Total Synthesis of Taxol. 2. Construction of A and C Ring Intermediates and Initial Attempts To Construct the ABC Ring System

K. C. Nicolaou,* J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada, and P. G. Nantermet

Contribution from the Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received July 7, 1994[⊗]

Abstract: A method for the formation of Taxol's ABC ring system has been developed. General methods for the synthesis of versatile synthons for Taxol's A ring (**8**) and C ring (**55**) are presented. A model study using a simplified C ring synthon (**17**) confirmed the viability of the sequential Shapiro-McMurry strategy for formation of Taxol's B ring. Careful exploration of the chemistry of various A-B ring conjugates allowed the development of a successful method for formation of the B ring in a more functionalized system.

Introduction

The preceding paper[1] established a convergent strategy toward Taxol (**1**, Figure 1) and described a number of chemical studies that provided direction toward the appropriate intermediates and final path. In this article we describe the construction of rings A and C and discuss the refinements to these methods that were necessary to arrive at the key building blocks that were utilized in the synthesis.

Construction of Ring A

In keeping with the themes of convergency and of using the Diels-Alder reaction as a means to construct both rings A and C of Taxol (**1**), we embarked on the synthesis of intermediates **9** and **10** as summarized in Scheme 1. The possibility of steric hindrance overriding the well-known electronic induction of regiocontrol in the Diels-Alder reaction[2] warranted concern initially. This worry proved unfounded, however, as the readily prepared diene **5**[3,4] and 1-chloroacrylonitrile (**6**) provided, through a Diels-Alder reaction that proceeded smoothly at 130 °C in a sealed tube, an 80% yield of desired product **7** as a single regioisomer, whose structure was confirmed by both spectroscopic and X-ray crystallographic analyses. Application of the protocol of Shiner[5,6] (KOH, ^{t}BuOH, 70 °C) freed the latent carbonyl group at C1 with concomitant acetate removal to give hydroxy ketone **8** (90%, based on 70% conversion). Reprotection of the primary hydroxyl group of **8** as either a *tert*-butyldimethylsilyl[8] or (methoxyethoxy)methyl[7] ether afforded compounds **9** (85% yield) and **10** (95% yield), respectively.

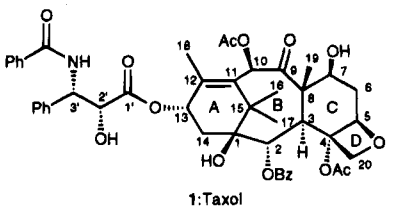
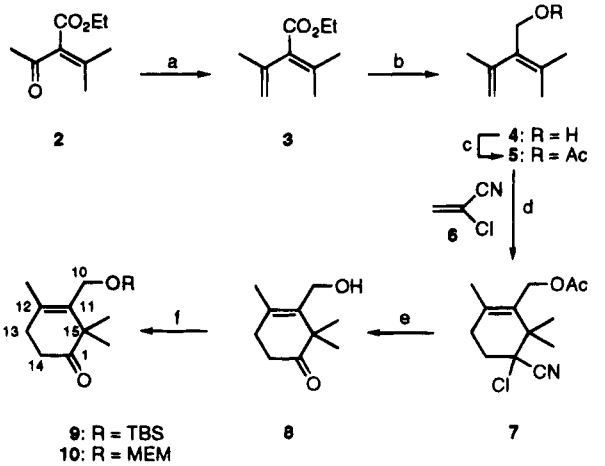


Figure 1. Structure and numbering of Taxol (**1**).

Scheme 1. Construction of Ring A Key Intermediates **8**-**10**[a]



[a] Reagents and conditions: (a) 1.2 equiv of MeMgBr, Et_2O, 0 → 25 °C, 8 h, then 0.2 equiv of *p*-TsOH, benzene, 65 °C, 3 h, 70%; (b) 2.2 equiv of *i*-Bu_2AlH, CH_2Cl_2, −78 → 25 °C, 12 h, 92%; (c) 1.1 equiv of Ac_2O, 1.2 equiv of Et_3N, 0.2 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0 → 25 °C, 1 h, 96%; (d) 1.0 equiv of **5**, 1.5 equiv of **6**, 130 °C, 72 h, 80%; (e) 6.0 equiv of KOH, *t*-BuOH, 70 °C, 4 h, 90% based on 70% conversion; (f) for **9**, 1.1 equiv of TBSCl, 1.2 equiv of imidazole, CH_2Cl_2, 25 °C, 2 h, 85%; for **10**, 1.2 equiv of MEMCl, 1.3 equiv of *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 3 h, 95%. TBS = Si-*t*-$BuMe_2$, MEM = (methoxyethoxy)methyl.

* Address correspondence to this author at the Scripps Research Institute or the University of California.

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1994.

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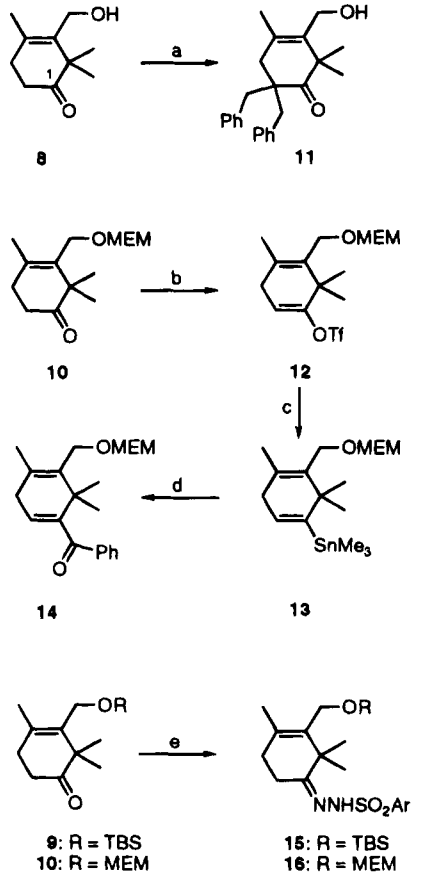
Scheme 2. Chemistry of A Ring Ketones **8**–**10** and Construction of Hydrazones **15** and **16**[a]



[a] Reagents and conditions: (a) 1.1 equiv of KH, 1.05 equiv of $PhCH_2Br$, THF, 0 → 25 °C, 1.5 h, 37%; (b) 1.1 equiv of LiN-*i*-Pr_2, DME, −78 °C, 2 h, then 1.07 equiv of *N*-phenyltrifluoromethanesulfonimide, DME, −78 → 0 °C, 4 h, 80%; (c) 0.90 equiv of $Me_3SnSnMe_3$, 6.35 equiv of LiCl, 0.02 equiv of $(Ph_3P)Pd$, THF, 60 °C, 18 h, 90%; (d) 1.0 equiv of PhCOCl, 0.05 equiv of $PhCH_2Pd(Cl)(Ph_3P)_2$, HMPA, 65 °C, 18 h, 65%; (e) for **15**, 1.0 equiv of (2,4,6-triisopropylbenzenesulfonyl)hydrazine, THF, 25 °C, 24 h, 88%; for **16**, 1.0 equiv of (2,4,6-triisopropylbenzenesulfonyl)hydrazine, MeOH 25 °C, 4 h, 85%. Ar = 2,4,6-triisopropylbenzene, TBS = Si-*t*-$BuMe_2$, MEM = (methoxyethoxy)methyl, HMPA = hexamethylphosphoramide.

Early attempts to engage ketones **9** or **10** in coupling with nucleophiles revealed their reluctance to enter in such reactions, probably due to both steric hindrance and ease of enolization. The reaction of **8** with benzyl bromide under basic conditions evidenced the latter by giving rise to dibenzyl derivative **11** (37%, Scheme 2), rather than the expected benzyl ether.

Having failed to induce the ring A derivatives **8**–**10** to undergo nucleophilic additions at their carbonyl site, it was then decided to umpolung the system, that is to convert it into a nucleophilic species. Early attempts utilized the vinyltin derivative **13** (Scheme 2), prepared from ketone **10** via triflate **12**[9] as summarized in Scheme 2, as a vinyllithium precursor or a nucleophillic partner in a Stille coupling[10] reaction. However, neither reaction proved fruitful with a functionalized ring C partner, even though a Stille coupling of **13** with benzoyl chloride did afford enone **14** (65% yield, Scheme 2). With some reluctance due to the expected steric hindrance, the formation of a hydrazone, a precursor to vinyllithium species, was then attempted. To our surprise and delight, hydrazones **15** and **16** were both easily prepared from the corresponding ketones **9** and **10** via addition of (triisopropylsulfonyl)hydrazine.[11] As will be discussed below, these hydrazones served admirably in Shapiro couplings[12,13] with appropriately functionalized ring C partners.

A Feasibility Study for the Shapiro–McMurry Strategy

With a suitable ring A vinyllithium precursor in hand, we were now ready to test the feasibility for the proposed Shapiro–McMurry strategy toward the taxoid skeleton. To this end the model aldehyde **21**,[14] representing Taxol's ring C, was prepared from diester **17**[15] via the sequence summarized in Scheme 3. Then, reaction of hydrazone **16** with 2.1 equiv of *n*-BuLi in THF at −78 °C followed by warming to 0 °C and addition of aldehyde **21** furnished a mixture of diastereomeric C2 alcohols (*ca.* 2:1) in 83% total yield. The major diastereoisomer, isolated chromatographically, was proven to be of the desired stereochemistry, as indicated in structure **22**, by X-ray crystallographic analysis on a subsequent intermediate (*vide infra*). Vanadium-catalyzed epoxidation of allylic alcohol **22** according to the Sharpless procedure[16] proceeded regio- and stereoselectively to afford epoxide **23** in 91% yield. Regioselective opening of this epoxide using lithium aluminum hydride[17] in Et_2O at 0–25 °C provided diol **24** in 96% yield. Following our tactical intention to preorganize the substrate prior to McMurry reactions,[18] we engaged the vicinal 1,2-diol system in **24** as the acetonide **25**.[19] Sequential removal of the primary alcohols' protecting groups and oxidation[20] with TPAP–NMO furnished dialdehyde **30** in 50% overall yield from **25** (Scheme 4). An X-ray crystallographic analysis of compound **30** confirmed its structure and those of its precursors (see ORTEP drawing, Figure 2).

Having secured dialdehyde **30** we were within sight of a tricyclic taxoid skeleton provided the pending McMurry coupling[18] would be successful. Mindful of Kende's precedent[21] which resulted in the formation of an olefin at the C9–C10 site instead of the C9–C10 diol system that we desired, we proceeded cautiously and systematically to develop proper conditions for this ring closure. After considerable experimentation it was found that exposure of dialdehyde **30** to Ti(0) generated from $TiCl_3$ and Zn–Cu couple in DME at 50 °C under high-dilution conditions gave the desired diol **31** in 40% yield

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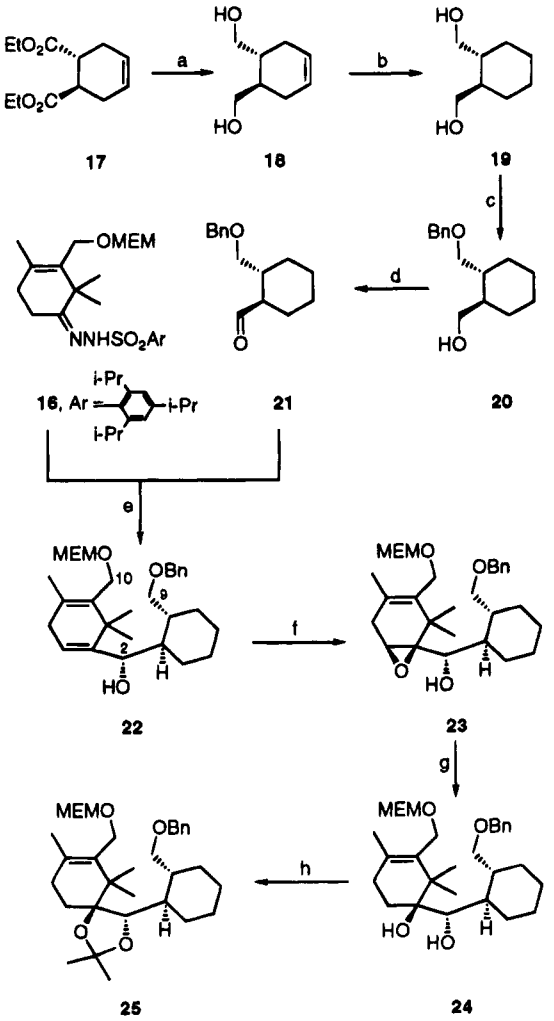
Scheme 3. Synthesis of the Acetonide Model System **25** by the Shapiro Reaction[a]



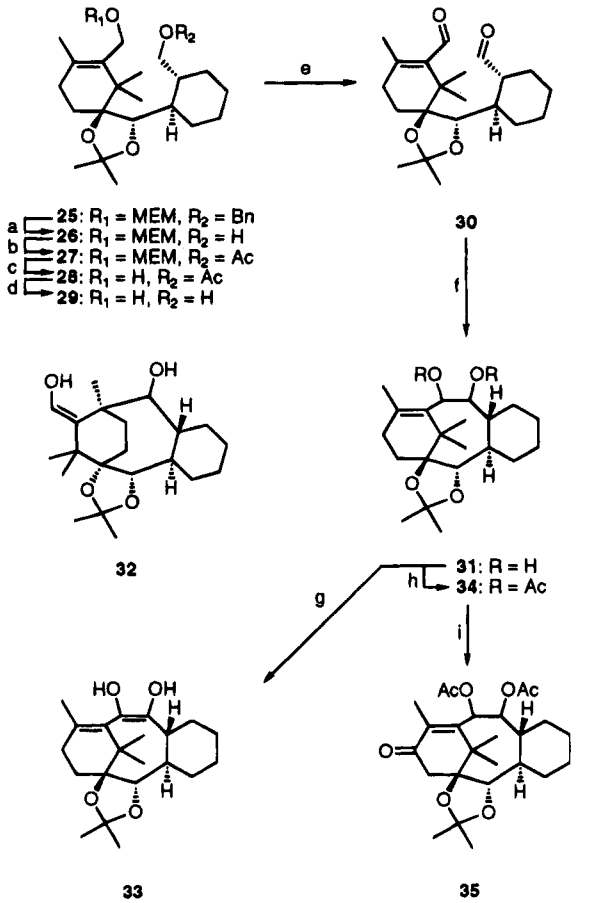
[a] Reagents and conditions: (a) 5.0 equiv of *i*-Bu_2AlH, CH_2Cl_2, −78 → 25 °C, 10 h, 95%; (b) H_2, 0.2 equiv of Pd/C, EtOAc, 3 h, 100%; (c) 1.0 equiv of KH, 1.0 equiv of $PhCH_2Br$, THF, 0 → 25 °C, 1.5 h, 85%; (d) 2.0 equiv of pyridinium dichromate (PDC), molecular sieves, CH_2Cl_2, 0 → 25 °C, 4 h, 90%; (e) **16**, 2.1 equiv of *n*-BuLi, THF, −78 °C, 0.5 h, then 0 °C, 10 min, 1.3 equiv of **21**, THF, 0 → 25 °C, 5 h, 83% (*ca.* 2:1 diastereomeric mixture); (f) 1.1 equiv of *t*-BuOOH, 0.014 equiv of $VO(acac)_2$, PhH, 25 °C, 2 h, 91%; (g) 2.0 equiv of $LiAlH_4$, Et_2O, 0 °C, 20 min, 25 °C, 6 h, 96%; (h) 2 equiv of 2,2-dimethoxypropane, 0.2 equiv of camphorsulfonic acid (CSA), CH_2Cl_2, 25 °C, 12 h, 85%. MEM = (methoxyethoxy)ethyl, Bn = CH_2Ph, acac = acetylacetonate.

as a mixture of two diastereoisomers (stereochemistry unassigned). This reaction produced no Δ C9−C10 olefin, although the C9−C12 coupled byproduct **32** was formed (25% yield) as also observed by Kende.[21] The mechanistic aspects of this reaction will be discussed in a subsequent paper in this series. Oxidation of the mixture of diols **31** with MnO_2[22] gave the dienediol **33** in 90% yield, and acetylation of **31** followed by PCC oxidation[23] led to enone **35** via diacetate **34**. The work presented in Schemes 3 and 4 demonstrated the viability of our Shapiro−McMurry strategy toward Taxol (**1**) and placed us in the position of facing the challenge of Taxol (**1**) itself.

Construction of C Ring Systems

a. The Diels−Alder Reaction. In contrast to the achiral ring A system, ring C of Taxol, with its numerous stereocenters

Scheme 4. Synthesis of the ABC Taxoid Systems **33** and **35** by the McMurry Reaction[a]



[a] Reagents and conditions: (a) H_2, 20% $Pd(OH)_2$ on C, EtOH, 25 °C, 2 h, 100%; (b) 1.2 equiv of Ac_2O, 1.3 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0 → 25 °C, 2.5 h, 97%; (c) 1.0 equiv of $TiCl_4$, CH_2Cl_2, −78 °C, 10 min, then −20 °C, 10 min, 65%; (d) 0.1 equiv of K_2CO_3, MeOH, 25 °C, 4 h, 91%; (e) 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 3.0 equiv of 4-methylmorpholine *N*-oxide (NMO), 4-Å sieves, CH_2Cl_2, 25 °C, 10 min, 87%; (f) 8.0 equiv of $TiCl_3$−$(DME)_{1.5}$, 15 equiv of Zn−Cu, DME, 50 °C, 5 h, 40% of **31**, 25% of **32**; (g) excess MnO_2, CH_2Cl_2, 25 °C, 20 min, 90%; (h) excess Ac_2O, excess pyridine, CH_2Cl_2, 25 °C, 0.5 h, 98%; (i) 30 equiv of pyridinium chlorochromate (PCC), 30 equiv of NaOAc, Celite, benzene reflux, 2 h, 71%. MEM = (methoxyethoxy)ethyl.

and high degree of oxygenation, presented a more serious challenge to the Diels−Alder approach. Early approaches examined the reaction of dienophile **40** (prepared from 1-hydroxy-2-propene (**36**) according to Scheme 5) and 3-carbomethoxy-2-pyrone (**43**) (Scheme 6). According to previous work by Corey[24] and Bryson[25] with the latter compound, and considering the substitution pattern of dienophile **40**, we expected this reaction to proceed regio- and stereoselectively to afford product **45** via intermediate **44**. Diene **45** was then expected to serve as a precursor to a fully functionalized ring C for coupling with ring A. In the event, however, this Diels−Alder reaction (155 °C, 24 h, 81% yield based on 51% conversion) proceeded with the opposite regiochemistry from that expected, furnishing product **47**, via presumed intermediate **46**, the latter undergoing a facile decarboxylation under the reaction conditions. A series of regio- and stereochemically controlled reactions, as shown in Scheme 6, converted cyclohexadiene system **47** into crystalline diol **51**. X-ray crystallographic analysis of **51** (see ORTEP drawing, Figure 2)

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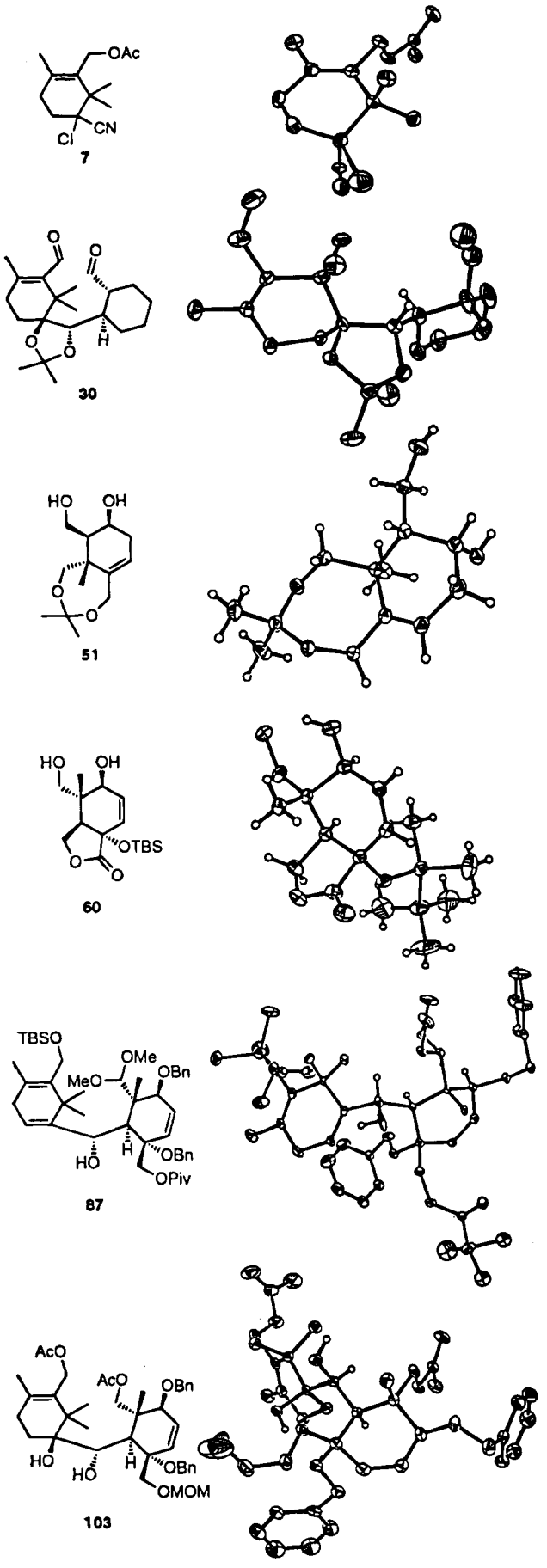
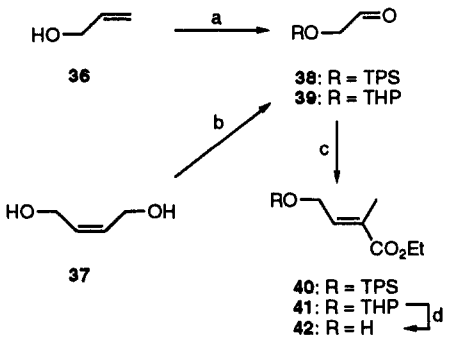


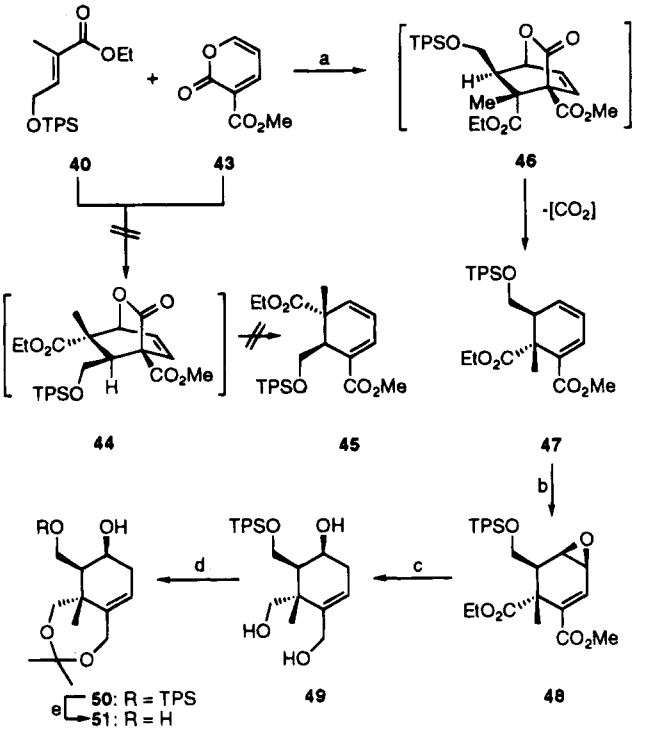
Figure 2. ORTEP drawings for intermediates **7**, **30**, **51**, **60**, **87**, **103**.

Scheme 5. Synthesis of Dienophiles **40**–**42**[a]



[a] Reagents and conditions: (a) 1.1 equiv of TPSCl, 1.15 equiv of imidazole, DMF, 0 °C, 1 h, then O_3, CH_2Cl_2, −78 °C, 1 h, then 2.2 equiv of Ph_3P, −78 °C → 25 °C; (b) 2.1 equiv of dihydropyran, 0.005 equiv of *p*-TsOH, CH_2Cl_2, 25 °C, 0.5 h, then O_3, CH_2Cl_2, −78 °C, 5 h, then 1.0 equiv of Ph_3P, −78 °C → 25 °C, 98%; (c) for **40**, 1.4 equiv of $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 25 °C, 20 h, 91% from **36**; for **41**, 1.03 equiv of $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C, 4 h, then 25 °C, 18 h, 90%; (d) 0.05 equiv of *p*-TsOH, MeOH, 25 °C, 18 h, 92%. TPS = Si-*t*-$BuPh_2$, THP = tetrahydropyranyl.

Scheme 6. Early Diels–Alder Attempts[a]



[a] Reagents and conditions: (a) 1.0 equiv of **40**, 2.0 equiv of **43**, neat, 155 °C, 24 h, 81% based on 51% conversion; (b) 4.0 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 4 h, 71% plus 19% of α epoxide; (c) excess *i*-Bu_2AlH, Et_2O, 0 °C, 2 h, 91%; (d) excess 2,2-dimethoxypropane, 0.05 equiv of camphorsulphonic acid (CSA), CH_2Cl_2, 25 °C, 1 h, 90%; (e) 1.0 equiv of *n*-Bu_4NF (TBAF), THF, 25 °C, 1 h, 95%. TPS = Si-*t*-$BuPh_2$.

confirmed its structure and those of its precursors and revealed the undesired regioselectivity of the Diels–Alder reaction.

Faced with this unfortunate regiochemical outcome, we then focused our attention on 3-hydroxy-2-pyrone (**52**, Scheme 7) as a diene in the Diels–Alder reaction. Although Corey[26] has demonstrated that this system would give the opposite regiochemical pathway from that required for our purposes, the pioneering work of Narasaka[27] afforded us the possibility for success in this endeavor. Scheme 7 demonstrates Narasaka's

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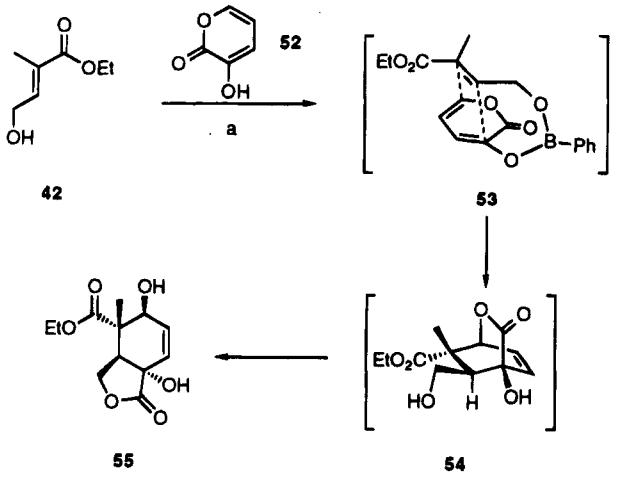
Scheme 7. Synthesis of Common C-Ring Intermediate **55**



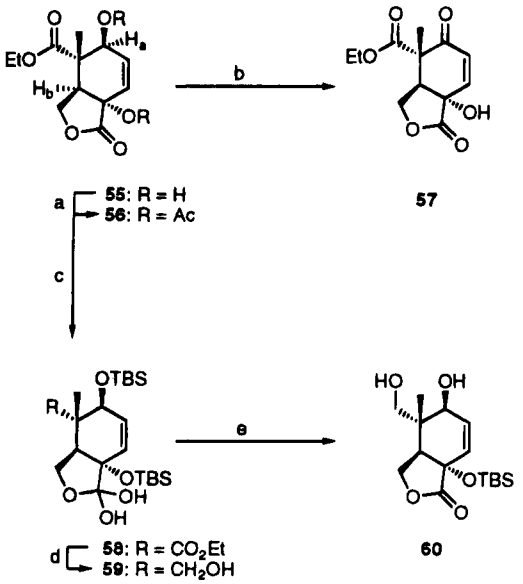
[a] Reagents and conditions: 1.4 equiv of **52**, 1.4 equiv of $PhB(OH)_2$, PhH, reflux (Dean–Stark trap), 48 h, then 1.4 equiv of 2,2-dimethyl-1,3-propanediol, 25 °C, 1 h, 79% based on 77% conversion of **42**.

principle of temporarily tethering the two reaction partners in order to dictate the regiochemistry of the Diels–Alder reaction. Thus, reaction of dienophile **42** (prepared from 1,3-dihydroxy-*cis*-2- butene (**37**), Scheme 6) with 2-hydroxy-2-pyrone (**52**) in the presence of phenylboronic acid under dehydrating conditions led, after decomplexation with excess 2,2-dimethyl-1,3-propanediol, to compound **55**. Evidently, the initially formed Diels–Alder product **54** promptly rearranges under the reaction conditions via intramolecular acyl transfer from the secondary to the primary hydroxyl group to afford the observed product in 79% yield based on 77% conversion of **42**.[28] Relief of strain in going from the [2.2.2] cycloaddition product **54** to the [3.4.0] bicyclic system **55** may be the primary reason for this facile rearrangement.

Scheme 8 demonstrates a number of useful transformations of compound **55** that led not only to confirmation of its structure but also to more advanced intermediates as required for our plans. Exhaustive acetylation of **55** led to diacetate **56** which exhibited significant downfield shifts in its proton NMR spectrum ($CDCl_3$, δ Ha, 4.59 → 5.84 and Hb, 3.10 → 3.90). Pyridinium dichromate (PDC) oxidation[29] of **55** furnished enone **57** in accord with the assigned structure (**55**), whereas persilylation of the same compound with TBSOTf[30] gave the *bis*(silyl ether) **58** isolated as a C20 hydrate. The latter compound underwent selective reduction with LAH in Et_2O at 0 → 25 °C to afford primary alcohol **59** (97% yield) which was monodesilylated with camphorsulfonic acid (CSA) in $MeOH:CH_2Cl_2$ to afford the crystalline lactone diol **60** in 94% yield. X-ray crystallographic analysis of **60** (see ORTEP drawing, Figure 2) confirmed its structure and those of its progenitors. An NMR experiment (500 MHz, $CDCl_3$) confirmed that neither acid (CSA) nor base (DMAP) causes any skeletal rearrangement of **55**, serving as a control for the reactions summarized in Scheme 8.

b. The First Attempt at a CD Ring System. Oxetane Is Formed but Interferes with Subsequent Chemistry. One of our early plans was to construct a CD ring system with the oxetane ring already in place before coupling with a ring A

Scheme 8. Structural Confirmation of **55**[a]



[a] Reagents and conditions: (a) 5.0 equiv of Ac_2O, 2.5 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 10 min, 100%; (b) 1.2 equiv of pyridinium dichromate (PDC), 4-Å molecular sieves, CH_2Cl_2, 25 °C, 1 h, 81%; (c) 4.0 equiv of *t*-$BuMe_2SiOTf$, 4.0 equiv of 2,6-lutidine, 0.1 equiv of DMAP, CH_2Cl_2, 0 °C, 4 h, 92%; (d) 1.1 equiv of $LiAlH_4$, Et_2O, 0 → 25 °C, 0.5 h, 97%; (e) 0.05 equiv of camphorsulfonic acid (CSA), CH_2Cl_2, MeOH, 25 °C, 1 h, 94%. TBS = Si-*t*-$BuMe_2$, Tf = SO_2CF_3.

hydrazone. To this end, diol **55** (Scheme 9) was dibenzylated using excess KH and benzyl bromide[31] to afford compound **61** which was then reduced with excess LAH in ether at 0 °C to give hydroxy lactol **62** as a 1:1 mixture of diastereoisomers (71% yield from **55**). Selective monoprotection of the primary alcohol using *tert*-butyldiphenylsilyl chloride (TPSCl) and imidazole in DMF[32] followed by further reduction of the lactol with LAH in THF at 25 °C furnished diol **64** in 78% yield. Reaction of **64** with pivaloyl chloride (1.05 equiv) under basic conditions led to a 1:3.2 mixture of the two pivaloate esters **65** and **66** which were chromatographically separated.

The next task was the introduction of an alcohol at C5. Even though a previous study[33] had shown that the primary hydroxyl group in a similar system could be used to direct the hydroboration of the cyclohexene double bond, the feasibility of using a mesylate (SO_2CH_3) as a possible directing group in this hydroboration[34] was explored. Such a method would more efficiently lead to the targeted oxetane system. Indeed hydroboration of **68**, prepared from **65** by standard mesylation, with borane in THF (0–25 °C) followed by oxidative workup, led to the formation of the C5 alcohol **69** as the major product and in 53% yield. Treatment of the latter compound with NaH in THF at 45 °C resulted in the formation of oxetane **70** in 86% yield, confirming the stereochemical orientation of the newly generated alcohol in **69**. Attempts to reach the targeted C2 aldehyde were, however, thwarted by failure to cleanly remove the pivaloate group from **70**, presumably due to interference from the oxetane ring under the reductive or basic conditions employed in these attempts. Nevertheless, this sequence confirmed the potential feasibility of constructing the oxetane ring by this method and rendered the aldehyde **67**

(28) For obvious practical reasons, large-scale reactions are performed with 1.0 equiv of diene and dienophile each and 0.95 equiv of $PhB(OH)_2$; diol **55** is typically obtained in ca. 60% yield based on ca. 50% conversion. The crude starting material mixture is recycled in the same process.

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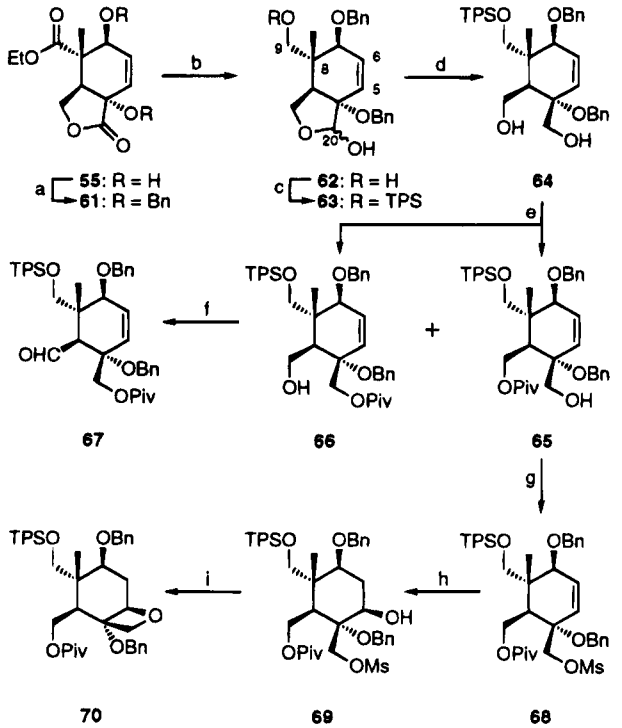
Scheme 9. Synthesis of Oxetane-Containing C-ring **70**[a]



[a] Reagents and conditions: (a) 3.5 equiv of $PhCH_2Br$, 3.5 equiv of KH, 0.05 equiv of n-Bu_4NI 0 °C → 25 °C, 2 h, 75%; (b) 2.0 equiv of $LiAlH_4$, Et_2O, 0 °C, 1 h, 94%; (c) 1.4 equiv of TPSCl, 1.5 equiv of imidazole, DMF, 0 °C, 2 h, 25 °C, 4 h, then excess n-Bu_4NF, THF, 10 h, 82% based on 54% conversion; (d) 1.3 equiv of $LiAlH_4$, THF, 0 °C → 25 °C, 0.5 h, 96%; (e) 1.05 equiv of PivCl, 1.5 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0 °C, 0.5 h, 55% of **66**, plus 17% of **65**, plus 24% of C2−C20 dipivalate, based on 84% conversion; (f) 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 1.5 equiv of 4-methylmorpholine N-oxide (NMO), CH_3CN, 25 °C, 1.5 h, 91%; (g) 1.5 equiv of MsCl, 2.0 equiv of DMAP, CH_2Cl_2, 0 °C → 25 °C, 1.5 h, 95%; (h) 10 equiv of BH_3·THF, THF, 25 °C, 10 h, then excess H_2O_2, aqueous $NaHCO_3$, 53%; (i) 5.0 equiv of NaH, THF, 45 °C, 3 h, 86%. Bn = CH_2Ph, TPS = Si-t-$BuPh_2$, Piv = CO-t-Bu, Ms = SO_2CH_3.

available through oxidation of **66** using the TPAP−NMO method.[20] The latter compound was utilized in a subsequent attempt to construct the ABC ring skeleton of Taxol (**1**) as will be discussed in a later section of this paper.

c. A Second Attempt at the CD Ring System. Success but the Oxetane Ring Interferes Again after the Shapiro Coupling. After our first attempt to construct a suitable CD aldehyde failed, we quickly redesigned our approach, choosing new protecting groups and targeting aldehyde **79** as a potential electrophile for the Shapiro coupling. Scheme 10 outlines the chemistry involved in this second approach. Thus, upon treatment with KH and TBSCl, intermediate **55** underwent skeletal rearrangement involving acyl migration from the primary to the secondary hydroxyl group, presumably driven by trapping of the primary hydroxyl as a silyl ether, to afford **71**. Protection of the tertiary alcohol as a methoxymethyl (MOM) ether[7] led to **72**. Reduction of the ester and lactone functionalities in **72** using excess LAH in THF formed triol **73**. Introduction of the benzylidene group[35] protected the C7−C9 diol system in the latter compound, furnishing **74** in 72% yield from **72**. The possibility of generating a C7 benzyl, C9 hydroxy derivative directly from the benzylidene[36] dictated the choice of this protecting group. Directed hydroboration of olefin

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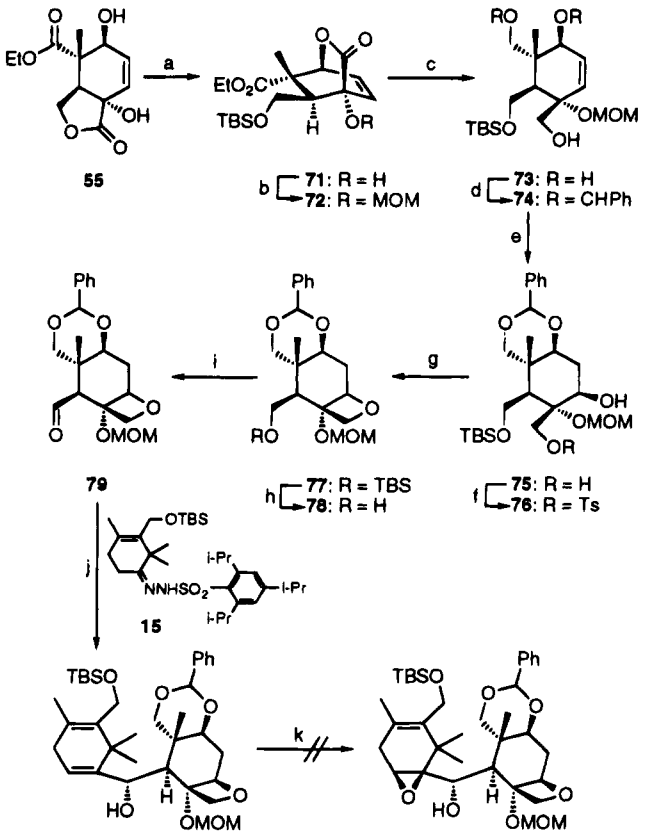
Scheme 10. Synthesis of ACD Ring System **81**[a]



[a] Reagents and conditions: (a) 2.0 equiv of KH, 1.2 equiv of TBSCl, THF, 25 °C, 0.5 h, 61%; (b) 2.0 equiv of MOMCl, 1.5 equiv of KH, CH_2Cl_2, 25 °C, 12 h, 92%; (c) 5.0 equiv of $LiAlH_4$, THF, 25 °C, 1 h; (d) 3.8 equiv of $PhCH(OMe)_2$, 0.05 equiv of camphorsulfonic acid (CSA), CH_2Cl_2, 25 °C, 72% from **72**; (e) 3.0 equiv of BH_3·THF, THF, 25 °C, 10 h, then excess H_2O_2, aqueous $NaHCO_3$, 37%; (f) 1.6 equiv of TsCl, 3.0 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 5 h; (g) 2.2 equiv of NaH, THF, 45 °C, 10 h, 78% from **75**; (h) excess n-Bu_4NF, THF, 25 °C, 2 h, 95%; (i) 3.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 2 h, 91%; (j) 1.2 equiv of **15**, 2.4 equiv of n-BuLi, THF, −78 °C, 0.5 h, 80%, then 0 °C; 1.0 equiv of **79**, THF, 0 °C, 0.5 h, 85% (*ca.* 5:3 mixture); (k) excess t-BuOOH, 0.05 equiv of $VO(acac)_2$, PhH, 25 °C, 2 h. MOM = methoxymethyl, TBS = Si-t-$BuMe_2$, Ts = SO_2-p-Tol, acac = acetylacetonate.

74 resulted in the formation of the C5 β-hydroxy compound **75** in 37% yield. Tosylation (80%) of the latter followed by exposure to NaH in THF at 45 °C led to oxetane **77** (78%) via tosylate **76**. Finally, desilylation of **77** using TBAF,[37] followed by Dess−Martin oxidation,[38] furnished aldehyde **79** via **78** in 86% overall yield. The Shapiro reaction proceeded well in combining hydrazone **15** and aldehyde **79** to produce alcohol **80** (85%, mixture of diastereoisomers, Scheme 10). Epoxide **81** could not, however, be cleanly obtained from the major isomer **80** using the vanadium-catalyzed procedure.

Due to the problems encountered in the two approaches discussed above, the strategy of having the oxetane installed in the molecule prior to the coupling reactions was abandoned in favor of schemes involving oxetane construction at a later stage.

d. Successful Progression to the McMurry Cyclization Stage. Having just experienced the complications of the highly

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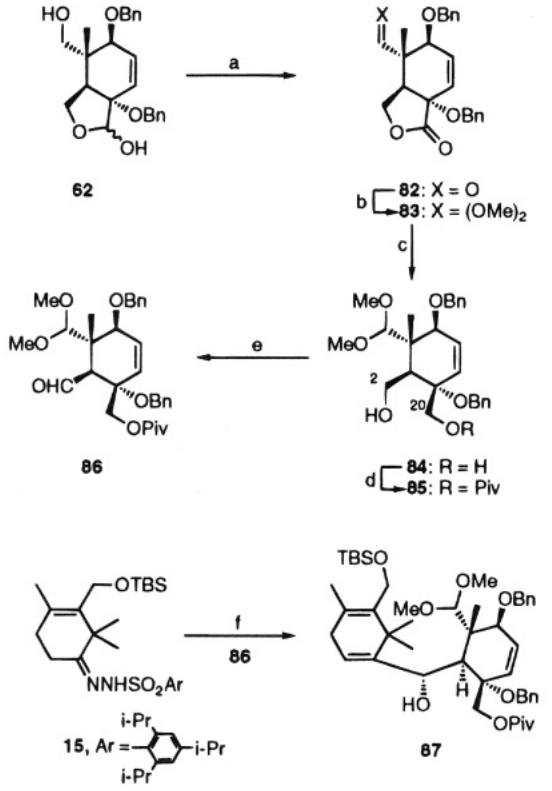
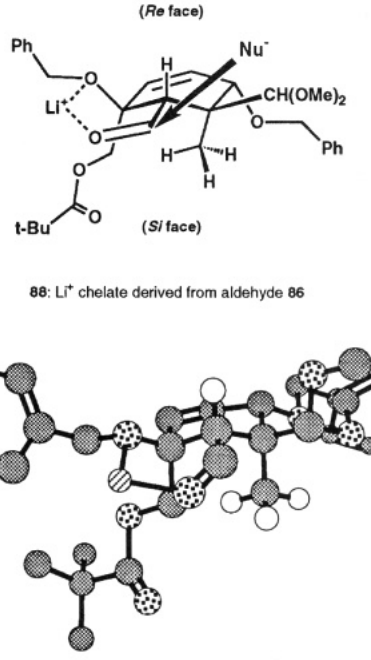
Scheme 11. Synthesis of A−C Ring System **87**[a]



[a] Reagents and conditions: (a) 3.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 0 °C → 25 °C, 12 h; (b) excess of $HC(OMe)_3$, 0.05 equiv of camphorsulfonic acid (CSA), MeOH, CH_2Cl_2, 25 °C, 12 h, 81% from **62**; (c) 1.2 equiv of $LiAlH_4$, THF, reflux, 1 h; (d) 1.5 equiv of PivCl, 5.0 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0 °C, 15 min, 70% from **83**; (e) 1.7 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 1.5 h, 83%; (f) **15**, 2.2 equiv of *n*-BuLi, THF, −78 °C, 0.5 h, then 0 °C; 1.2 equiv of **86**, THF, −40 °C, 5 min, 74%. Bn = CH_2Ph, Piv = CO-*t*-Bu, TBS = Si-*t*-$BuMe_2$.

oxygenated intermediates of the previous schemes, we decided to minimize such problems by targeting aldehyde **86** (Scheme 11). Oxidation of intermediate **62**, readily available as described in Scheme 10, with Dess−Martin[38] reagent afforded aldehyde lactone **82**. Protection of the aldehyde as a methoxy acetal[39] produced compound **83** (81% yield from **62**) which was then reduced with LAH in THF at reflux to give diol **84**. Treatment of the latter compound with pivaloyl chloride in the presence of DMAP[40] selectively protected the C20 alcohol as a pivaloate ester, leading to intermediate **85** in 70% yield from **83**. Molecular models revealed the C2 hydroxyl group of **84** to be more crowded [interference from bis(methoxy) group] than the C20 hydroxyl group (pseudo axial position) and thus the selectivity observed. Finally, oxidation with either TPAP−NMO[20] or Dess−Martin reagent[38] easily converted compound **85** to aldehyde **86** (83% yield).

With the aldehyde **86** in hand, we then proceeded to the Shapiro reaction utilizing hydrazone **15** as the precursor to the vinyllithium reagent. This coupling reaction furnished alcohol **87** as a single diastereoisomer in 74% yield. X-ray crystallographic analysis allowed the assignment of the stereochemistry of this intermediate (see ORTEP drawing, Figure 2). The stereoselectivity of this reaction can be explained by invoking 6-membered ring chelate intermediate **88**, as shown in Figure 3. In this model, the *re* face of the aldehyde is more accessible to nucleophilic attack than the *si* face due to shielding by the C8 methyl and C20 pivaloyl groups.



88: Li^+ chelate derived from aldehyde **86**

Figure 3. Stereoselectivity of the Shapiro reaction. The model was generated with Chem3d, most hydrogens are omitted for clarity.

Early attempts to unblock the aldehyde group of **87** under acidic conditions failed due to formation of a cyclic hemiacetal with the C2 hydroxyl group. Epoxidation of the allylic system in **87** proved rather slow and, therefore, the C20 hydroxyl group was called upon to assist in this reaction. Treatment of **87** with LAH in ether resulted in the formation of diol **89** (88% yield) which underwent smooth epoxidation with ^{t}BuOOH in the presence of $VO(acac)_2$ catalyst to afford epoxide **90** in 82% yield (Scheme 12).

At this point our plan involved engaging the two hydroxyl groups of our latest intermediate (**90**) in a cyclic system in order to both prevent the undesired hemiacetal formation and to preorganize the substrate prior to the construction of ring B. To this end, diol **90** was treated with phosgene in the presence of pyridine[41] in an attempt to produce the 7-membered ring carbonate. These conditions, however, produced exclusively the tetrahydrofuran derivative **91**, presumably via nucleophilic attack by the C2 hydroxyl group on the activated C20 chloroformyl intermediate. To circumvent this problem, both alcohols were engaged in a cyclic lactone by exposure of diol **90** to Dess−Martin reagent,[38] giving the γ-lactone **92** in 61% yield.

Removal of the silyl group from compound **92**, followed by oxidation with Dess−Martin reagent,[38] afforded aldehyde **94**, via intermediate alcohol **93**, in 71% overall yield. Revealing the C9 aldehyde by exposure to trifluoroacetic acid[42] (TFA) at 0 °C, produced, in addition to dialdehyde **95** (51% yield), the conjugated system **96** (24%) (Scheme 13), presumably arising from **95** via acid-induced epoxide opening.

Several attempts to cyclize dialdehyde **95** using the McMurry reaction under a variety of conditions were unsuccessful. The only detectable product was the diol **97**, apparently produced by reduction of both aldehyde groups. It became clear that this particular design did not favor the required ring closure and that we had to design yet another synthetic sequence.

e. First Attempt with the C1−C2-Carbonate Approach. Aiming to enforce a different conformation in the McMurry substrate, we decided to introduce a C1−C2-carbonate ring.

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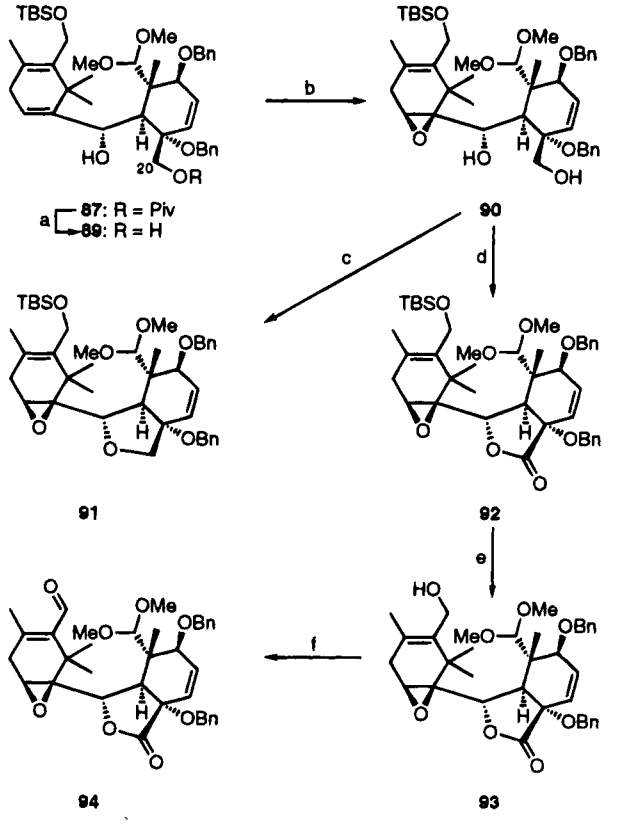
(40) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(41) Haworth, W. N.; Porter, C. R. *J. Chem. Soc.* **1930**, 151.
(42) Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.

Scheme 12. Synthesis of Lactone **93**[a]

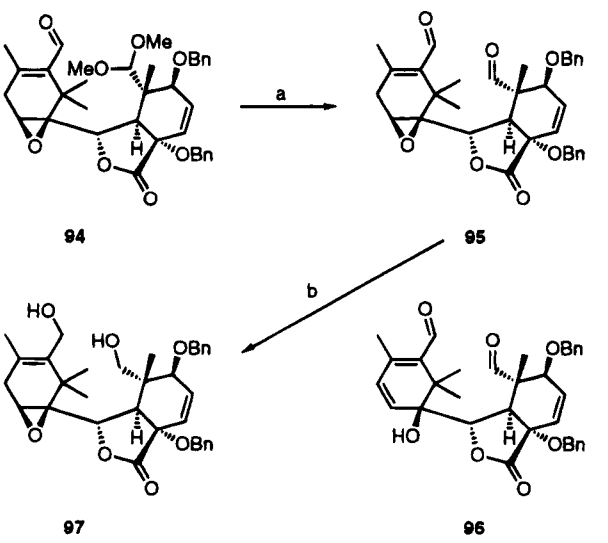


[a] Reagents and conditions: (a) 2.0 equiv of $LiAlH_4$, Et_2O, −10 °C, 5 min, 88%; (b) 2.0 equiv of *t*-BuOOH, 0.25 equiv of $VO(acac)_2$, PhH, 25 °C, 0.5 h, 82%; (c) 5.0 equiv of phosgene, pyridine, 75 °C, 2.5 h, 35%; (d) 10 equiv of Dess−Martin periodinane, CH_2Cl_2, 50 °C, 1 h, 61%; (e) excess *n*-Bu_4NF, THF, 25 °C, 2 h; (f) 5.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 0.5 h, 71% from **92**. TBS = Si-*t*-$BuMe_2$, Bn = CH_2Ph, Piv = CO-*t*-Bu, acac = acetylacetonate.

Molecular modeling (Sybyl) indicated that this functionality would preorganize the expected intermediate geometry by bringing the two aldehydes to the same face of the molecule. Learning from our previous experience with protecting groups, we decided to utilize aldehyde **67** (prepared as described in Scheme 9, above) and hydrazone **15** as partners for the Shapiro reaction. Thus (as shown in Scheme 14) the Shapiro reaction produced compound **98**, as a single isomer (stereochemistry confirmed by X-ray crystallographic analysis of subsequent intermediate **103**) in 82% yield. Deprotection with LAH afforded diol **99** (87% yield). Vanadium-catalyzed epoxidation of **99** with ^{t}BuOOH led stereoselectively to epoxide **100** in 95% yield. Regioselective epoxide opening with LAH gave triol **101** in 78% yield based on 81% conversion. Selective protection of the primary alcohol in **101** as a MOM ether proceeded smoothly under standard conditions to afford compound **102** in almost quantitative yield. Diacetate **103** was prepared using acetic anhydride and DMAP (83% yield). X-ray crystallographic analysis of the latter compound confirmed the previously proposed stereochemistry (see ORTEP drawing, Figure 2).

By this time both our model studies and degradation work[1] pointed to a carbonate protecting group at C1−C2 as the most suitable device for our synthetic scheme. In order to install the latter into our intermediate (**102**), it was necessary to use rather strong conditions (excess KH, phosgene, ether:HMPA, 1:1, 25 °C, 88% yield based on 57% conversion) as compared to those used in making the taxoid carbonate II.[1] The flexibility of the 1,2-diol **102** as compared to the rigidity of the corresponding taxoid diol employed in the degradation studies is

Scheme 13. First Attempt at the McMurry Cyclization[a]



[a] Reagents and conditions: (a) trifluoroacetic acid neat, 0 °C, 15 min, 51%; (b) 10 equiv of $TiCl_3$·$(DME)_{1.5}$, 15 equiv of Zn−Cu, DME, 60 °C, 4 h, **95** added over 5 h (syringe pump), then 55 °C, 3 h, 34% based on 43% conversion. Bn = CH_2Ph.

probably responsible for this relative unreactivity. The carbonate **104** was then desilylated with fluoride ion and oxidized with TPAP−NMO[20] to afford dialdehyde **106** via the corresponding diol (**105**) in 80% overall yield.

With the requisite dialdehyde **106** in hand, we proceeded to investigate its conversion to a cyclic taxoid system through McMurry coupling. In traversing the temperature range from 0 to 70 °C, no cyclic coupling products were observed; at 85 °C, however, a 15% yield of the cyclic olefin **107** (Scheme 14) was isolated, suggesting that the desired cyclic diol might remain elusive even with these rigid precursors. The conclusion was that further preorganization was needed in order to lower the activation energy to avoid deoxygenation of carbons 9 and 10 during the McMurry cyclization.

Conclusion

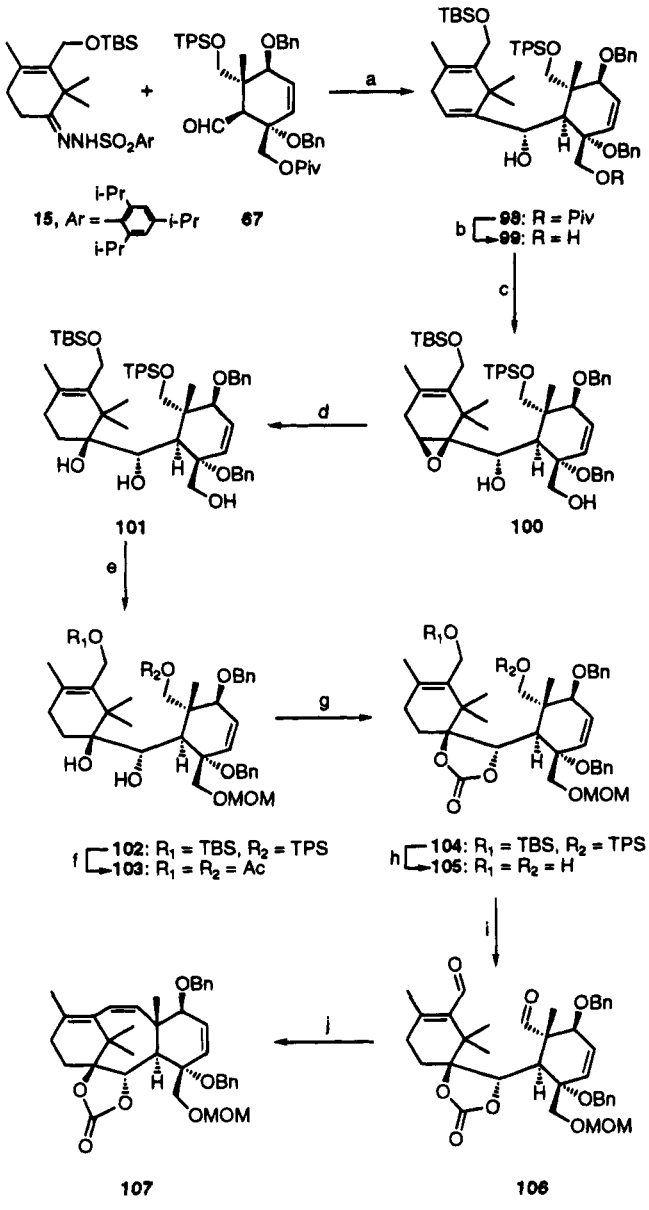
In this paper we described the evolution of the chemistry that eventually led to a successful construction of a taxoid system containing the ABC ring framework of Taxol (**1**). While the construction of a suitable ring A fragment proceeded smoothly via a Diels−Alder approach, that of a suitable ring C fragment presented more difficulties. Although the highly functionalized and stereochemically defined ring C intermediate was easily produced via a boron template controlled reaction, the finetuning of the functional groups for proper elaboration required considerable experimentation. Through the process of design, experimentation, and redesign, however, enough knowledge was gathered that made the final push toward a suitable ABC taxoid ring system possible. This final and successful approach is discussed in the following paper.

Experimental Section

General Techniques. For a description of general technique, see the first paper in this series.[1] Experimental techniques and data for compounds **10**−**14**, **16**, **18**−**35**, **47**−**51**, **57**, **58**, **61**−**80**, **82**−**87**, and **89**−**107** can be found in the supplementary material.

Diene 3. A solution of ketone **2** (245.0 g, 1.44 mol) in Et_2O (1500 mL) at 0 °C was treated with methylmagnesium bromide (576 mL of a 3.0 M solution in Et_2O, 1.73 mol). The reaction mixture was allowed to warm to 25 °C and stirred for 8 h. After cooling to 0 °C, the reaction was quenched with aqueous NH_4Cl (600 mL). The organic layer was separated and washed with H_2O (2 × 400 mL) and brine (400 mL).

Scheme 14. Formation of the ABC taxoid system **107** by a McMurry cyclization[a]



[a] Reagents and conditions: (a) 1.3 equiv of **15**, 2.6 equiv of *n*-BuLi, THF, −78 °C, 0.5 h, then 0 °C, 1.0 equiv of **67**, THF, −78 °C, 20 min, 82%; (b) 2.0 equiv of $LiAlH_4$, Et_2O, 25 °C, 0.5 h, 87%; (c) 2.0 equiv of *t*-BuOOH, 0.05 equiv of $VO(acac)_2$, PhH, 25 °C, 0.5 h, 95%; (d) 15 equiv of $LiAlH_4$, Et_2O, 25 °C, 3 h, 78% based on 81% conversion; (e) 10 equiv of MOMCl, 12 equiv of *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 10 h, 99%; (f) excess *n*-Bu_4NF (TBAF), THF, 25 °C, 2 h, then 4.0 equiv of Ac_2O, 6.0 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 2 h, 83%; (g) 5.0 equiv of phosgene, 5.0 equiv of KH, Et_2O, HMPA, 25 °C, 1 h, 88% based on 57% conversion; (h) excess TBAF, THF, 25 °C, 1 h, 88%; (i) 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 3.0 equiv of 4-methylmorpholine *N*-oxide (NMO), $CH_3CN-CH_2Cl_2$ (1:1), 25 °C, 0.5 h, 91%; (j) 10 equiv of $TiCl_3$·$(DME)_{1.5}$, 20 equiv of Zn−Cu, DME, reflux, 3 h, **106** added over 1 h, then 1.5 h, 15%. Piv = CO-*t*-Bu, TBS = Si-*t*-$BuMe_2$, Bn = CH_2Ph, TPS = Si-*t*-$BuPh_2$, MOM = methoxymethyl.

The combined aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to give the corresponding alcohol which was taken in the next step without further purification.

A solution of the previous alcohol in benzene (600 mL) was treated with *p*-toluenesulfonic acid (54 g, 276 mmol) and heated to 65 °C for 3 h. After being cooled to 25 °C, the reaction mixture was treated with Et_3N (39 mL, 280 mmol), diluted with Et_2O (600 mL), washed with H_2O (400 mL), aqueous $NaHCO_3$ (400 mL), and brine (400 mL), dried ($MgSO_4$), concentrated (bath temperature <30 °C), and distilled (40−45 °C, 0.05 mmHg) to give **3** (169 g, 70%) as a colorless liquid: R_f = 0.35 (silica, 2% Et_2O in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (d, *J* = 1.0 Hz, 1 H, HC=C), 4.74 (d, *J* = 1.0 Hz, 1 H, HC=C), 4.14 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 1.97 (s, 3 H, $CH_3C=CH_2$), 1.80 (s, 3 H, $CH_3C=C$), 1.78 (s, 3 H, $CH_3C=C$), 1.24 (t, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$).

Alcohol 4. A solution of ester **3** (169 g, 1.01 mol) in CH_2Cl_2 (1000 mL) at −78 °C was treated with diisobutylaluminum hydride (2220 mL of a 1.0 M solution in CH_2Cl_2, 2.22 mol) and stirred at −78 °C for 0.5 h. The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was slowly poured into a mixture of ice (600 mL) and glacial acetic acid (300 mL), and the resulting mixture was stirred for 3.5 h. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layer was washed with brine (2 × 500 mL), dried ($MgSO_4$), concentrated (bath temperature <25 °C), and purified by flash chromatography (silica, 20% Et_2O in petroleum ether) to give **4** (117.4 g, 92%) as a pale yellow oil: R_f = 0.26 (silica, 20% Et_2O in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (b d, *J* = 1.0 Hz, 2 H, C=CH_2), 4.71 (b d, *J* = 1.0 Hz, 2 H, C=CH_2), 4.16 (s, 2 H, CH_2OH), 1.82 (t, *J* = 1.0 Hz, 3 H, $(CH_3)C=CH_2$), 1.76 (s, 3 H, C=$(CH_3)_2$), 1.71 (s, 3 H, C=$(CH_3)_2$).

Acetate 5. A solution of alcohol **4** (113.6 g, 0.9 mol) in CH_2Cl_2 (1000 mL) at 0 °C was treated with Et_3N (150.5 mL, 1.08 mol), 4-(dimethylamino)pyridine (DMAP, 22 g, 0.18 mol), and Ac_2O (94.3 mL, 1.0 mol). The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was washed with H_2O (2 × 300 mL) and brine (300 mL), and the combined aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 5% Et_2O in petroleum ether) to give **5** (145.4 g, 96%) as a pale yellow oil: R_f = 0.66 (silica, 20% Et_2O in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (s, 1 H, C=CH_2), 4.64 (s, 3 H, C=CH_2 and CH_2OAc), 2.02 (s, 3 H, $COCH_3$), 1.77 (s, 3 H, $CH_3C=C$), 1.75 (s, 3 H, $CH_3C=C$), 1.71 (s, 3 H, $CH_3C=C$).

Chloro Nitrile 7. A mixture of diene **5** (90.3 g, 537 mmol) and freshly distilled 2-chloroacrylonitrile (65 mL, 806 mmol, purchased from Tokyo-Kasei) was stirred at 130 °C in a sealed tube for 72 h. During the course of the reaction, the reaction mixture turned dark brown. The reaction mixture was allowed to cool to 25 °C and purified by flash chromatography (silica, 10% Et_2O in petroleum ether) to give **7** (110 g, 80%) as clear crystals: mp 86−88 °C, from Et_2O; R_f = 0.25 (silica, 10% Et_2O in petroleum ether); IR (thin film) ν_{max} 2979, 2938, 1730, 1436, 1370, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2 H, CH_2OAc), 2.48−2.29 (band, 4 H, 13-CH_2 and 14-CH_2), 2.07 (s, 3 H, $COCH_3$), 1.75 (s, 3 H, 18-CH_3), 1.39 (s, 3 H, 16-CH_3), 1.28 (s, 3 H, 17-CH_3); FAB HRMS (NBA/CsI) *m/e* 388.0080, M + Cs^+ calcd for $C_{13}H_{18}ClO_2N$ 388.0080.

Hydroxy Ketone 8. A solution of chloro nitrile **7** (15 g, 58.7 mmol) and KOH (19.8 g, 352 mmol) in *t*-BuOH (293 mL) was heated to 70 °C and stirred for 4 h. After being cooled to 25 °C, the reaction mixture was diluted with EtOAc (1000 mL) and washed with H_2O (2 × 300 mL) and brine (300 mL). The combined aqueous layer was extracted with EtOAc (4 × 200 mL), and the combined organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 30% EtOAc in benzene) to give **7** (4.5 g, 30%) and **8** (6.2 g, 90% based on 70% conversion) as a pale orange oil: R_f = 0.30 (silica, 30% EtOAc in benzene); IR (thin film) ν_{max} 3410, 2980, 2930, 1710, 991 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (s, 2 H, CH_2OH), 2.53 (t, *J* = 8.5 Hz, 2 H, 13-CH_2), 2.38 (t, *J* = 8.5 Hz, 2 H, 14-CH_2), 1.84 (s, 3 H, 18-CH_3), 1.44 (b s, 1 H, OH), 1.19 (s, 6 H, 16-CH_3 and 17-CH_3); FAB HRMS (NBA/NaI) *m/e* 191.1048, M + Na^+ calcd for $C_{10}H_{16}O_2$ 191.1050.

TBS Ether 9. A solution of alcohol **8** (4.00 g, 23.8 mmol) and imidazole (1.95 g, 28.6 mmol) in CH_2Cl_2 (40 mL) at 0 °C was treated with *tert*-butyldimethylsilyl chloride (TBSCl, 3.96 g, 26.2 mmol), allowed to warm to 25 °C, and stirred for 2 h. After dilution with Et_2O (300 mL), the reaction mixture was washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 5 → 10% Et_2O in petroleum ether) to give **9** (5.71 g, 85%) as a pale yellow oil: R_f = 0.48 (silica, 10% Et_2O in petroleum ether); IR (thin film) ν_{max} 2929, 2857, 1716, 1462, 1377, 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 2 H, 10-CH_2), 2.51

(t, J = 7.0 Hz, 2 H, 13-CH_2), 2.36 (t, J = 7.0 Hz, 2 H, 14-CH_2), 1.74 (s, 3 H, 18-CH_3), 1.18 (s, 6 H, 16-CH_3 and 17-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.05 (s, 6 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 135.6, 131.8, 59.2, 41.2, 35.7, 30.5, 25.8, 24.6, 22.5, 18.2, −5.5; FAB HRMS (NBA/CsI) *m/e* 697.3056, M + Cs^+ calcd for $C_{16}H_{30}O_2Si$ 697.3085.

TBS Hydrazone 15. A solution of ketone **9** (2.79 g, 9.88 mmol) in THF (33 mL) at 25 °C was treated with (2,4,6-triisopropylbenzenesulfonyl)hydrazine (2.95 g, 9.88 mmol) and stirred for 24 h. The reaction mixture was concentrated, and the solid residue was dissolved in a minimum amount of Et_2O (10 mL). The solution was diluted with petroleum ether (50 mL) and cooled to −20 °C to induce crystallization. After removal of the mother liquor by filtration, the crystalline material was washed with petroleum ether (30 mL) and dried in vacuo to give **15** (4.89 g, 88%) as colorless crystals: mp 135−137 °C, from Et_2O−petroleum ether; R_f = 0.24 (silica, 20% Et_2O in petroleum ether); IR (thin film) ν_{max} 3250, 2957, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (b s, 1 H, NH), 7.21 (s, 2 H, Ar), 4.28 (septet, J = 7.0 Hz, 2 H, *o*-$CH(CH_3)_2$), 4.14 (s, 2 H, 10-CH_2), 2.95 (septet, J = 7.0 Hz, 1 H, *p*-$CH(CH_3)_2$), 2.44 (t, J = 7.0 Hz, 2 H, 13-CH_2), 2.21 (t, J = 7.0 Hz, 2 H, 14-CH_2), 1.75 (s, 3 H, 18-CH_3), 1.33 (d, J = 7.0 Hz, 12 H, *o*-$CH(CH_3)_2$), 1.32 (d, J = 7.0 Hz, 6 H, *p*-$CH(CH_3)_2$), 1.13 (s, 6 H, 16-CH_3 and 17-CH_3), 0.92 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.10 (s, 6 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 152.9, 151.1, 136.0, 131.5, 131.4, 124.0, 123.4, 59.0, 42.2, 34.1, 30.6, 29.8, 26.0, 26.0, 25.9, 25.9, 25.8, 24.9, 24.8, 24.7, 24.6, 23.5, 21.4, 19.5, 18.3, −5.4; FAB HRMS (NBA) *m/e* 563.3716, M + H^+ calcd for $C_{31}H_{54}O_3N_2SSi$ 563.3703.

Aldehyde 39. A solution of 1,4-dihydroxy-*cis*-2-butene (137 g, 1.56 mol) and *p*-toluenesulfonic acid (1.35 g, 7 mmol) in CH_2Cl_2 (2000 mL) at 25 °C was treated with dihydropyran (300 mL, 3.29 mol), dropwise, over the period of 0.5 h. After being stirred for 10 min, the mixture was treated with Et_3N (2.0 mL, 14 mmol), reduced in volume to a total of 2 L, treated with decolorizing carbon, filtered through a pad of silica gel, and concentrated to give a yellow oil that was taken to the next step without further purification: R_f = 0.30 (silica, 25% EtOAc in hexanes); IR (thin film) ν_{max} 2950, 2800, 1200, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.65 (t, J = 5.0 Hz, 2 H, CH), 4.55 (b s, 2 H, OCHO), 4.19 (m, 2 H, CH_2CH_2O), 4.03 (m, 2 H, CH_2CH_2O), 3.77 (m, 2 H, $CHCH_2O$), 3.42 (m, 2 H, OCH_2CH), 1.75−1.43 (band, 12 H, CH_2); ^{13}C NMR (125 Hz, $CDCl_3$) δ 129.0, 97.7, 62.6, 61.9, 30.4, 25.3, 19.2; FAB HRMS (NBA/NaI) *m/e* 279.1572, M + Na^+ calcd for $C_{14}H_{24}O_4$ 279.1572.

A solution of the previous alkene (200 g, 0.78 mol) in CH_2Cl_2 (600 mL) was treated with ozone at −78 °C until the solution turned blue. The reaction was quenched by the careful addition of triphenylphosphine (205 g, 0.78 mol) in portions. The mixture was allowed to warm to 25 °C over the period of 8 h, concentrated, washed with Et_2O (3 × 500 mL), and filtered. The combined washes were concentrated and purified by flash chromatography (silica, 25% EtOAc in hexanes) to give aldehyde **39** (220 g, 98%) as a clear oil: R_f = 0.20 (silica, 25% EtOAc in hexanes); IR (thin film) ν_{max} 2944, 2889, 1739, 1136, 1078, 1033; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1 H, HCO), 4.63 (t, J = 4.0 Hz, 1 H, OCHO), 4.22 (d, J = 18.0 Hz, A of AB, $COCH_2O$), 4.16 (d, J = 18.0 Hz, B of AB, $COCH_2O$), 3.83 (m, 2 H, CH_2CH_2O), 3.50 (m, 2 H, CH_2CH_2O), 2.00 − 1.50 (band, 4 H, CH_2); ^{13}C NMR (125 Hz, $CDCl_3$) δ 201.2, 99.4, 72.9, 62.5, 30.2, 25.1, 19.6; FAB HRMS (NBA/NaI) *m/e* 167.0684, M + Na^+ calcd for $C_7H_{12}O_3$ 167.0684.

Silyl Ether 40. Aldehyde 38 from 36. To a solution of allylic alcohol **36** (11.6 g, 200.0 mmol) and imidazole (15.7 g, 230.9 mmol) in DMF (200 mL) was added *tert*-butylchlorodiphenylsilane (58.4 mL, 220.0 mmol) dropwise at 0 °C. The solution was stirred at 0 °C for 1 h. After dilution with Et_2O (500 mL), the solution was washed with aqueous NH_4Cl (100 mL), H_2O (3 × 50 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated to give the corresponding crude silyl ether (66.2 g) which was taken to the next step without further purification.

A fraction of the crude silyl ether (13.0 g) was dissolved in CH_2Cl_2 (300 mL) and treated with O_3 at −78 °C for 1 h. The reaction was quenched with Ph_3P (25.0 g, 96.0 mmol) at −78 °C, and the resulting mixture was allowed to warm to 25 °C. After being stirred at 25 °C for 0.5 h, the reaction mixture was diluted with toluene (100 mL) and concentrated to give crude aldehyde **38** as a yellowish solid (40.7 g) which was taken to the next step without further purification.

Aldehyde 38: R_f = 0.60 (silica, 50% Et_2O in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1 H, CHO), 7.67−7.37 (band, 10 H, Ar), 4.21 (s, 2 H, CH_2), 1.09 (s, 9 H, *t*-Bu).

Conversion of 38 to 40. To a solution of the crude aldehyde **38** (13.2 g) in CH_2Cl_2 (200 mL) was added (carbethoxyethylidene)-triphenylphosphorane (22.3 g, 62.0 mmol) in one portion. The reaction mixture was stirred at 25 °C for 20 h, concentrated, and purified by flash chromatography (silica, 5 → 10% Et_2O in petroleum ether) to give **40** (13.7 g, 91% from **36**) as an oil: R_f = 0.80 (silica, 20% Et_2O in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.36 (band, 10 H, Ar), 6.87 (t, J = 5.6 Hz, CH=), 4.36 (d, J = 5.6 Hz, 2 H, CH_2), 4.20 (q, J = 7.2 Hz, 2 H, $COOCH_2$), 1.64 (s, 3 H, Me), 1.30 (t, J = 7.2 Hz, 3 H, $COOCH_2CH_3$), 1.05 (s, 9 H, *t*-Bu).

Ester 41. A solution of aldehyde **39** (159 g, 1.10 mol) in CH_2Cl_2 (600 mL) at 0 °C was treated with a solution of (carbethoxymethylene)-triphenylphosphorane (408 g, 1.13 mol) in CH_2Cl_2 (1200 mL) over the period of 4 h. The solution was allowed to warm to 25 °C and stirred for 18 h. The mixture was concentrated, suspended in 30% Et_2O in hexanes, and filtered through a pad of silica gel to give **41** (222 g, 90%) as an oil: R_f = 0.40 (silica, 30% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (m, 1 H, =CH), 4.59 (m, 1 H, OCHO), 4.37 (m, 1 H, A of AB, CH_2CH_2O), 4.13 (band, 3 H, $=CCH_2O$ and CH_3CH_2O), 3.80 (m, 1 H, B of AB, CH_2CH_2O), 3.47 (m, 1 H, B of AB, $=CCH_2O$), 1.79 (s, 3 H, CH_3), 1.76−1.47 (band, 6 H, CH_2), 1.23, (t, J = 7.0 Hz, 3 H, CH_3CH_2).

Alcohol 42. A solution of ether **41** (222 g, 0.97 mol) in MeOH (2500 mL) at 25 °C was treated with *p*-toluenesulfonic acid (1 g) and stirred at 25 °C for 18 h. The mixture was treated with Et_3N (2 mL), concentrated, redissolved in EtOAc (1500 mL), washed with aqueous $NaHCO_3$ (2 × 100 mL), H_2O (2 × 100 mL), and brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to give a clear oil that was purified by flash chromatography (silica, 40% ethyl acetate in hexanes) to give **42** (128 g, 92%) as a colorless oil: R_f = 0.20 (silica, 30% EtOAc in hexanes); IR (thin film) ν_{max} 3434, 2983, 2934, 1713, 1650, 1446, 1368, 1261, 1132, 1031, 731; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (b s, 1 H, =C*H*), 4.11 (d, J = 6.0 Hz, 2 H, OCH_2CH), 3.98 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 3.90 (s, 1 H, OH), 1.61 (s, 3 H, CH_3C), 1.09 (t, J = 7.0 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 Hz, $CDCl_3$) δ 167.5, 140.6, 127.5, 60.4, 58.8, 13.7, 12.0; FAB HRMS (NBA/CsI) *m/e* 276.9841, M + Cs^+ calcd for $C_7H_{12}O_3$ 276.9846.

Diol 55. A. Small-Scale Procedure. A mixture of dienophile **42** (1.44 g, 10 mmol), diene **52** (1.52 g, 13.6 mmol), and $PhB(OH)_2$ (1.7 g, 13.9 mmol) in benzene (30 mL) was stirred at reflux with azeotropic removal of water (Dean−Stark trap) for 48 h. After the solution was cooled to 25 °C, the reaction was quenched with 2,2-dimethyl-1,3-propanediol (1.45 g, 13.9 mmol) and the resulting mixture was stirred at 25 °C for 1 h, concentrated, and purified by flash chromatography (silica, 10 → 50% EtOAc in hexanes) to give dienophile **42** (0.33 g, 23%), diene **52** (0.51 g, 34%), and diol **55** (1.56 g, 79% based on 77% conversion) as a yellow oil.

B. Large-Scale Procedure. A mixture of dienophile **42** (70.0 g, 0.49 mol), diene **52** (54.4 g, 0.49 mol), and $PhB(OH)_2$ (56.3 g, 0.45 mol) in benzene (1000 mL) was stirred at reflux with azeotropic removal of water (Dean−Stark trap) for 144 h. After the solution was cooled to 25 °C, the reaction was quenched with 1,3-propanediol (36.8 mL, 0.51 mol) and the resulting mixture was stirred at 25 °C for 2.5 h, concentrated, and purified by flash chromatography (silica, 10 → 50% EtOAc in hexanes) to give dienophile **42** and diene **52** (64.7 g, 52%, 1:1 mixture), plus diol **55** (34.88 g, 58% based on 48% conversion) as a yellow oil: R_f = 0.13 (silica, 50% EtOAc in hexanes); IR (thin film) ν_{max} 3423, 2987, 1766, 1715, 1257, 1202, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (dd, J = 10.0, 4.0 Hz, 1 H, 6-H), 5.78 (b d, J = 10.0 Hz, 1 H, 5-H), 4.57 (dd, J = 9.5, 7.5 Hz, 1 H, 2-H), 4.57−4.55 (band, 1 H, 7-H), 4.42 (dd, J = 9.5, 8.5 Hz, 1 H, 2-H), 4.15 (q, J = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 4.18−4.12 (band, 1 H, 4-OH), 3.07 (b t, J = 8.5 Hz, 1 H, 3-H), 3.04 (b d, J = 5.0 Hz, 1 H, 7-OH), 1.25 (s, 3 H, 19-CH_3), 1.94 (t, J = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 175.6, 133.0, 124.9, 71.6, 66.8, 62.4, 47.3, 46.6, 42.0, 15.4, 13.8; FAB HRMS (NBA/NaI) *m/e* 279.0859, M + Na^+ calcd for $C_{12}H_{16}O_6$ 279.0845.

Bis(silyl ether) 58. A solution of diol **55** (28.5 g, 111 mmol), 2,6-lutidine (102 mL, 445 mmol), and 4-(dimethylamino)pyridine (DMAP, 1.50 g, 12.2 mmol) in CH_2Cl_2 (250 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 52.0 mL, 445 mmol) and stirred at 0 °C for 4 h. The reaction mixture was added to aqueous $NaHCO_3$ (100 mL), extracted with Et_2O (2 × 150 mL), washed with aqueous $CuSO_4$ (2 × 100 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 5 → 15% Et_2O in petroleum ether) to give **58** (49.6 g, 92%) as a white solid: R_f = 0.62 (silica, 15% Et_2O in petroleum ether); IR (thin film) ν_{max} 2960, 2936, 2857, 1746, 1256 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.19 (dd, J = 8.5, 5.0 Hz, 1 H, 6-H), 6.10 (dd, J = 8.5, 1.0 Hz, 1 H, 5-H), 4.12 (dd, J = 8.5, 4.5 Hz, 1 H, 2-H), 4.11 (dd, J = 5.0, 1.0 Hz, 1 H, 7-H), 3.83−3.70 (band, 2 H, $CO_2CH_2CH_3$), 3.40 (d, J = 8.5 Hz, 1 H, 2-H), 2.83 (d, J = 4.5 Hz, 1 H, 3-H), 1.22 (s, 3 H, 19-CH_3), 1.02 (s, 9 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.97 (s, 9 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.32 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.30 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.21 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.15 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6) δ 174.0, 133.5, 132.4, 119.0, 80.0, 70.9, 62.8, 60.6, 53.0, 45.9, 26.0, 25.9, 20.5, 18.4, 14.0; FAB HRMS (NBA/NaI) *m/e* 617.1731, M + Na^+ calcd for $C_{24}H_{44}O_6Si_2$ 617.1731.

Alcohol 59. A solution of ester **58** (49.6 g, 102 mmol) in Et_2O (500 mL) at 0 °C was treated with $LiAlH_4$ (110 mL of a 1 M solution, 110 mmol), allowed to warm to 25 °C, and stirred at 25 °C for 0.5 h. After the solution was cooled to −78 °C, the reaction was quenched with EtOAc (25 mL) and aqueous NH_4Cl (150 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 20 → 45% Et_2O in petroleum ether) to give **59** (43.9 g, 97%) as a white solid: R_f = 0.22 (silica, 30% Et_2O in petroleum ether); IR (thin film) ν_{max} 2955, 2931, 2857, 1471, 1280, 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, J = 8.5, 5.3 Hz, 1 H, 6-H), 6.20 (dd, J = 8.5, 1.7 Hz, 1 H, 5-H), 4.10 (dd, J = 8.0, 4.1 Hz, 1 H, 2-H), 3.95 (dd, J = 5.3, 1.7 Hz, 1 H, 7-H), 3.58 (d, J = 8.0 Hz, 1 H, 2-H), 3.25 (dd, J = 10.4, 4.3 Hz, 1 H, 9-H), 3.15 (dd, J = 10.4, 4.3 Hz, 1 H, 9-H), 1.60 (b t, J = 4.3 Hz, 1 H, 9-OH), 1.47 (d, J = 4.1 Hz, 1 H, 3-H), 1.22 (s, 3 H, 19-CH_3), 0.92 (s, 9 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.86 (s, 9 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.17 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.15 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.12 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.10 (s, 3 H, $Si(C(CH_3)_3)(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6) δ 132.8, 131.7, 119.0, 80.0, 72.0, 69.6, 63.1, 46.0, 44.7, 26.0, 25.7, 18.9, 18.2, 18.0, −2.9, −3.0, −3.1, −3.2; FAB HRMS (NBA/CsI) *m/e* 575.1636, M + Cs^+ calcd for $C_{22}H_{42}O_5Si_2$ 575.1625.

Diol 60. A solution of alcohol **59** (43.9 g, 99 mmol) in CH_2Cl_2 (250 mL) and MeOH (20 mL) was treated with camphorsulfonic acid (CSA, 0.52 g, 5 mmol) and stirred at 25 °C for 1 h. After dilution with CH_2Cl_2 (300 mL), the reaction was quenched with aqueous $NaHCO_3$ (150 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 50% Et_2O in petroleum ether) to give diol **60** (32.6 g, 94%) as white crystals: mp 109−111 °C, from EtOAc−hexanes; R_f = 0.38 (silica, Et_2O); IR (thin film) ν_{max} 3433, 2932, 2859, 1766, 1469, 1384, 1081, 1023; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (ddd, J = 18.0, 3.0, 1.5 Hz, 1 H, 5-H), 5.82 (dd, J = 18.0, 1.5 Hz, 1 H, 6-H), 4.38 (A of ABX, dd, J = 9.5, 7.5 Hz, 1 H, 2-H), 4.33 (B of ABX, ddd, J = 9.5, 5.0, 1.0 Hz, 1 H, 2-H), 4.24 (b s, 1 H, 7-H), 3.57 (A′ of A′B′, d b, J = 11.0 Hz, 1 H, 9-H), 3.39 (B′ of A′B′, b d, J = 11.0 Hz, 1 H, 9-H), 2.70−2.33 (band, 2 H, 9-OH and 7-OH), 2.55 (X of ABX, dd, 7.5, 5.0 Hz, 1 H, 3-H), 0.88 (s, 3 H, 19-CH_3), 0.83 (s, 9 H, $Si(C(CH_3)_3)(CH_3)_2$), 0.16 (s, 6 H, $Si(C(CH_3)_3)(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 135.1, 124.4, 74.5, 68.7, 67.7, 66.4, 47.5, 41.9, 25.6, 18.1, 12.9, −2.7, −3.1; FAB HRMS (NBA) *m/e* 329.1772, M + H^+ calcd for $C_{16}H_{28}O_5Si$ 329.1784.

Acknowledgment. We thank Drs. Dee H. Huang, Gary Siuzdak, and Raj Chadha for NMR, mass spectroscopic, and X-ray crystallographic assistance, respectively. This work was financially supported by NIH, The Scripps Research Institute, fellowships from Mitsubishi Kasei Corporation (H.U.), R.W. Johnson−ACS Division of Organic Chemistry (E.J.S.), The Office of Naval Research (R. K. G.), Glaxo, Inc. (C.F.C.), Mr. Richard Staley (C.F.C.), Rhône-Poulenc Rorer (P.G.N.), and grants from Merck Sharp & Dohme, Pfizer, Inc., Schering Plough, and the ALSAM Foundation.

Supplementary Material Available: Experimental techniques and data for compounds **10−14**, **16**, **18−35**, **47−51**, **57**, **58**, **61−80**, **82−87**, and **89−107** (44 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.

JA942193U