 (Synthesis of Eleutherobin and Analogs) of the approved Statement of Work.

Task 4. Synthesis of Eleutherobin and Analogs.

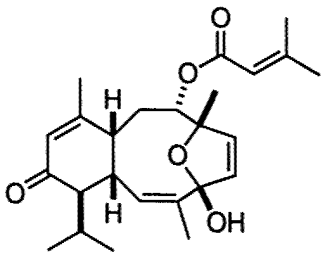
Eleutherobin (**1**, Figure 1) is a marine natural product that was first isolated in low yield from the rare Western Australian soft coral *Eleutherobia albiflora*[1] and subsequently as an isolation artifact from MeOH extracts of the Caribbean soft coral *Erythropodium caraeorum* in higher yield.[2] Eleutherobin is a member of the eunicellin family of diterpenoids possessing the bicyclo[8.4.0]tetradecane core carbon skeleton and, along with other structurally similar "eleuthesides" including sarcodictyin A (**2**)[3] and valdivone A (**3**),[4] is distinguished from other eunicellins by addition of a C(4)-C(7) oxygen bridge. Eleutherobin is an antimitotic agent which exhibits potent in vitro cytotoxicity with IC_{50} values of 10.7 nM and 13.7 nM against HCT116 human colon carcinoma and A2780 human ovarian carcinoma cell lines respectively.[1a] Mechanistically, eleutherobin has been shown to stabilize microtubules against depolymerization by competing for the paclitaxel (Taxol) binding site,[1a, 5] placing it in an exclusive group of cytotoxic agents, including the epothilones, discodermolide, and laulimolide, which induce mitotic arrest by this mode of action.[6]



eleutherobin, **1**



sarcodictyin A, **2**

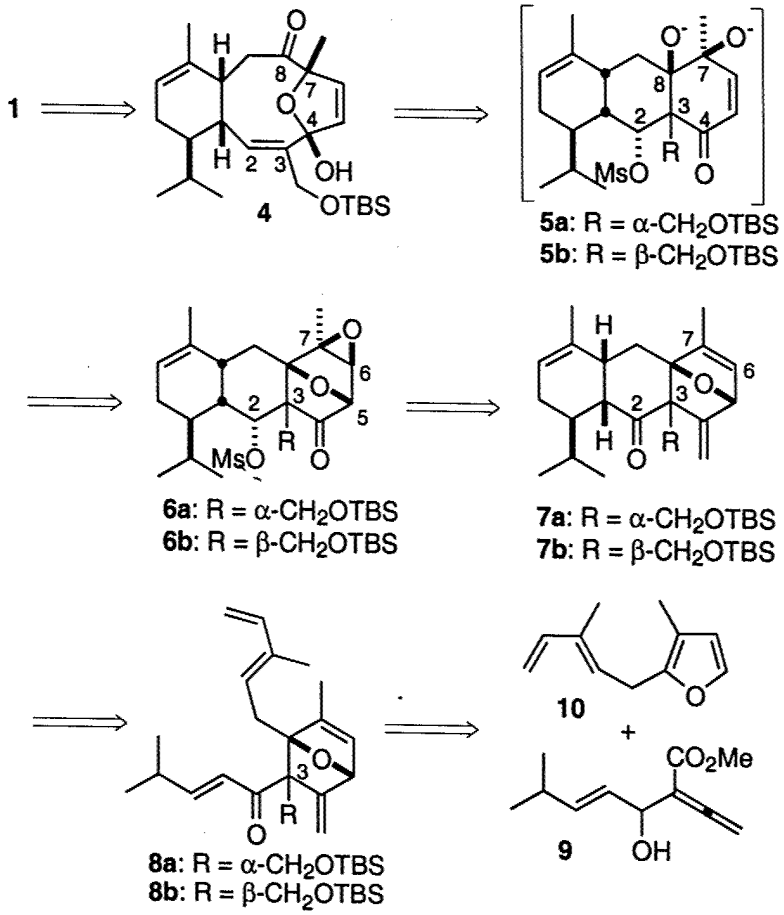


valdivone A, **3**

The scarce availability, challenging molecular structure, and chemotherapeutic potential of eleutherobin have made it an attractive target and have stimulated several synthetic efforts,[7] including total syntheses by the Nicolaou[8] and Danishefsky[9] groups. In most of the published approaches, construction begins with a functionalized cyclohexene and proceeds in the left-to-right direction relying on a macrocylization step for the formation of the 10-membered carbocycle. In this paper, we report a conceptually novel strategy for the synthesis of the eleutheside carbon framework.

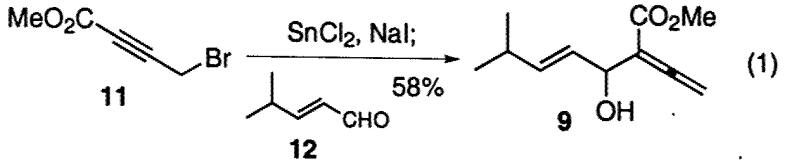
Retrosynthetic Analysis. The clear challenge in the synthesis of **1** is the construction of the oxabicyclo[6.2.1]undecane ring system present in the natural product, and, thus, we set tricycle **4** as our initial target (Scheme 1). Key to our approach is the recognition that the carbocyclic ring system of **4** could result from C(3)-C(8) bond cleavage (eleutherobin numbering) of a more accessible pentacycle such as **6a/b**.[10] In theory, **4** would be available from **6a/b** in a single chemical step in which $2e^-$ reduction of the C(4) ketone would induce ketyl formation and trigger a cascade of (1) reductive cleavage of the C(5)-O bond, (2) β-elimination of the epoxide from the resulting enolate to give bracketed intermediate **5a/b**, (3) cleavage of the C(3)-C(8) bond with elimination of a C(2) leaving group to establish the 10-membered carbocyclic eunicellin carbon core, and (4) hemiketalization between the C(7) hydroxyl and C(4) ketone as observed in a similar system in the Nicolaou total synthesis.[8] In the early stages of planning, we chose **6b** as the most suitable fragmentation substrate, but did not rule out the use of its C(3) epimer **6a**. It was anticipated that C(3)-C(8) bond cleavage would occur through a concerted Grob mechanism,[11] and thus, expected that **6b** would produce **4**, with the desired C(2)-C(3) (*Z*)-olefin geometry, upon mesylate elimination, while **6a** would produce the undesired (*E*)-olefin. We recognized, however, that C(3)-C(8) bond cleavage could also occur through a retro-aldol fragmentation/β-elimination sequence and expected that both

6a and **6b** would produce **4**, with the desired C(2)-C(3) (*Z*)-olefin geometry, by this pathway based on relative product thermodynamic stability calculations.[12] Furthermore, **6a** and **6b** would be derived from tetracycles **7a** and **7b**, respectively, which, in turn, were the expected products of *endo*-selective intramolecular Diels-Alder cycloadditions of **8a** and **8b**. Previous research in the Winkler group on intramolecular Diels-Alder reactions like those proposed here has demonstrated that while they typically occur with high *endo* selectivity, preexisting stereocenters can play a pivotal role in their stereochemical outcome.[13] For that reason, we felt that the C(3) stereochemistry may be crucial in the establishment of the C(1), C(10), and C(14) stereocenters and that an investigation of its influence on the proposed cycloaddition was warranted. As such, intramolecular cycloaddition of both **8a** and **8b**, themselves derivatives of Diels-Alder adducts of allenoate **9** and bis(diene) **10**, would be examined. The rapid incorporation of structural and sterochemical complexity made possible by our use of this sequential Diels-Alder approach[14] was expected to greatly shorten and simplify the synthesis.

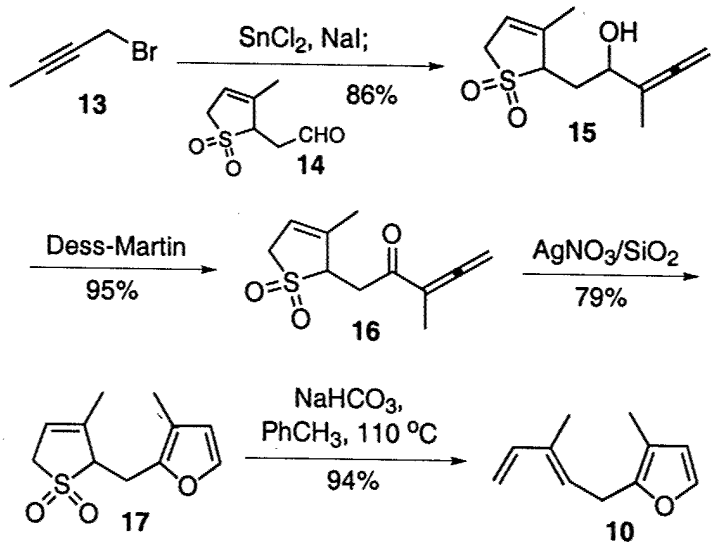


Furan/Allene Diels-Alder Cycloaddition. The first goal of our synthetic studies was the development of efficient syntheses of Diels-Alder dienophile **9** and bis(diene) **10**. Hydroxy allenoate **9** was prepared in a single step from known methyl 4-bromobut-2-ynoate **11**[15] and commercially available 4-methyl-2-pentenal **12** (Equation 1) utilizing the

protocol developed by Mukaiyama and Harada.[16] Thus, generation of the stannane from **11** in DMPU followed by addition of aldehyde **12** provided acceptable yields of **9** on multigram scale.

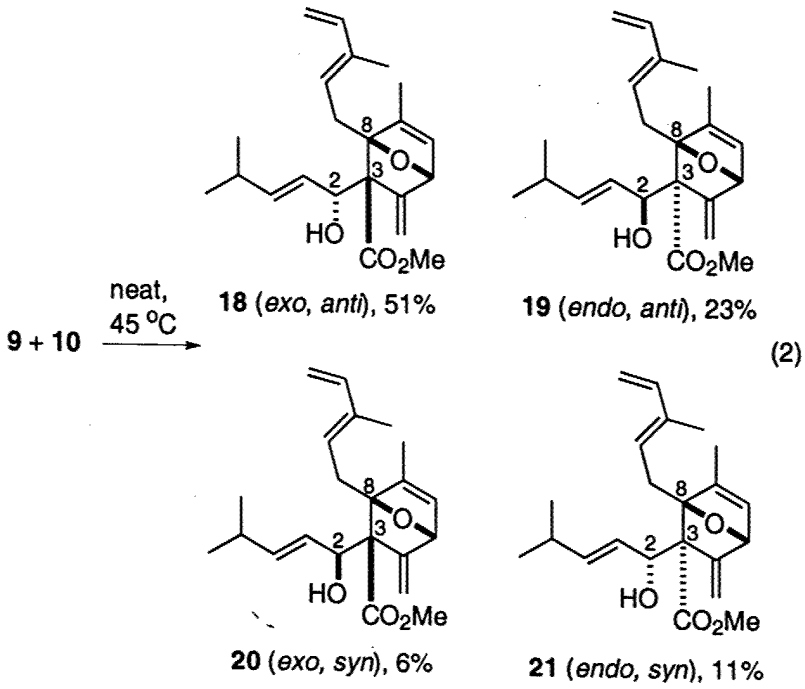


Synthesis of bis(diene) **10** commenced with a similar organometallic addition of the stannane derived from commercially available 1-bromo-2-butyne **13** to known sulfolene aldehyde **14**[17] to give allenic alcohol **15** as an inseparable mixture of isomers in 86% yield (Scheme 2). Dess-Martin oxidation[18] and Ag(I)-mediated isomerization[19] of the resulting allenone **16** provided furan **17**, which was converted to bis(diene) **10** by extrusion of sulfur dioxide upon heating in refluxing toluene in presence of an acid scavenger. Overall, the four step sequence furnished 61% yield of **10** from aldehyde **14** and allowed easy access to large quantities of this material.



With dienophile **9** and bis(diene) **10** in hand, we turned our attention to their Diels-Alder cycloaddition.[20] Upon heating a neat mixture of **9** and **10** at 45 °C for 72 hours, the formation of four new compounds was observed by TLC analysis of the reaction mixture. After separation by silica gel chromatography and extensive NMR experimentation, the four products were assigned as isomeric Diels-Alder adducts **18-21** (Equation 2). As we had anticipated, the cycloaddition had occurred with high chemo- and regiochemical control to provide products that were isomeric only in the stereochemical relationships between C(2), C(3), and C(8) (eleutherobin numbering). The relationship between the C(3) and C(8) stereocenters results from the *exo/endo* selectivity of the Diels-Alder reaction, and the relationship between the C(2) hydroxyl and C(3) carbomethoxy group results from facial selectivity. Furan [4+2] cycloadditions commonly occur with *exo* selectivity as a result of their reversibility,[20] and the reaction of **9** and **10** proved no different and gave *exo* isomers **18** and **20** in the 57% combined yield

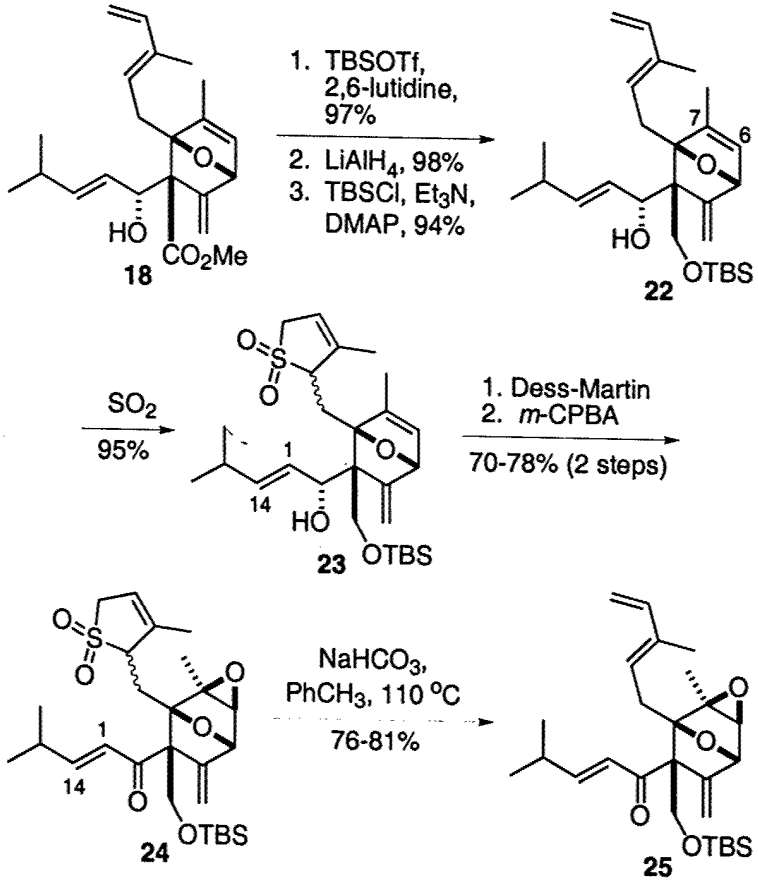
compared to 34% combined yield of *endo* isomers **19** and **21**. Significant facial selectivity was also observed with C(2)-C(3) *anti* adducts **18** and **19** favored relative to *syn* adducts **20** and **21**. The combined yield of the cycloaddition was a gratifying 91%, and, although all of these products could be accommodated in our synthetic plan, only the major *exo* isomer **18** and the major *endo* isomer **19** were carried on for ease of analysis. It should be noted that while the typical yields of **18** or **19** were average to low, multigram quantities of either isomer could be obtained, since the undesired adducts could be recycled. Refluxing a dilute solution of unwanted isomers in toluene effected retro-Diels-Alder reaction and allowed quantitative recovery of dienophile **9** and bis(diene) **10**, which could be recyclized to produce an identical mixture of **18**:**19**:**20**:**21**.



Intramolecular Diels-Alder: The *Exo* Series. Since *exo* Diels-Alder adduct **18** was produced as the major isomer in the furan/allene cycloaddition, we chose to examine its use in our synthetic approach first. The use of **18** (rather than **19**) held the additional benefit of containing the desired C(3) stereochemistry. Recall from Scheme 1 that proposed fragmentation of **6b**, retrosynthetically related to **18**, would produce the desired C(2)-C(3) (*Z*)-olefin geometry whether it occurred by a concerted Grob pathway or a retro-aldol/β-elimination process. Therefore, use of **6b** rather than **6a**, and, thus, **18** rather than **19**, eliminated our concern about the mechanistic ambiguity of this key step.

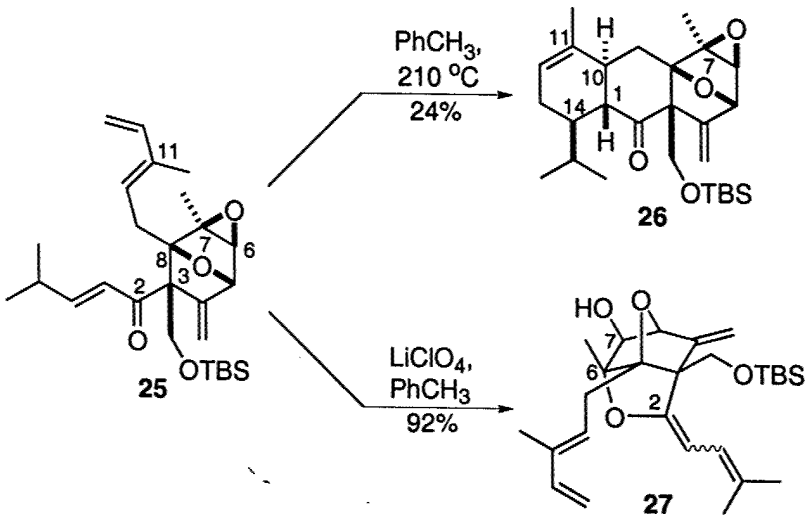
Elaboration of **18** into an appropriate intramolecular Diels-Alder substrate (e.g., **8b**, Scheme 1) began with protection of the secondary alcohol as its TBS ether (Scheme 3). This was followed by reduction of the methyl ester, with concomitant TBS deprotection, and selective primary alcohol protection to give allylic alcohol **22** in 89% yield for three steps. The initial protection step was required to avoid facile reto-aldol

fragmentation of **18** upon exposure to reducing agents. With **22** in hand, only oxidation of the secondary alcohol remained to provide a suitable cycloaddition substrate. Unfortunately, desired Diels-Alder substrate **8b**, the product of oxidation of **22**, proved to be exceedingly unstable to retro-Diels-Alder reaction to regenerate bis(diene) **9** along with a presumed allenyl vinyl ketone. We reasoned that functionalization of the C(6)-C(7) olefin would eliminate the unwanted reaction pathway, and since our retrosynthetic plan required C(6)-C(7) oxygenation, we chose to epoxidize the oxanorbornene olefin. To this end, protection of the terminal diene by treatment with SO_2 in a sealed tube provided 95% combined yield of sulfolene **23** as a separable mixture of diastereomers which were carried on individually. To avoid direction of epoxidizing agent to the C(1)-C(14) olefin, alcohol **23** was oxidized with the Dess-Martin periodinane[18] to provide a sensitive enone. Immediate treatment with *m*-CPBA afforded **24** in which epoxidation had occurred from the less hindered β–face of the oxanobornene bicycle. The terminal diene was then liberated by heating in refluxing toluene to induce cheleotropic extrusion of sulfur dioxide, which afforded Diels-Alder substrate **25**.



With reliable access to **25**, we were eager to explore the viability of its intramolecular Diels-Alder cycloaddition for the stereoselective construction of the cyclohexene portion of eleutherobin. We were aware that the cyclization of **25** would be less facile than that of more simple systems studied previously, as it had not occurred

upon removal of the diene protecting sulfolene (at 110 °C) as had been observed in these cases.[13e] We were surprised to find, however, that no reaction of **25** took place at temperatures of less than 210 °C ($PhCH_3$, propylene oxide, sealed tube) and disappointed to find that only 24% yield of a single Diels-Alder adduct could be isolated from the reaction (Scheme 4). Furthermore, NMR analysis of the adduct revealed it to be C(1)-C(10) *trans*-fused **26**, the product of *exo*-selective cycloaddition. The relative unreactivity of **25** (compared to simpler systems) is likely a result of the C(3) stereochemistry, which is crucial in defining the spatial relationship between the diene and dienophile. Although *cis* on the oxonorbornene bicycle, the reacting C(3) and C(8) substituents adopt pseudoaxial and pseudoequatorial orientations, respectively, placing them at some distance from one another in space. The unexpected *exo*/*endo* preference can be attributed to an unfavorable steric interaction between the C(7) and C(11) methyl groups in the *endo* transition state which is alleviated by reaction via the *exo* transition state leading to observed adduct **26**.



In attempt to reverse the observed selectivity in the cycloaddition of **25**, we hoped to take advantage of the well documented ability of Lewis acid additives to promote *endo* selectivity.[21] Unfortunately, the presence of the C(6)-C(7) epoxide rendered **25** incompatible with Lewis acid promoters typically employed (Scheme 4). Under a variety of conditions, only the tricycle **27**, the product of epoxide opening by the C(2) carbonyl and enolization, was isolated (albeit in high yield). Again, this result is a consequence of the stereochemistry at C(3) in which the nucleophilic C(2) ketone is positioned within bonding distance of the electrophilic C(6) position. Our inability to effect the desired *endo*-selective Diels-Alder cycloaddition of **25** under thermal or Lewis acidic conditions forced us to abandon its use.

KEY RESEARCH ACCOMPLISHMENTS:

A highly efficient synthesis of the bis-diene and bisdienophile moieties have been developed.

Preliminary results indicate that the key Diels-Alder methodology works well and leads to the preparation of tricyclic compounds. However, the second Diels Alder reaction cannot be readily achieved in an endo manner, which is a requirement for the preparation of the key substrate for fragmentation.

REPORTABLE OUTCOMES:

A full paper is being prepared based on the results outlined in this final report;

Daniel Macks has obtained a Ph.D. degree and is currently a postdoctoral research associate at Memorial Sloan Kettering Institute in New York.

Kevin Quinn is now an assistant professor at Holy Cross College. Colin MacKinnon is currently a Research Scientist at Evotec in Oxford, England. Stephen Hiscock is a Research Scientist at Astra Zeneca in the UK.

CONCLUSIONS:

Intramolecular Diels Alder reaction of the two exo products was not successful. Therefore further studies on the Diels Alder reaction of the endo products will be examined to prepare the substrate for the fragmentation approach to the synthesis of eleutherobin.

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Graduate:	Columbia University. September 1977-December 1981. M.A. 1978, M.Phil., Ph.D. 1981. Thesis Advisor: Professor Gilbert Stork.
Undergraduate:	Harvard College. September 1973-June 1977. A. B. cum laude in Chemistry, 1977.
PROFESSIONAL EXPERIENCE:	Merriam Professor of Chemistry, University of Pennsylvania, January 2001-
	Professor, University of Pennsylvania Department of Chemistry, July 1996-
	Founding Member, University of Pennsylvania Center for Cancer Pharmacology, May 1998-present
	Associate Professor, University of Pennsylvania, Department of Chemistry, July 1990-June 1996
	Member, University of Pennsylvania Cancer Center, July 1993-present
	Assistant Professor, University of Chicago, Department of Chemistry, September 1983-June 1990
AWARDS & HONORS:	American Chemical Society Cope Scholar Award, 2000 Chairman, Philadelphia Organic Chemists' Club, 1995

American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

PROFESSIONAL ACTIVITIES
Consultant, Wyeth-Ayerst Pharmaceuticals (1998-)
Associate Editor, *Organic Letters* (1999-)
INVITED LECTURES SINCE 1990:
Merck, Sharp & Dohme (West Point, PA)
Smith, Kline and Beckmann
Invited Lecturer, Symposium on Organic Synthesis, Great Lakes Regional ACS Meeting, Dekalb, Illinois
Invited Lecturer, Molecular Recognition Meeting, Office of Naval Research, Charleston, S.C
Invited Lecturer, Symposium on Heterocyclic Chemistry, National ACS Meeting, Washington, D.C
Squibb Institute for Medical Research (Princeton, NJ)
University of Rochester
Squibb Institute for Medical Research (New Brunswick, NJ)
Boehringer-Ingelheim Pharmaceuticals
Brandeis University
University of Delaware
ICI Pharmaceuticals
New York Academy of Sciences
North Jersey ACS Meeting
Invited Lecture, 1992 Meeting of the American Society for Photobiology
Organizer and Lecturer, Symposium on Studies Toward the Total Synthesis of Taxol, National ACS Meeting, San Francisco, CA. (April 8, 1992)
Dupont Agricultural Products
Burroughs Wellcome
University of Virginia
Sandoz Institute
Sterling Winthrop
Bryn Mawr College
Invited Lecturer, Symposium on Organic Chemistry, Great Lakes Regional ACS Meeting, Ann Arbor, Michigan
Invited Lecturer, Symposium on Organic Synthesis, Middle Atlantic Regional ACS Meeting, Baltimore, Maryland
Technion-Israel Institute of Technology
Pfizer Central Research
Sandoz Institute
Hebrew University of Jerusalem
R. W. Johnson
University of Montreal
Plenary Lecturer, Wyeth-Ayerst Fourth Annual Chemical Sciences Symposium
H. Martin Friedmann Lecturer, Rutgers University, 1993
Merck (West Point, PA)
American Cyanamid
Rhone-Poulenc Agricultural

Plenary Lecture, Interamerican Photochemical Society
University of Maryland
R. W. Johnson Pharmaceutical Research
Wyeth-Ayerst
Sepracor
Boehringer-Ingelheim
Florida State University
Northwestern University
UCLA
University of Minnesota
Parke-Davis
Pfizer
Penn State University
Smith Kline Beecham
Temple University
Amgen
University of Chicago
Dupont Pharmaceuticals
Invited Speaker, Symposium on Solid Support Chemistry, Middle Atlantic Regional ACS Meeting, May 1999
Plenary Lecturer, Symposium on Heterocycles, Canadian Institute of Chemistry, June 1999
Invited Speaker, Gordon Conference on Heterocycles, July 2000
University of Western Ontario
Boehringer-Ingelheim, Montreal
Villanova University
Johnston Mathey
Lederle Laboratories
Genetics Institute
University of Pittsburgh
New York Academy of Sciences
Merck-Frosst Lecturer, University of Sherbrooke
Bristol-Myers Squibb Lecturer, MIT
Albany Molecular Sciences
University of California, Irvine
Merck (West Point, PA)
University of Ottawa
Aventis Pharmaceuticals
Parke-Davis Lecturer, Michigan State University, 2000
Plenary Lecturer, French-American Chemical Society, 2002
Pfizer Lecturer, University of Waterloo, 2002

2002-2003
Novartis Lecturer, University of Texas at Austin
University of Rochester
Emory University

Alan Johnson Lecturer, University of Sussex, UK
Invited Speaker, Gordon Research Conference on Natural Products, July 2003

PUBLICATIONS :

1. L. Blaszczak, J. Winkler, S. O'Kuhn, "A New Synthesis of Olefins from Ketones via Coupling of Lithium Dialkylcuprates with Enol Phosphate Diesters," *Tetrahedron Lett.* **1976**, 4405-4408.
2. G. Stork, C. Shiner, J. Winkler, "Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems," *J. Am. Chem. Soc.* **1982**, *104*, 310-312.
3. G. Stork, J. Winkler, C. Shiner, "Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone," *J. Am. Chem. Soc.* **1982**, *104*, 3767-3768.
4. G. Stork, J. Winkler, N. Saccomano, "Stereochemical Control in the Construction of Vicinally Substituted Cyclopentanes and Cyclohexanes. Intramolecular Conjugate Addition of β-Ketoester Anions," *Tetrahedron Lett.* **1983**, 465-468.
5. J. Winkler, E.Coutouli-Argyropoulou, R. Leppkes, R. Breslow, "An Artificial Transaminase Carrying A Synthetic Macrocyclic Binding Group," *J. Am. Chem. Soc.* **1983**, *105*, 7198-7199.
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EXPERIMENTAL PROCEDURES

(Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **7a**, **8a**, **9**, **10**, and **15-27** and unnumbered intermediates, and X-ray data for **7a**)

Dienophile 9. To a solution of 5.97 g of propargyl bromide **11** (33.8 mmol) in 130 mL of DMPU at room temperature were added 7.27 g of $SnCl_2$ (38.4 mmol) and 5.75 g of NaI (38.4 mmol). The resulting yellow slurry was stirred in the absence of light for 4 hours. The mixture was cooled to 0 °C, and a solution of 3.01 g of aldehyde **12** (30.7 mmol) in 60 mL of DMPU was added dropwise over 30 minutes. The orange reaction mixture was allowed to warm to room temperature over 3 hours and stirred in the dark for an additional 16 hours. The reaction was diluted with Et_2O and quenched by addition of 100 mL of 30% aq. NH_4F. The phases were separated, and the aqueous phase was extracted with Et_2O (5x75 mL). The combined organic extracts were washed successively with H_2O and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:1 hexanes/EtOAc) gave 3.49 g (58%) of dienophile **9** as a slightly yellow oil. Data for **9**: R_f 0.27 (3:1 hexanes/EtOAc); **IR** (thin film) 3431, 2957, 2869, 1964, 1716, 1464, 1437, 1383, 1363, 1261, 1080, 1010, 971 cm^{-1}; **^1H NMR** ($CDCl_3$, 500 MHz) δ 5.72 (ddd, *J*=7.8, 6.5, 1.1 Hz, 1H), 5.51 (ddd, *J*=7.8, 6.6, 1.3 Hz, 1H), 5.24 (d, *J*=2.0 Hz, 2H), 4.89 (d, *J*=4.5 Hz, 1H), 3.76, (s, 3H), 2.99 (s, 1H), 2.29 (sept, *J*=5.8 Hz, 1H), 0.97 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.1, 140.1, 126.1, 102.1, 80.8, 70.4, 70.2, 52.3, 30.6, 22.1, 22.0; **HRMS** calcd for $C_{11}H_{16}O_3(M^+)$ 196.1099, found 196.1077.

Allenic alcohol 15. To a solution of 4.40 mL of 1-bromobut-2-yne (50.3 mmol) in 150 mL of DMPU at room temperature were added 10.44 g of $SnCl_2$ (55.1 mmol) and 8.25 g of NaI (55.1 mmol). The resulting yellow slurry was stirred in the absence of light for 5 hours during which time complete dissolution of solids was observed. The mixture was cooled to 0 °C, and a solution of 8.34 g of aldehyde **14** (47.9 mmol) in 75 mL of DMPU was added dropwise over 30 minutes. The orange reaction mixture was allowed to warm to room temperature over 4 hours and stirred in the dark for an additional 20 hours. The reaction was diluted with Et_2O and quenched by addition of 100 mL of 30% aq. NH_4F. The phases were separated, and the aqueous phase was extracted with Et_2O (5x100 mL). The combined organic extracts were washed successively with H_2O and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:2 to 1:1 pet. ether/Et_2O) provided 9.39 g (86%) of allenic alcohol **15** as a pale yellow oil. Data for **15** (as an inseparable 3.5:1 mixture of diastereomers): R_f 0.66 (EtOAc); **IR** (thin film) 3494, 2923, 2851, 1958, 1440, 1299, 1114 cm^{-1}; **^1H NMR** ($CDCl_3$, 500 MHz) δ 5.68 (bs, 1H, major), 5.66 (bs, 1H, minor), 4.88-4.79 (m, 2H), 4.35 (m, 1H, major), 4.28 (m, 1H, minor), 3.92 (d, *J*=10.3 Hz, 1H, major), 3.74 (s, 1H, major), 3.72 (m, 1H, minor), 3.64 (d, *J*=6.0 Hz, 1H, minor), 2.23-1.92 (m, 4H), 1.88 (d, *J*=0.8 Hz, 3H, minor), 1.85, (d, *J*=1.0 Hz, 3H, major), 1.77 (t, *J*=3.1 Hz, 3H, minor) 1.76 (t, *J*=3.2 Hz, 3H, major); **^{13}C NMR** ($CDCl_3$, 125 MHz)

δ 204.6, 138.6 (major), 138.2 (minor), 117.0 (minor), 116.9 (major), 101.9 (minor), 100.7 (major), 77.7 (minor), 77.4 (major), 70.1 (major), 68.5 (minor), 64.6 (major), 63.8 (minor), 55.7 (minor), 55.6 (major), 33.3 (major), 33.1 (minor), 18.2 (major), 17.9 (minor), 15.0 (minor), 14.7 (major); **HRMS** calcd for $C_{11}H_{17}O_3S$ (MH^+) 229.0898, found 229.0895.

Allenic ketone 16. To a solution of 5.60 g of allenic alcohol **15** (24.7 mmol) in 300 mL of CH_2Cl_2 at 0 °C was added 8.30 g of $NaHCO_3$ (98.8 mmol) followed by 18.8 g of Dess-Martin periodinane (44.4 mmol). The slurry was stirred at 0 °C for 1 hour before the reaction was diluted with Et_2O and quenched with 100 mL of sat. $Na_2S_2O_3$. After stirring the biphasic mixture vigorously for 20 minutes, the layers were separated, and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic extracts were washed with sat. $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. The drying agent was removed by filtration, and the solvents were removed in vacuo. Purification by silica gel chomatography (2:1 pet. ether/EtOAc) provided 5.30 g (95%) of allenic ketone **16** as a white foam. Data for **16**: R_f 0.46 (1:1 pet. ether/EtOAc); **IR** (thin film) 2962, 2925, 1956, 1934, 1682, 1307, 1113 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.66 (br s, 1H), 5.25 (dq, *J*=14.3, 3.0 Hz, 1H), 5.20 (dq, *J*=14.3, 3.0 Hz, 1H), 4.18 (t, *J*=5.9 Hz, 1H), 3.80-3.66 (m, 2H), 3.31 (dd, *J*=18.4, 7.5 Hz, 1H), 2.97 (dd, *J*=18.1, 5.6 Hz, 1H), 1.83 (t, *J*=3.0 Hz, 3H), 1.78 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 196.2, 137.8, 117.2, 103.4, 79.7, 62.7, 55.9, 36.8, 17.9, 13.0, 1.0; **HRMS** calcd for $C_{11}H_{15}O_3S$ (MH^+) 227.0742, found 227.0740.

Furan 17. To a solution of 6.33 g of allenic ketone **16** (28.0 mmol) in 150 mL of hexane and 30 mL of CH_2Cl_2 at room temperature was added 11.90 g of $AgNO_3$ on SiO_2 (10 wt. %, 7.0 mmol) in a single portion. The suspension was stirred at room temperature in the absence of light of 2 hours before it was diluted with Et_2O and filtered through a short pad of Celite. Solvents were removed in vacuo, and purification by silica gel chromatography (3:1 hexanes/EtQAc) gave 5.01 g (79%) of furan **17** as a pale yellow oil. Data for **17**: R_f 0.33 (3:1 hexanes/EtOAc); **IR** (thin film) 2922, 1510, 1443, 1306, 1248, 1210, 1150, 1116, 1090, 1044 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.24 (d, *J*=2.0 Hz, 1H), 6.15 (d, *J*=1.8 Hz, 1H), 5.65 (m, 1H), 3.82 (t, *J*=6.5 Hz, 1H), 3.64-3.67 (m, 2H), 3.23 (dd, *J*=15.5, 6.5 Hz, 1H), 2.92 (dd, *J*=15.5, 7.4 Hz, 1H), 1.97 (s, 3H), 1.69 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 145.1, 140.8, 139.0, 117.6, 116.6, 113.1, 65.2, 55.2, 24.9, 18.0, 9.8; **HRMS** calcd for $C_{11}H_{15}O_3S$(MH^+) 227.0742, found 227.0741.

Bis(diene) 10. To a solution of 5.88 g of sulfolene **17** (25.9 mmol) in 430 mL of $PhCH_3$ was added 6.30 g of $NaHCO_3$ (77.7 mmol), and the suspension was heated to reflux for 6 hours. After cooling to room temperature, the reaction mixture was filtered to remove $NaHCO_3$, and concentrated in vacuo. Purification by silica gel chromatography (20:1 pet. ether/Et_2O) provided 3.94 g (94%) of bis(diene) **10** as a colorless oil. Data for **10**: R_f 0.40 (20:1 pet. ether/Et_2O); **IR** (thin film) 2924, 1606, 1510, 1444, 1261, 1150, 1087 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.20 (d, *J*=1.8 Hz, 1H), 6.36 (dd, *J*=17.4, 10.7 Hz, 1H), 6.14 (d, *J*=1.7 Hz, 1H), 5.58 (dt, *J*=6.8, 0.5 Hz, 1H), 5.13 (d, *J*=17.1 Hz, 1H), 4.96 (d, *J*=10.7 Hz, 1H), 3.41 (d, *J*=7.3 Hz, 2H), 1.96 (s, 3H), 1.83 (s, 3H); **^{13}C NMR** ($CDCl_3$,

125 MHz) δ 149.1, 141.1, 140.1, 134.0, 128.0, 113.9, 112.9, 11.4, 25.4, 11.7, 9.7; **HRMS** calcd for $C_{11}H_{14}O(M^{=})$ 162.1045, found 162.1033.

Diels-Alder Adducts 18-21. To a 25 mL round bottom flask were added 1.65 g of bis(diene) **10** (10.2 mmol) and 2.00 g of dienophile **9** (10.2 mmol). The neat mixture was heated to 45 °C and stirred for 72 hours at this temperature during which time it partially solidified. Purification of the adducts by silica gel chromatography (3:1 to 2:1 to 1:1 pet. ether/Et_2O) provided 1.86 g (51%) of *exo*, *anti*-adduct **18**, 839.9 mg (23%) of *endo*, *anti*-adduct **19**, 401.7 mg (11%) of *endo*, *syn*-adduct **21**, and 219.0 mg (6%) of *exo*, *syn*-adduct **20**.

Data for *exo*, *anti*-adduct **18**: R_f 0.56 (7:3 pet. ether/Et_2O); mp=99-101 °C; **IR** (thin film) 3474, 2951, 1708, 1428, 1245, 992, 892 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.34 (dd, *J*=17.5, 6.6 Hz, 1H), 6.09 (m, 1H), 5.54 (ddd, *J*=15.4, 7.7, 0.86 Hz, 1H), 5.53 (t, *J*=6.4 Hz, 1H), 5.50 (dd, *J*=15.4, 6.4 Hz, 1H), 5.07 (d, *J*=17.2 Hz, 1H), 5.06 (d, *J*=0.5 Hz, 1H), 4.94 (d, *J*=1.0 Hz, 1H), 4.92 (d, *J*=10.7 Hz, 1H), 4.82 (d, *J*=0.8 Hz, 1H), 3.83 (d, *J*=11.7 Hz, 1H), 3.72 (s, 3H), 3.40 (dd, *J*=11.7, 4.2 Hz, 1H), 3.21 (dd, *J*=16.5, 7.7 Hz, 1H), 2.52 (dd, *J*=16.6, 6.0 Hz, 1H), 2.27 (sext, *J*=6.8 Hz, 1H), 1.90 (m, 3H), 1.77 (d, *J*=0.6 Hz, 3H), 0.95 (dd, *J*=6.8, 1.2 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.0, 148.0, 147.0, 141.9, 141.3, 135.8, 131.3, 127.1, 126.2, 111.1, 108.4, 96.7, 82.2, 79.1, 63.4, 52.3, 30.9, 29.7, 22.2, 22.1, 13.2, 12.1; **HRMS** calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2221.

Data for *endo*, *anti*-adduct **19**: R_f 0.23 (7:3 pet. ether/Et_2O); **IR** (thin film) 3476, 2941, 1707, 1414, 1261, 999, 856 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.36 (dd, *J*=17.4, 10.8 Hz, 1H), 6.13 (bs, 1H), 5.68 (dd, *J*=15.5, 6.5 Hz, 1H), 5.66 (dd, *J*=15.5, 7.7 Hz, 1H), 5.49 (t, *J*=6.7 Hz, 1H), 5.27 (s, 1H), 5.21 (s, 1H)) 5.09 (d, *J*=17.4 Hz, 1H), 4.93 (d, *J*=10.8 Hz, 1H), 4.87 (s, 1H), 4.72 (dd, *J*=7.7, 4.4 Hz, 1H), 3.67 (s, 3H), 3.11 (dd, *J*=16.6, 7.6 Hz, 1H), 3.00 (dd, *J*=16.6, 6.0 Hz, 1H), 2.46 (bs, 1H), 2.30 (m, 1H), 1.80 (s, 3H), 1.67 (s, 3H), 0.98 (d, *J*=6.7 Hz, 3H), 0.97 (d, *J*=6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.4, 146.8 (2C), 141.8, 141.2, 135.7, 133.1, 127.3, 127.0, 111.0, 108.2, 94.4, 81.8, 77.0, 62.5, 51.7, 30.9, 26.8, 22.1 (2C), 13.3, 12.1; **HRMS** calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2226.

Data for *endo*, *syn*-adduct **21**: R_f 0.44 (7:3 pet. ether/Et_2O); **IR** (thin film) 3467, 2957, 2927, 2869, 1746, 1715, 1433, 1262, 977, 897 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.37 (dd, *J*=17.4, 10.8 Hz, 1H), 6.18 (bs, 1H), 5.69 (ddd, *J*=15.5, 6.7, 0.9 Hz, 1H), 5.51 (t, *J*=6.0 Hz, 1H), 5.48 (dd, *J*=15.5, 7.0 Hz, 1H), 5.31 (s, 1H), 5.19 (s, 1H), 5.13 (d, *J*=17.4 Hz, 1H), 4.95 (d, *J*=10.8 Hz, 1H), 4.92 (s, 1H), 4.85 (d, *J*=7.3 Hz, 1H), 3.86 (s, 1H), 3.62 (s, 3H), 3.25 (dd, *J*=16.8, 7.6 Hz, 1H), 3.03 (dd, *J*=16.8, 5.8 Hz, 1H), 2.30 (m, 1H), 1.84 (s, 3H), 1.61 (s, 3H),0.99 (d, *J*=6.7 Hz, 3H), 0.97 (d, *J*=6.7 Hz, 3H) ; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.9, 148.6, 146.5, 141.4, 141.1, 135.7, 132.3, 127.3, 126.2, 111.1, 108.2, 94.5, 81.4, 76.1, 63.4, 52.4, 30.9, 28.6, 22.1, 21.9, 14.4, 12.1; **HRMS** calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2227.

Data for *exo*, *syn*-adduct **20**: R_f 0.26 (7:3 pet. ether/Et_2O); **IR** (thin film) 3521, 2957, 2928, 2870, 1715, 1434, 1260, 986, 896 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.35 (dd, *J*=17.4, 10.8 Hz, 1H), 6.11 (bs, 1H), 5.76 (dd, *J*=15.6, 6.7 Hz, 1H), 5.66 (dd, *J*=15.6, 6.2 Hz, 1H), 5.55 (t, *J*=6.8 Hz, 1H), 5.15 (s, 1H), 5.12 (s, 1H), 5.09 (d, *J*=17.4 Hz, 1H), 4.96 (s, 1H), 4.93 (d, *J*=10.8 Hz, 1H), 4.08 (dd, *J*=6.8, 6.8 Hz, 1H), 3.74 (s, 3H), 4.08 (d,

J=7.4 Hz, 1H), 2.94 (dd, *J*=16.5, 8.0 Hz, 1H), 2.64 (dd, *J*=16.5, 5.6 Hz, 1H), 2.30 (m, 1H), 1.78 (s, 3H), 1.76 (s, 3H),1.00 (d, *J*=6.8 Hz, 3H), 0.99 (d, *J*= 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 170.1, 144.6, 143.3, 141.1, 141.0, 136.3, 133.4, 126.4, 125.3, 111.4, 110.1, 95.5, 82.2, 73.4, 61.6, 51.7, 30.8, 26.0, 22.2 (2C), 12.9, 12.2; **HRMS** calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2219.

TBS ether 22. To a solution of 500.1 mg of acohol **18** (1.40 mmol) in 15 mL of CH_2Cl_2 at -30 °C was added 450 μL of 2,6-lutidine (4.0 mmol) followed by dropwise addition of 450 μL of TBSOTf (2.0 mmol). The yellow solution was allowed to warm to 0 °C over 1 hour and stirred at this temperature for 30 minutes. The reaction was cooled to 0 °C and quenched by addition of 20 mL of sat. $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (3x20 ml). The combined organic extracts were washed with 1M HCl and brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (9:1 pet. ether/Et_2O) gave 638.6 mg (97%) of the TBS ether as a pale yellow oil. Data for the TBS ether: R_f 0.60 (3:2 pet. ether/Et_2O); **IR** (thin film) 2957, 2936, 1723, 1247, 1052, 834 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.37 (dd, *J*=17.4, 10.7 Hz, 1H), 6.09 (bs, 1H), 5.64 (ddd, *J*=15.6, 9.2, 0.9 Hz, 1H), 5.57 (t, *J*=6.8 Hz, 1H), 5.39 (dd, *J*=15.6, 6.4 Hz, 1H), 5.08 (d, *J*=17.4 Hz, 1H), 5.06 (s, 1H), 4.98 (s, 1H), 4.91 (d, *J*=10.7 Hz, 1H), 4.90 (s, 1H), 4.03 (d, *J*=9.2 Hz, 1H), 3.71 (s, 3H), 3.07 (dd, *J*=17.2, 7.6 Hz, 1H), 2.90 (dd, *J*=17.2, 5.3 Hz, 1H), 2.28 (m, 1H), 1.80 (d, *J*=1.6 Hz, 3H), 1.78 (s, 3H), 0.99 (d, *J*=6.3 Hz, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 172.0, 147.6, 146.5, 142.4, 141.4, 135.2, 132.0, 128.1, 127.6, 110.5, 108.3, 95.5, 81.8, 79.5, 64.6, 51.7, 30.8, 28.9, 26.1 (3C), 21.8, 21.5, 18.3, 14.8, 12.2, -2.3, -3.8; **HRMS** calcd for $C_{28}H_{44}O_4SiNa$ (MNa^+) 495.2907, found 495.2903.

To a solution of the 120.0 mg of the TBS ether (0.254 mmol) in 2.5 mL of THF at -20 °C was added 0.71 mL of a 1.0M Et_2O solution of lithium aluminum hydride (0.71 mmol) dropwise over 30 minutes. The colorless solution was allowed to warm to room temperature over 1 hour and stirred at this temperature for an additional 30 minutes. The reaction mixture was cooled to -78 °C and quenched by dropwise addition of 1 mL of EtOAc. After warming to room temperature, 5 mL of sat. sodium potassium tartrate (Rochelle's salt) was added, and the mixture was stirred vigorously until two distinct phases were obvserved. The layers were separated, and the aqueous phase was extracted with Et_2O (4x10 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (4:1 pet. ether/Et_2O) provided 82.2 mg (98%) of the diol as a waxy solid. Data for the diol: R_f 0.24 (3:1 pet. ether/Et_2O); **IR** (thin film) 3355, 3086, 2958, 2926, 1434, 1058, 975, 929, 892 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.40 (dd, *J*=17.4, 10.7 Hz, 1H), 6.02 (bd, *J*=1.3 Hz, 1H), 5.74 (ddd, *J*=15.4, 7.9, 1.2 Hz, 1H), 5.64 (bt, *J*=6.8 Hz, 1H), 5.58 (dd, *J*=15.4, 6.6 Hz, 1H), 5.09 (d, *J*=17.4 Hz, 1H), 4.99 (s, 1H), 4.92 (d, *J*=10.7 Hz, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.06 (dd, *J*=11.0, 3.0 Hz, 1H), 3.94 (dd, *J*=11.0, 5.0 Hz, 1H), 3.68 (dd, *J*=7.7, 5.6 Hz, 1H), 3.23 (dd, *J*=17.0, 7.4 Hz, 1H), 3.05 (dd, *J*=17.0, 6.1 Hz, 1H), 2.79 (bs, 1H), 2.42 (bd, *J*=5.5 Hz, 1H), 2.35 (m, 1H) 1.91 (d, *J*=1.7 Hz, 3H), 1.81 (s, 3H), 1.02, (d, *J*=6.7 Hz, 3H), 1.01 (d, *J*=6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 149.6, 147.6, 142.2, 141.4, 135.3,

129.6, 128.6, 126.8, 110.6, 106.4, 95.9, 81.9, 79.3, 65.6, 55.3, 30.9, 28.8, 22.2, 22.1, 13.6, 12.1; **HRMS** calcd for $C_{21}H_{30}O_3Na$ (MNa^+) 353.2093, found 353.2096.

To a solution of 303.0 mg of the diol (0.92 mmol), 11.2 mg of DMAP (0.092 mmol) and 250 μL of Et_3N (1.84 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added 166.4 mg of TBSCl (1.10 mmol). The yellow solution was allowed to warm to room temperature and stirred at this temperature for 5 hours. The reaction was diluted with 20 ml of Et_2O and quenched by addition of 10 ml of H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3x20 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (5:1 pet. ether/Et_2O) provided 383.9 mg (94%) of TBS ether **22** as a sticky oil. Data for **22**: R_f 0.70 (7:3 pet. ether/Et_2O); **IR** (thin film) 3514, 2956, 2930, 1469, 1258, 1062, 838 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.40 (dd, *J*=17.3, 10.7 Hz, 1H), 5.97 (bq, *J*=1.4 Hz, 1H), 5.68 (ddd, *J*=15.5, 7.4, 1.2 Hz, 1H), 5.62 (bt, *J*=6.6 Hz, 1H), 5.59 (dd, *J*=15.5, 6.0 Hz, 1H), 5.08 (d, *J*=17.4 Hz, 1H), 4.93 (s, 1H), 4.91 (d, *J*=10.7 Hz, 1H), 4.72 (bs, 1H), 4.71 (s, 1H), 4.02 (d, *J*=11.0 Hz, 1H), 3.92 (s, 2H), 3.57 (dd, *J*=11.0, 7.3 Hz, 1H), 3.25 (dd, *J*=17.1, 7.3 Hz, 1H), 2.92 (dd, *J*=17.1, 5.8 Hz, 1H), 2.35 (m, 1H), 1.93 (d, *J*=1.7 Hz, 3H), 1.79 (s, 3H), 1.03 (d, *J*=6.7 Hz, 1H), 1.02 (d, *J*=6.7 Hz, 3H), 0.97 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.2, 147.9, 141.5, 140.9, 135.1, 129.0 (2C), 127.2, 110.4, 106.2, 96.0, 82.0, 79.5, 67.5, 55.8, 30.7, 29.6, 25.9 (3C), 22.3, 22.1, 17.8, 13.6, 12.1, -5.8, -5.9; **HRMS** calcd for $C_{27}H_{45}O_3Si$ (MH^+) 445.3138, found 445.2845.

Sulfolene 23. To a mixture of the 33.0 mg of diene **22** (0.0742 mmol) and a crystal of hydroquinone cooled to -78 °C was added 3 mL of sulfur dioxide. The mixture was warmed until effervescence occurred, and the tube was sealed and heated at 53 °C for 20 hours. The mixture was cooled to -78 °C and then opened and slowly and allowed to warm to room temperature. The residue was dissolved in CH_2Cl_2 and filtered to remove hydroquinone. Solvent was removed in vacuo, and purification by silica gel chromatography (2:1 to 1:1 pet. ether/Et_2O) gave 36.0 mg (95%) of sulfolene **23** as a separable 1.25:1 mixture of diastereomers.

Data for major diastereomer **23** (20.0 mg, 53%): R_f 0.05 (7:3 pet. ether/Et_2O); **IR** (thin film) 3519, 2956, 2928, 2855, 1313, 1252, 1113, 1045, 840 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.06 (bd, *J*=1.0 Hz, 1H), 5.68 (ddd, *J*=15.5, 7.5, 1.2 Hz, 1H), 5.66 (bs, 1H), 5.58 (dd, *J*=15.5, 6.0 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 4.71 (s, 1H), 4.15 (dd, *J*=10.7, 1.4 Hz, 1H), 4.09 (d, *J*=11.1 Hz, 1H), 3.89 (d, *J*=11.1 Hz, 1H), 3.73 (m, 1H), 3.67-3.59 (m, 2H), 3.52 (dd, *J*=10.9, 7.5 Hz, 1H), 2.96 (dd, *J*=16.0, 9.8 Hz, 1H), 2.69 (d, *J*=16.0 Hz, 1H), 2.33 (m, 1H), 1.99 (d, *J*=1.6 Hz, 3H), 1.93 (bs, 3H), 1.02 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.0, 145.5, 141.2, 137.9, 131.1, 126.9, 117.1, 116.2, 106.6, 95.1, 82.4, 79.4, 67.6, 65.3, 56.6, 30.7, 27.2, 25.8 (3C), 22.2, 22.1, 18.6, 17.8, 13.6, -5.9, -5.9; **HRMS** calcd for $C_{27}H_{44}O_5SSiNa$ (MNa^+) 531.2577, found 531.2587.

Data for minor diastereomer **23** (16.0 mg, 42%): R_f 0.21 (7:3 pet. ether/Et_2O); **IR** (thin film) 3508, 2956, 2927, 2859, 1466, 1309, 1252, 1065, 837 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.02 (bs, 1H), 5.65 (dd, *J*=15.6, 6.9 Hz, 1H), 5.62 (bs, 1H), 5.58 (dd, *J*=15.6, 5.7 Hz, 1H), 4.94 (s, 1H), 4.72 (s, 2H), 3.91 (d, *J*=10.7 Hz, 1H), 3.85 (dd, *J*=10.7, 1.1 Hz,

1H), 3.76 (d, *J*=11.2 Hz, 1H), 3.70 (m, 1H), 3.65-3.58 (m, 2H), 3.56 (dd, *J*=11.2, 6.9 Hz, 1H), 3.40 (dd, *J*=16.2, 1.8 Hz, 1H), 2.33(m, 1H), 2.28 (dd, *J*=16.2, 7.2 Hz, 1H), 2.07 (d, *J*=1.7 Hz, 3H), 1.89 (d, *J*=1.2 Hz, 3H), 1.02 (d, *J*=6.7 Hz, 3H), 1.01 (d, *J*=6.7 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 150.6, 147.6, 141.9, 141.6, 130.4, 127.3, 116.4, 106.8, 96.1, 82.5, 79.4, 67.8, 64.6, 56.9, 55.5, 31.1, 28.6, 26.2 (3C), 22.7, 22.5, 18.9, 18.3, 13.8, -5.4, -5.6; **HRMS** calcd for $C_{27}H_{44}O_5SSiNa$ (MNa^+) 531.2577, found 531.2566.

Epoxide 24. To a solution of 23.0 mg of the major diastereomeric alcohol **23** (0.0452 mmol) and 11 μL of pyridine (0.136 mmol) in 1 mL of CH_2Cl_2 at 0 °C was added 48.3 mg of Dess-Martin periodinane (0.113 mmol) in a single portion. The reaction mixture was stirred 0 °C for 1 hour and then at room temperature for 3 hours before being diluted with Et_2O and quenched by addition of 2 mL of a 4:3:3 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$/H_2O. The mixture was stirred vigorously for 20 minutes and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3x5 ml). The combined organic extracts were washed with sat. $NaHCO_3$ and brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Due to the instability of the enone, it was carried on in the next step without purification.

The crude enone was dissolved in 1.5 mL of CH_2Cl_2, and 19.0 mg of $NaHCO_3$ (0.226 mmol) was added. The slurry was cooled to 0 °C, and a solution of 11.7 mg of *m*-CPBA (0.0678 mmol) in 0.5 mL of CH_2Cl_2 was added dropwide. The reaction mixture was stirred 0 °C for 1 hour at which time an additional 11.7 mg of *m*-CPBA (0.0678 mmol) in 0.5 mL of CH_2Cl_2 was added. The reaction was quenched after stirring for 2 hours at 0 °C by addition of 2 mL of a 4:3:3 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$/H_2O. The mixture was stirred vigorously and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3x10 ml). The combined organic extracts were washed with sat. $NaHCO_3$ and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (2:1 pet. ether/Et_2O) provided 18.4 mg (78% for two steps) of major diastereomeric epoxide **24** as a pale yellow oil. Data for major diastereomeric epoxide **24**: R_f 0.53 (Et_2O); **IR** (thin film) 2958, 2929, 2857, 1676, 1617, 1311, 1256, 1116, 840 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.85 (dd, *J*=15.3, 6.8 Hz, 1H), 5.71 (d, *J*=15.3 Hz, 1H), 5.66 (bs, 1H), 5.42 (s, 1H), 5.37 (s, 1H), 4.70 (s, 1H), 4.40 (d, *J*=8.5 Hz, 1H), 3.98 (bd, *J*=8.1 Hz, 1H), 3.76 (m, 1H), 3.68 (m, 1H), 3.66 (d, *J*=8.1 Hz, 1H), 3.31 (s, 1H), 2.66 (dd, *J*=16.2, 8.6 Hz, 1H), 2.45 (m, 1H), 2.39 (dd, *J*=16.2, 1.3 Hz, 1H), 1.91 (bs, 3H), 1.42 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.80 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 199.9, 154.8, 146.7, 137.49, 124.4, 117.2, 112.3, 88.7, 79.6, 67.9, 67.8, 62.8, 58.4, 56.5, 56.4, 31.2, 25.7 (3C), 23.9, 21.3, 21.2, 18.2, 18.1, 13.6, -5.6, -5.9; **HRMS** calcd for $C_{27}H_{43}O_6SSi(MH^+)$ 523.2549, found 523.2569.

Following a similar two step procedure with the minor diastereomeric sulfolene **23** (16.0 mg, 0.0315 mmol) provided 11.5 mg (70% for two steps) of the minor diastereomeric epoxide **24**. Data for **XX**: R_f 0.69 (Et_2O); **IR** (thin film) 2958, 2929, 2856, 1676, 1617, 1307, 1256, 1113, 839 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.89 (dd, *J*=15.3, 6.9 Hz, 1H), 5.68 (dd, *J*=15.5, 1.0 Hz, 1H), 5.63 (bs, 1H), 5.37 (s, 2H), 4.58 (s,

1H), 4.34 (d, *J*=8.5 Hz, 1H), 3.98 (bs, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.50 (d, *J*=11.1 Hz, 1H), 3.32 (s, 1H), 2.11 (dd, *J*=16.2, 2.7 Hz, 1H), 2.46 (m, 1H), 2.69 (dd, *J*=16.2, 6.2 Hz, 1H), 1.88 (bs, 3H), 1.38 (s, 3H), 1.06 (d, *J*=6.8 Hz, 3H), 1.05 (d, *J*=6.8 Hz, 3H), 0.81 (s, 9H), -0.02 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 198.1, 155.0, 146.4, 140.3, 124.2, 119.6, 116.3, 112.4, 89.3, 79.4, 67.8, 67.1, 62.1, 58.4, 56.3, 55.4, 31.2, 25.7 (3C), 25.0, 21.3 (2C), 18.1, 13.1, -5.6, -5.8; **HRMS** calcd for $C_{27}H_{43}O_6SSi$ (MH^+) 523.2549, found 523.2589.

Diene 25. To a solution of 24.2 mg of major diastereomeric sulfolene **24** (0.0459 mmol) in 10 mL of $PhCH_3$ at room temperature were added 37.1 mg of $NaHCO_3$ (0.449 mmol) and 10.0 mg of hydroquinone (0.0918 mmol). The suspension was heated to reflux for 2 hours and then cooled to room temperature. The reaction mixture was diluted with 10 mL of Et_2O and 10 mL of H_2O and transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (9:1 pet. ether/Et_2O) provided 17.3 mg (81%) of diene **25** as a pale yellow oil.

Following a similar procedure with the minor diastereomeric sulfolene **24** (20.8 mg, 0.0402 mmol) provided 13.8 mg (76%) of diene **25**. Data for **25**: R_f 0.63 (1:1 pet. ether/Et_2O); **IR** (thin film) 2958, 2929, 2857, 1676, 1617, 1257, 1092, 1001, 838 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.85 (dd, *J*=15.4, 6.6 Hz, 1H), 5.71 (dd, *J*=15.4, 1.1 Hz, 1H), 5.42 (dd, *J*=17.4, 10.7 Hz, 1H), 5.67 (bt, *J*=6.9 Hz, 1H), 5.38 (s, 1H), 5.37 (s, 1H), 5.11 (d, *J*=17.4 Hz, 1H), 4.95 (d, *J*=10.7 Hz, 1H), 4.62 (s, 1H), 4.40 (d, *J*=8.4 Hz, 1H), 3.52 (d, *J*=8.4 Hz, 1H), 3.30 (s, 1H), 2.95 (dd, *J*=16.5, 7.8 Hz, 1H), 2.67 (dd, *J*=16.5, 6.1 Hz, 1H), 2.45 (m, 1H), 1.82 (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.81 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 199.7, 154.4, 147.2, 141.3, 135.8, 125.7, 124.7, 112.1, 111.2, 90.2, 79.6, 67.9, 67.4, 58.7, 56.7, 31.2, 26.2, 25.7 (3C), 21.3 (2C), 18.1, 13.3, 12.0, -5.5, -5.8; **HRMS** calcd for $C_{27}H_{43}O_4Si$ (MH^+) 459.2930, found 459.2872.

Pentacycle 26. A solution of 25.0 mg of diene **25** (0.0545 mmol) and 0.39 mL of propylene oxide (5.45 mmol) in 18 mL of xylenes in a sealable tube was frozen, placed under vacuum (0.1 mmHg), and then sealed and heated to 210 °C for 6 hours. The mixture was cooled to room temperature, and solvents were removed in vacuo. Purification by silica gel chromatography (10:1 to 5:1 pet. ether/Et_2O) gave 6.0 mg (24%) of pentacycle **26** as a waxy film. Data for **26**: R_f 0.60 (1:1 pet. ether/Et_2O); **IR** (thin film) 2928, 1708, 1459, 1257, 1093, 837, 778 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.53 (bs, 1H), 5.29 (s, 1H), 5.13 (s, 1H), 4.62 (s, 1H), 4.49 (d, *J*=10.2 Hz, 1H), 3.61 (d, *J*=8.4 Hz, 1H), 3.16 (s, 1H), 2.87 (dd, *J*=10.1, 10.1 Hz, 1H), 2.74 (m, 1H), 2.61 (m, 1H), 2.48 (dd, *J*=13.3, 5.1 Hz, 1H), 2.22 (dd, *J*=13.4, 13.4 Hz, 1H), 2.07-1.88 (m, 3H), 1.79 (s, 3H), 1.38 (s, 3H), 0.83 (s, 9H), 0.71 (d, *J*=6.9 Hz, 3H), -0.02 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 206.7, 143.3, 134.3, 123.7, 108.6, 88.6, 78.6, 69.0, 66.9, 59.0, 58.9, 49.8, 40.4, 38.5, 27.0, 26.6, 26.0 (3C), 23.6, 20.9, 20.8, 17.0, 15.4, 15.3, -5.1, -5.7; **HRMS** calcd for $C_{27}H_{43}O_4Si$ (MH^+) 459.2930, found 459.2922.

Tricycle 27. To a solution of 49.9 mg of diene **25** (0.113 mmol) in 22.5 mL of $PhCH_3$ was added 30.3 mg of $LiClO_4$ (0.282 mmol) in a single portion. The mixture was heated to 100 °C for 1 hour before it was cooled to room temperature and 10 mL of pH 7 phosphate buffer was added. The layers were separated, and the aqueous phase was extracted with Et_2O (2x10 mL). The combined organic extracts were dried over $MgSO_4$. Drying agent was removed by filtration, and solvents were removed in vacuo. Purification by silica gel chromatography (3:2 pet. ether/Et_2O) provided 46.0 mg (92%) of tricycle **27** a viscous oil. Data for **27**: R_f 0.20 (3:2 pet. ether/Et_2O); **IR** (thin film) 3411, 2956, 2928, 2858, 1675, 1633, 1257, 1060, 839 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.35 (dd, *J*=17.3, 10.8 Hz, 1H), 6.02 (d, *J*=11.3 Hz, 1H), 5.58 (t, *J*=6.4 Hz, 1H), 5.20 (d, *J*=11.3 Hz, 1H), 5.18 (s, 1H), 5.09 (d, *J*=17.3 Hz, 1H), 4.94 (d, *J*=10.7 Hz, 1H), 4.53 (s, 1H), 3.79 (d, *J*=10.6 Hz, 1H), 3.75 (d, *J*=9.5 Hz, 1H), 3.72 (d, *J*=10.6 Hz, 1H), 2.78 (dd, *J*=16.9, 6.9 Hz, 1H), 2.72 (dd, *J*=16.9, 6.9 Hz, 1H), 1.98 (d, *J*=9.6 Hz, 1H), 1.78 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.35 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 155.9, 150.4, 141.1, 135.5, 130.2, 126.2, 118.1, 111.1, 107.6, 94.3, 94.0, 91.4, 85.9, 82.6, 61.9, 56.8, 26.2, 26.0, 25.7 (3C), 18.2, 18.1, 15.3, 11.9, -5.7, -5.7; **HRMS** calcd for $C_{27}H_{43}O_4Si$ (MH^+) 459.2930, found 459.2919.