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From *D*-camphor to the taxanes. Highly concise rearrangement-based approaches to taxusin and taxol *

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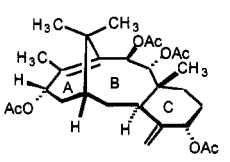
Abstract: Many trees and shrubs of the *Taxus* family elaborate a fascinating collection of structurally complex polycyclic diterpenoids, the synthesis of which provides a valuable forum for assessing state-of-the-art methodology. Taxusin and taxol have received the greatest level of interest. From among the many researchers inspired to explore the laboratory preparation of these targets, several have succeeded admirably. However, the approaches have most often been very lengthy. The goal of our research effort has been to implement a strategy generic to both molecules. The anticipation was that two central structural rearrangements, each with its own nuances of tailored design, would expedite construction of their common carbocyclic framework and permit notably concise enantiocontrolled access from *D*-camphor as the key building block. The successes that have been realized during this investigation are summarized herein.

PURPOSE OF THE INVESTIGATION

Our involvement with the de novo acquisition of taxusin (**1**) and taxol (**2**) has been fueled in large part by the enchanting structural features of these molecules and the much heralded antitumor efficacy of **2**, particularly in patients beset with refractory ovarian, breast, and lung cancers.[1] In combination with the unusual mode of action of **2**, which exhibits a remarkable capacity for stabilizing microtubule assembly and deterring cell division,[2] the intrinsically exciting promise shown by taxol for benefiting human health has commanded unrivaled attention.

The studies to be described herein were formulated not only to reach these targets, but do so in as correlated a fashion as possible, and with the utmost brevity. At the initiation of these efforts, only a single pioneering synthesis of *ent*-taxusin had been realized.[3] The intervening time has been witness to a significantly more expedient approach to **1**[4] as well as to five elegant syntheses of **2**.[5-9]



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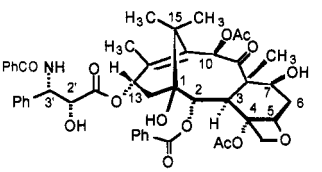

2

A second inducement was a projected unrivaled opportunity to deploy the anionic oxy-Cope rearrangement[10] in the specific context of bridgehead olefin construction.[11] Indeed, Nature has produced a far greater number of this generic type of novel unsaturated product than is generally appreciated. Therefore, a real need exists for improvising direct methods for elaborating in a global sense the relatively abundant and diverse members of this structural class.

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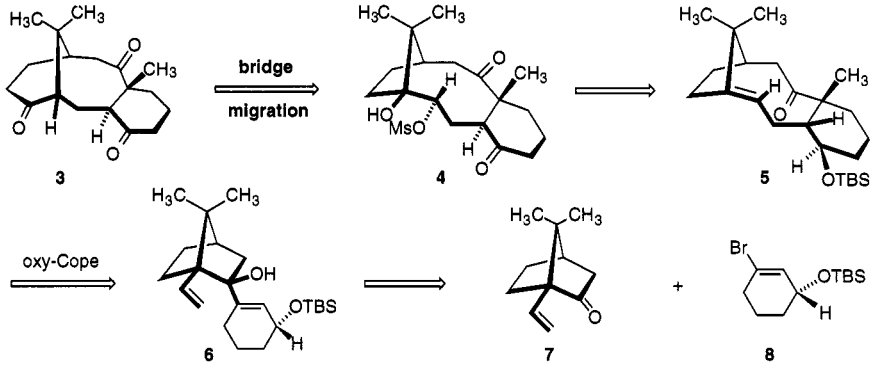
SYNTHETIC PLANNING

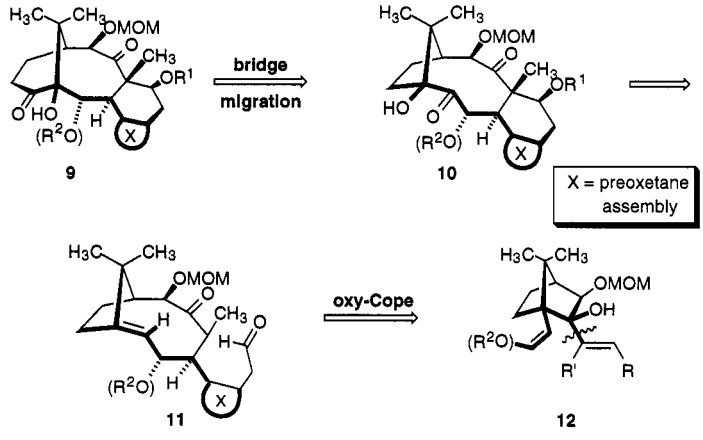
While taxusin and taxol share the identical tricyclo[9.3.1.$0^{3,8}$]pentadecane framework, it is obvious at a glance that **2** is significantly more oxygenated than **1**. One of the more obvious points of contrast is bridgehead carbon C-1, which carries hydroxyl functionality in **2**. Also distinctive is the added oxygen functionality at C-2, C-4, and particularly C-7. Here, taxol is recognized to have aldol characteristics, a feature that holds special significance in our synthetic design and harmonizes the construction of these sectors in notably direct ways.

The retrosynthetic analysis illustrated in Scheme 1 defines an implicitly workable approach to taxusin. In order to reach **5**, endo coupling of either **8** or its enantiomer (as the respective lithio derivative) to the readily available enone **7** (100% ee)[12] was envisioned to set the stage for the targeted anionically-accelerated [3,3] sigmatropic event. The prospect for C-3 epimerization and dihydroxylation of **5** was intended to deliberately address the stereoelectronic requirements of the pinacol-like 1,2 Wagner-Meerwein shift required for proper bridge migration and generation of **3**. The availability of this triketone would leave only issues surrounding functional group manipulation to be dealt with.



Scheme 1

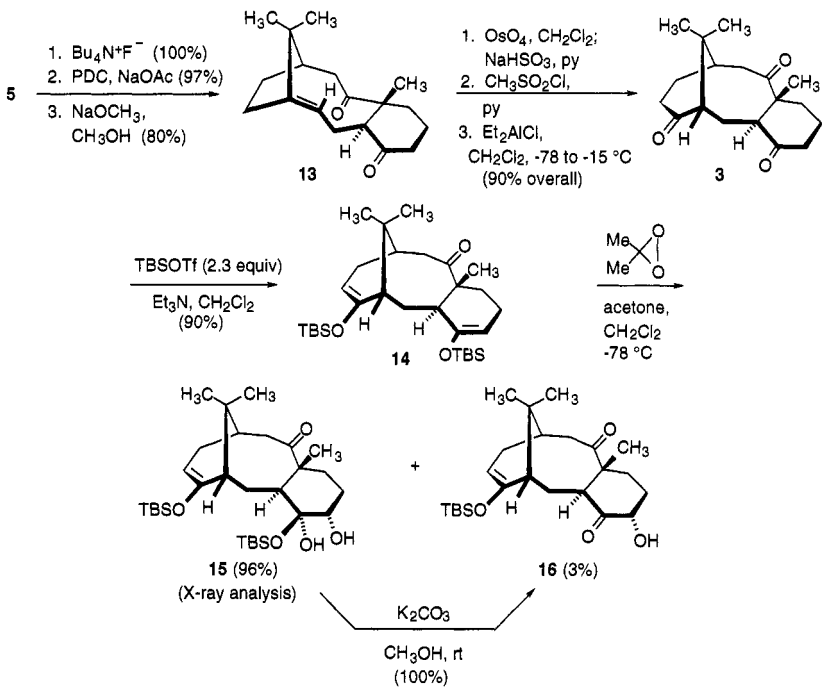
The prospectus for a related approach to taxol, shown in Scheme 2, deliberately leaves open many crucial particulars. The most notable of these is the unspecified nature (loosely defined as "X") of the functional group array that will ultimately serve to generate the oxetane ring. Several choices of relatively different merit are available. Also unaddressed are the manner and timing to be used for introduction of the C-2 oxygen center. Again, several protocols are possible including carrying the R^2O substituent through from **12** and α-oxygenating a suitably protected form of **10**. It is clear, however, that this matter requires attention prior to the α-ketol rearrangement that forms the basis for obtaining **9**. Note that construction of the C-ring with proper installation of the C-7,8,9 triad is to be accomplished via intramolecular aldolization.



Scheme 2

THE PATHWAY TO TAXUSIN

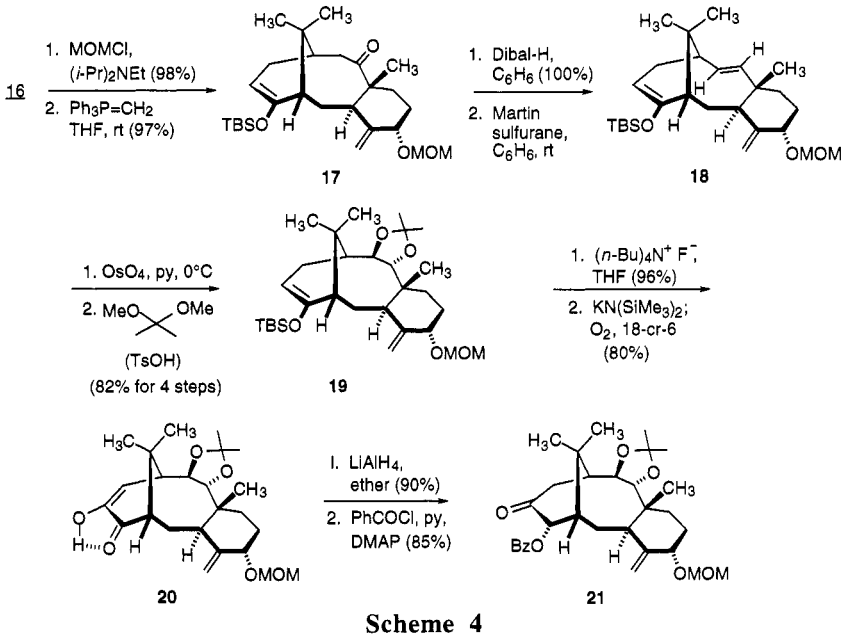
The earliest experiments aimed at **1** showed that (+)- and (-)-**8** were most effectively obtained by enantioselective hydrolysis of the choroacetate with lipase P-30,[13] that arrival at **6** required use of the cerate in order to curtail enolization, and that the oxy-Cope rearrangement of **6** to give **5** was highly atropselective[14] because of strict adherence to a so-called "endo-chair" transition state.[15] In effect, only five laboratory steps were required to advance from **7** to **13** (Scheme 3). Furthermore, the conversion of **13** to **3** could be readily implemented (Scheme 3). High efficiency can be routinely achieved if the bridge migration is promoted with diethylaluminum chloride.[16] Mangzhu Zhao subsequently recognized that the three ketone carbonyls in **3** could be readily distinguished. The transformation to **14**, which aptly demonstrates the steric crowding present in the area of C-9 and C-10, made possible the convenient stereocontrolled introduction of the necessary hydroxyl substituent at C-5.[17]



Scheme 3

Given these findings, our attention was next directed to the expedient oxygenation of C-10 and C-13. It behooved us to introduce the penultimate carbon initially via Wittig olefination. Dibal-H reduction of **17** *in benzene* results in reduction of the "carbonyl-down" conformer to deliver the α-alcohol, dehydration of which leads stereospecifically to cyclononene **18**, the less thermodynamically stable of the two possible trans diastereomers (Scheme 4).[17] Since **18** undergoes osmylation preferably at this site and only from the direction external to the ring, the oxygenation pattern found in **19** evolves as required for taxusin. The A-ring enolate anion generated from **19** is particularly amenable to oxidation, as are many related compounds.[18] Arrival at α-diketone **20** is consequently greatly facilitated. Reduction of **20** with lithium aluminum hydride is preceded by deprotonation of the enol, thereby transiently protecting that substituent from nucleophilic attack. Subsequent benzoylation afforded the very desirable product **21**, which capped completed construction of the B and C rings that had already materialized in **19**. Most significantly, only twenty laboratory steps are needed to arrive at this highly advanced stage.

The oxygen atom at C-14, originally introduced into **13** for the ultimate purpose of enabling the Wagner-Meerwein shift, had not yet outworn its usefulness. As shown in Scheme 5, its presence allows for kinetically favored deprotonation at C-12 where a methyl group and bridgehead olefinic center must be introduced. While an exocyclic double bond (as in **22**) or its intracyclic variant (as in **25**) can be readily established, and subsequent reductive cleavage of the α-benzoyloxy group is highly chemoselective, the

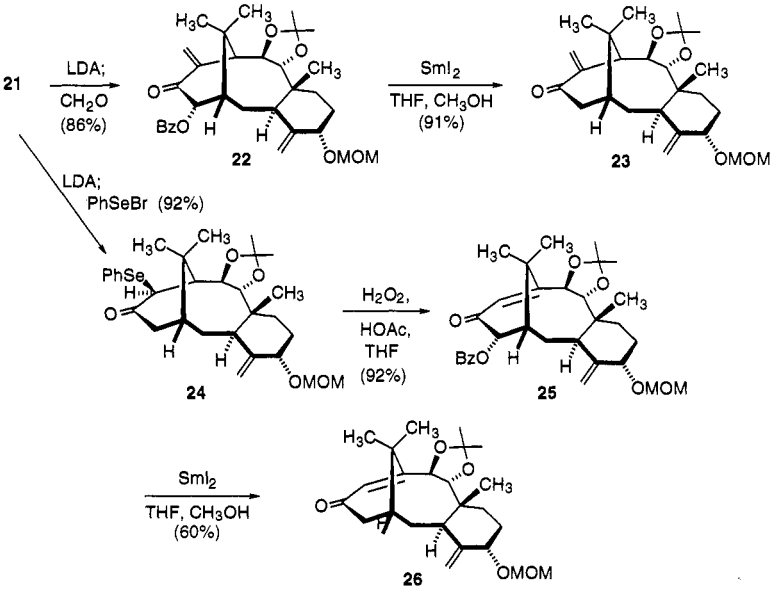


Scheme 4

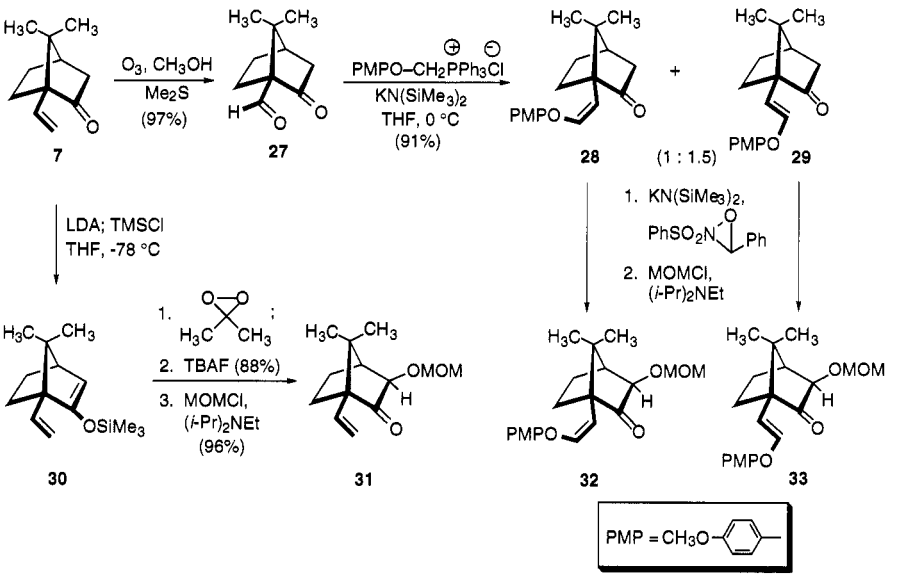
need exists to merge these two tactics. The lecture will address appropriate means for accomplishing this task.

AN ABBREVIATED ROUTE TO TAXOL

We explored, in the first instance, the possibility of adapting synthetic building blocks of type **8** in a similarly direct way to taxol construction.[19,20] When it came to be recognized that introduction of the C-7 oxygen in this manner was problematical,[21] the retrosynthetic model embodied in Scheme 2 was adopted. The first objective was to examine the interplay of heightened functionalization of **7** with the efficiency of the oxy-Cope process. Much to our amazement, these camphor-based ketones undergo α-oxygenation predominantly from the exo direction (Scheme 6). For example, dimethyldioxirane oxidation of silyl enol ether **30** gives the α-ketol with an exo preference of 94-100%. Alternatively, the enolates of **28** and **29** enter into reaction with the Davis oxaziridine to give mixtures rich in **32** (5:1) and **33** (7:1).[22] It will be



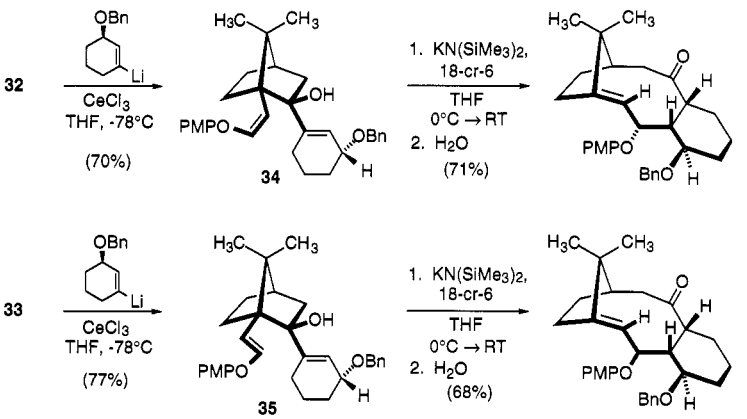
Scheme 5



Scheme 6

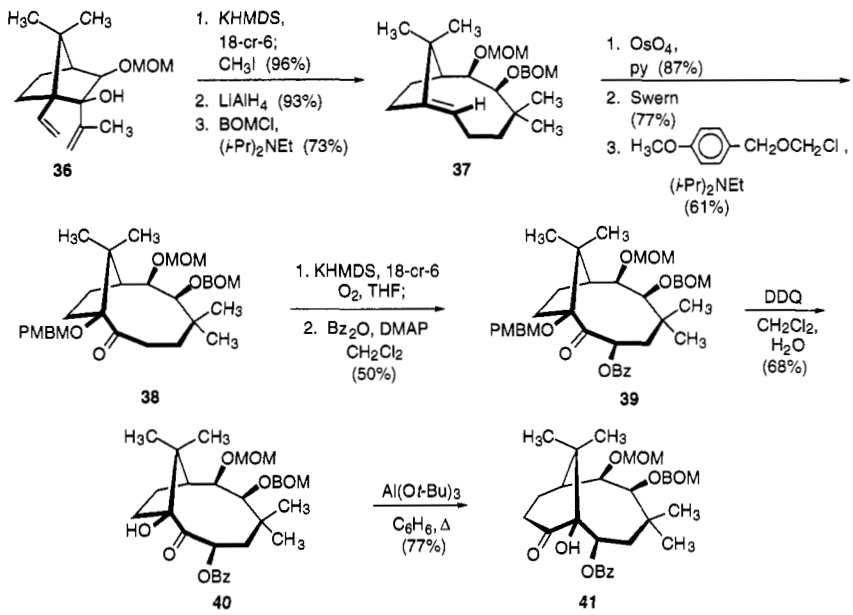
recognized that the exo-oriented OMOM substituent in **31-33** is destined to become the C-10 oxygenated center in taxol. Likewise, the -OPMP substituent will find itself ultimately positioned at C-2.

This array of functionality proved to be most accommodating and especially conducive to our goals. Thus, the steric bulk of the OMOM group further enhanced endo addition to the adjacent carbonyl. Also, its inductive effect sufficiently reduced the acidity of the α-carbonyl proton that direct condensation with alkenyllithium reagents was now possible. In addition, the subsequent charge-accelerated sigmatropic rearrangement of the resulting exo carbinols delivered tricyclic products that feature the characteristic B-ring oxygenation pattern resident in **2** (Scheme 7). The process is stereospecific for **34** and **35** as a consequence of continued adherence to the "exo-chair" transition state geometry.[22]



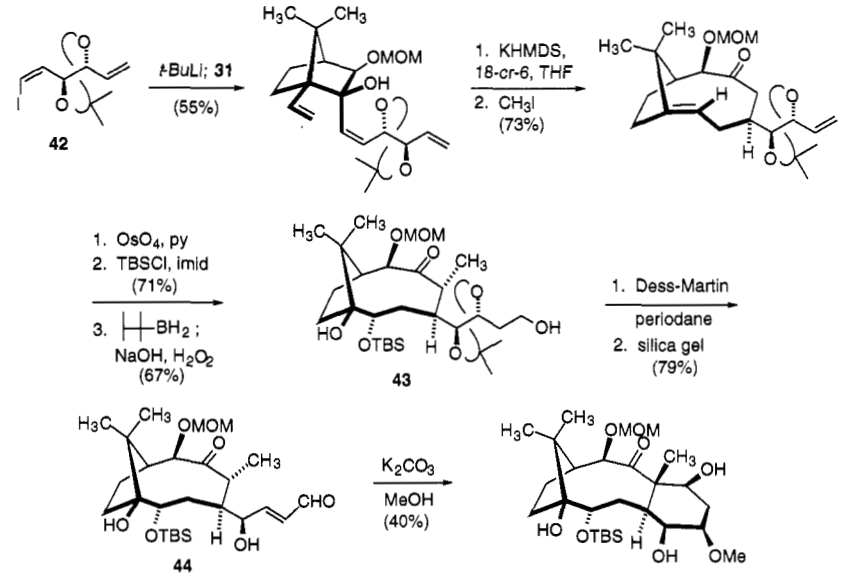
Scheme 7

Although the thermodynamics associated with the pending α-ketol equilibration had been evaluated early and shown to involve strain release in the desired direction,[23,24] this key transformation had yet to be performed when the nearby C-2 center was oxygen-substituted (as in **10** → **9**). The urge to show workability was followed up by the rapid assembly of prototype **40** from the readily available carbinol **36** as shown in Scheme 8.[25] Subsequent exposure of **40** to aluminum tri-*tert*-butoxide led efficiently to **41**. Another important dimension of this scheme was the fashion in which the benzoate group was introduced - *viz.*, by oxygenation of the enolate anion of **38**.



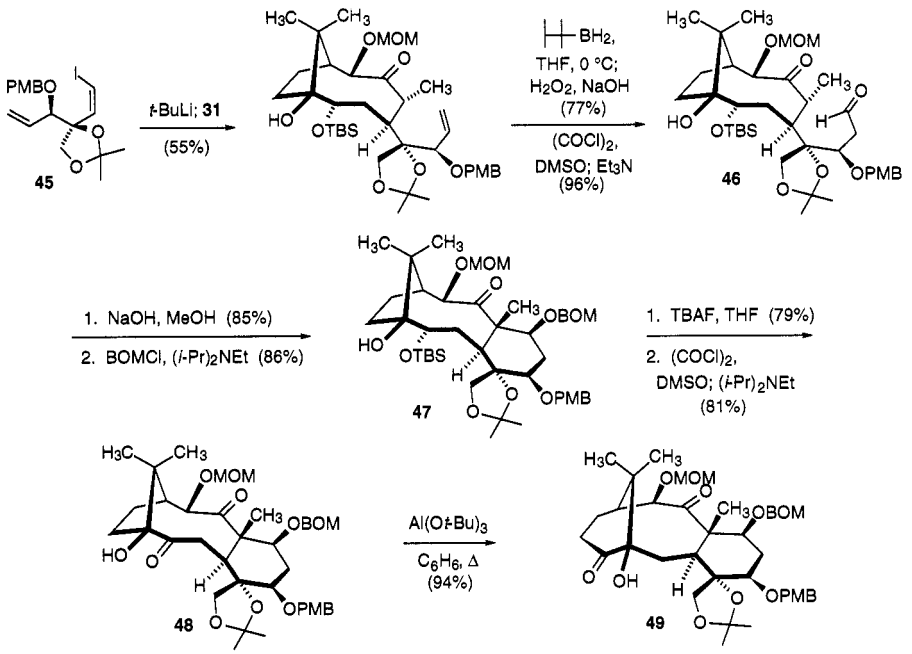
Scheme 8

The task of devising the proper C-ring synthon now had to be addressed. The enantiomerically pure (*Z*)-vinyl iodide **42**, conveniently available from D-ribose functioned admirably well up to the point of aldol cyclization (Scheme 9). The aldehyde obtained from **43** enters into ring closure, but only after β-elimination (see **44**) and recapture of methanol.[26] This was not acceptable.



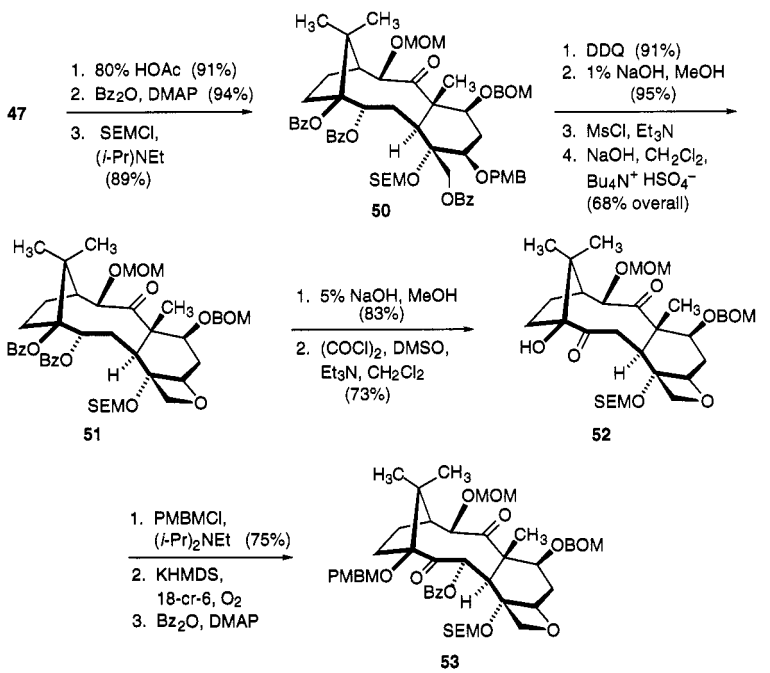
Scheme 9

Maneuvers of this type can be completely bypassed if a (*Z*)-iodide of type **45** is utilized instead.[27] The latter is produced from (*R*)-glyceraldehyde acetonide and likewise sets the stereocenters resident at C-7 and C-8 in their proper absolute configuration (Scheme 10). The convergent coupling of **45** to **31** provides a forum for the rapid elaboration of aldehyde **46**, the aldol cyclization of which proceeds without β-elimination. The outcome is the acquisition of **47**, Swern oxidation of which affords **48** and ultimately its α-ketol tautomer **49**. When exploration of the α-oxygenation of **48** and protected forms thereof commenced, it quickly became apparent that the steric shielding provided by the acetonide subunit precluded all possibility of engaging these enolates in reaction.



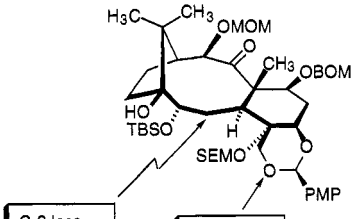
Scheme 10

Recognition of this fact was adequate inducement to install the oxetane ring first. Thus, preference was given to selective hydrolysis of **47** and generation of tribenzoate **50** (Scheme 11). Although the cyclization of ring D proceeded without event and **53** could now be crafted from **51** according to precedent,[25] this protocol is certainly too lengthy and awkward for our purposes.



Scheme 11

The extensive array of steps associated with the oxetane assembly process in Scheme 11 can be dramatically reduced to only two in molecules related to **54**. In addition, no steric blockade is experienced at C-2 as long as an acetonide is absent. The manner in which these considerations can be effectively united will be made clear in our lecture.



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