

Recent advances in the synthesis of taxoids: 2015-2020

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Dedicated to Prof. Peter A. Jacobi for his lifetime contributions to organic synthesis

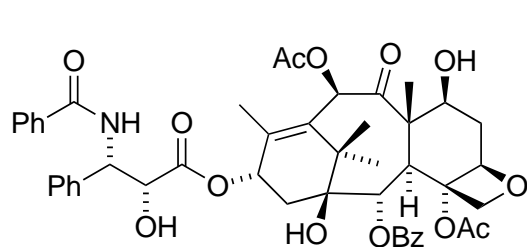
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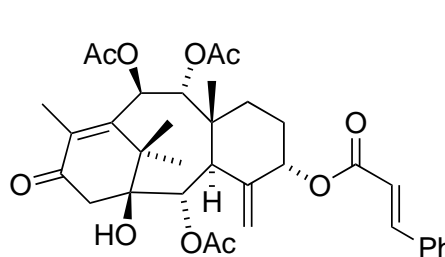
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Abstract

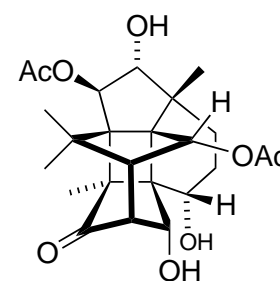
Taxol is a highly oxygenated, polycyclic diterpene first isolated from the bark of the Pacific yew tree. The impressive antitumor activity of this compound led to intense synthetic activity over the past 30 years. The first syntheses were reported more than 25 years ago, and earlier synthetic efforts have been amply reviewed. This review will focus on the literature for the period 2015-2020 including formal and total syntheses of taxol, 1-hydroxytaxinine, taxabaccatin III, and canataxpropellane.



Taxol



1-Hydroxytaxinine



Canataxpropellane

Keywords: total synthesis, taxane-type diterpenes

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1. Introduction

Taxol[®] or paclitaxel was first isolated in 1964 by Wall and co-workers from the extracts of the bark of *Taxus brevifolia*, also known as the pacific yew tree.¹ This complex polycyclic molecule belongs to the taxane diterpene family, of which there are now more than 550 known compounds,² and was found to have impressive activity against KB cells. In 1992, taxol was approved by the FDA for treatment of recurrent ovarian cancer and in 1994 for the treatment of breast cancer. It was also reported that taxol has a significant effect in the treatment of different types of cancer such as lung and liver cancer.^{3,4} The anti-cancer activity of taxol results from its ability to inhibit tumor cell proliferation through enhancement of tubulin polymerization and to act as a promotor of microtubule assembly which leads to the stabilization of microtubules.⁵

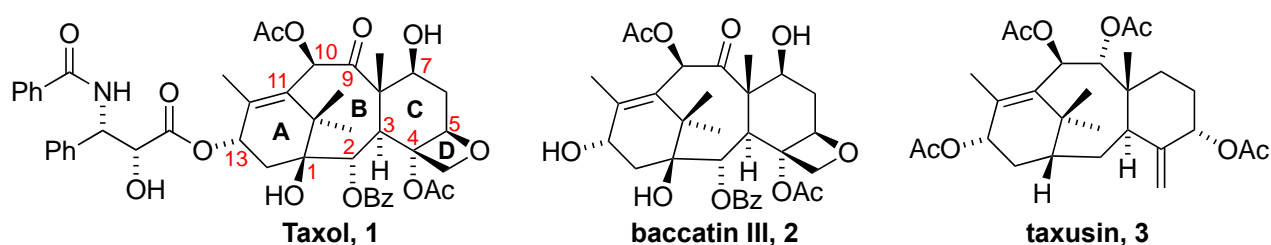


Figure 1. Structures of taxol (**1**), baccatin III (**2**), and taxusin (**3**).

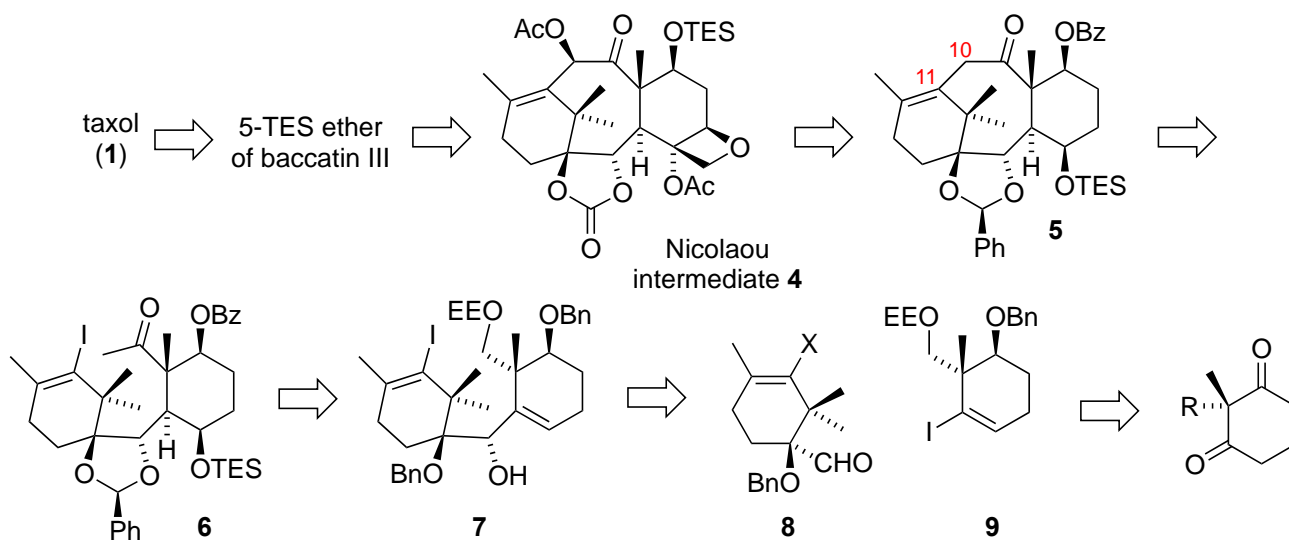
Taxol **1**, (Figure 1) is a highly oxygenated diterpene with a unique chemical structure characterized by a distorted eight-membered (B) ring fused with two peripheral 6-membered rings (A and C), referred to as a 6/8/6 skeleton, with an oxetane ring (D) fused with the C ring. It has acetyl groups at C4 and C10, a benzoyl group at C2, free hydroxyl groups at C1 and C7, and a unique β -phenylisoserine side chain at C13. The natural supply of taxol is relatively low (0.5-1 kg taxol from 4,500 kg pacific yew tree bark). Methanolysis of **1** leads to baccatin III (**2**); C7 protected analogs of **2** have been highly utilized in the penultimate steps for the synthesis of taxol. Due to the scarcity of natural taxol as well as its complex polycyclic structure, intense synthetic activity commenced resulting in the first total syntheses by the groups of Holton^{6,7} and Nicolaou.⁸⁻¹² These

were followed in the next 6 years by total syntheses from the groups of Danishefsky,^{13,14} Wender,^{15,16} Kuwajima,^{17,18} and Mukaiyama.¹⁹⁻²² In 2006 Takahashi's group reported a formal total synthesis which relied on use of an automated synthesizer.²³ Another common synthetic target is the less oxidized taxusin (**3**).²⁴⁻²⁸ These syntheses have been amply covered in detail in several excellent review articles;²⁹⁻³⁴ the reader is directed to these for syntheses completed in the prior millennium. In addition, the various syntheses leading to the β -phenylisoserine side chain of taxol has been reviewed.³⁵ For this reason, the present review will focus on those total and formal syntheses of taxoids reported in the period 2015-2020.

2. Formal Syntheses of Taxol

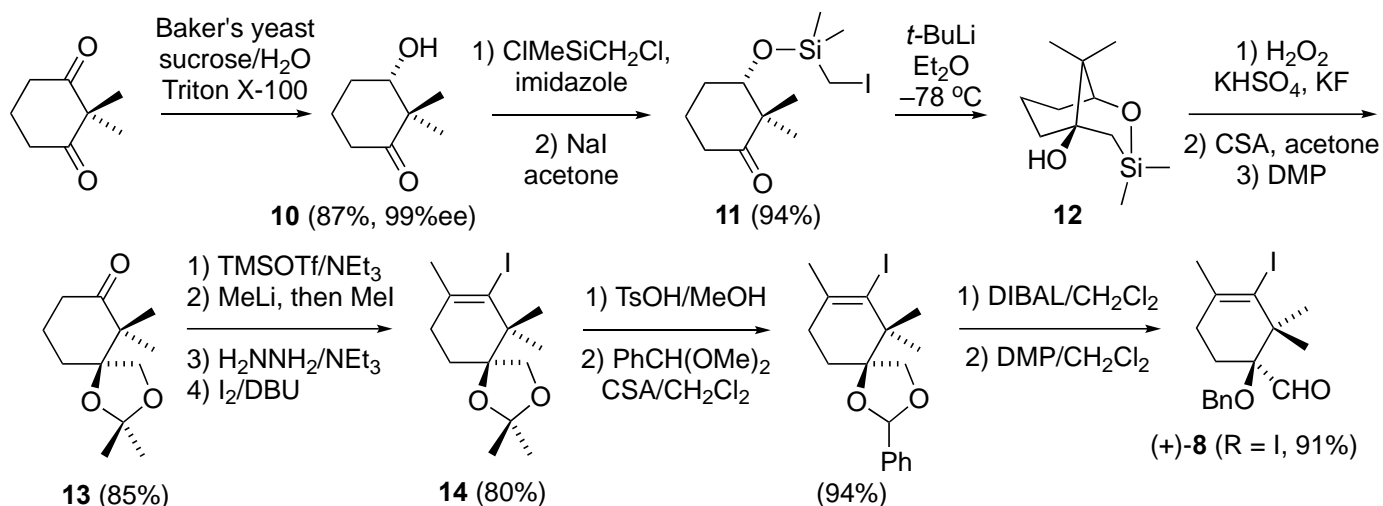
2.1. Nakada formal synthesis (A + C \rightarrow AC \rightarrow ABC \rightarrow ABCD)

In early 2015, Nakada's group reported^{36,37} a formal total synthesis of taxol converging on cyclic carbonate **4** (Scheme 1) an intermediate in the Nicolaou^{8,12} synthesis. This was traced backwards to the tricyclic ketone **5**. It was envisioned that the C10-C11 bond of **5** would be generated by a Pd-catalyzed intramolecular alkenylation of **6**. The crucial C2-C3 bond formation would take place by addition of a vinyl lithium derived from **9** with aldehyde **8**. Both optically active precursors **8** and **9** would be generated by Baker's yeast mediated desymmetrizations of 2,2-disubstituted-1,3-cyclohexadiones.



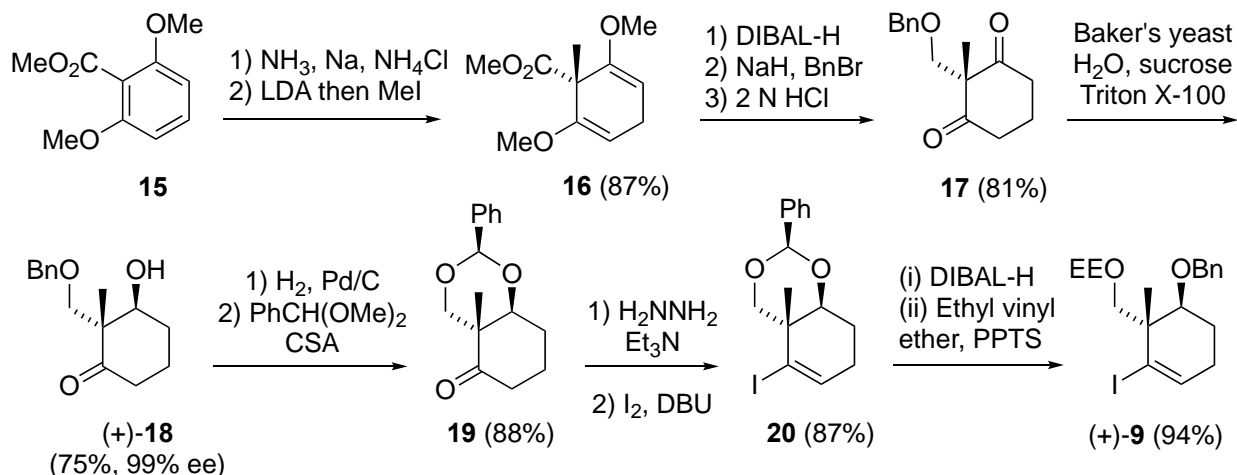
Scheme 1. Retrosynthetic analysis of taxol according to Nakada's approach.

Baker's yeast mediated reduction of 2,2-dimethyl-1,3-cyclohexandione³⁸ gave **10** in good chemical yield and excellent enantioselectivity (Scheme 2). Silylation with chloromethyldimethylsilyl chloride, followed iodination under Finkelstein conditions afforded **11**.³⁹ Lithium-halogen exchange of **11** triggered an intramolecular alkylation to generate the corresponding chiral tertiary bicyclic alcohol **12**. Tamao oxidation followed by acetonide formation and Dess-Martin oxidation yielded ketone **13**. α -Methylation of **13** proceeded via the silyl enol ether, hydrazone generation and oxidation using iodine gave **14**. Swapping the cyclic acetonide for a cyclic benzylidene acetal, followed by reductive cleavage at the less hindered oxygen and Dess-Martin oxidation gave (+)-**8** (R = I). While Nakata's group developed multiple routes to vinylhalides **8**,^{37,40} the present route gave the highest overall yield and enantioselectivity.



Scheme 2. Synthesis of the ring A fragment (+)-8 (R = I).

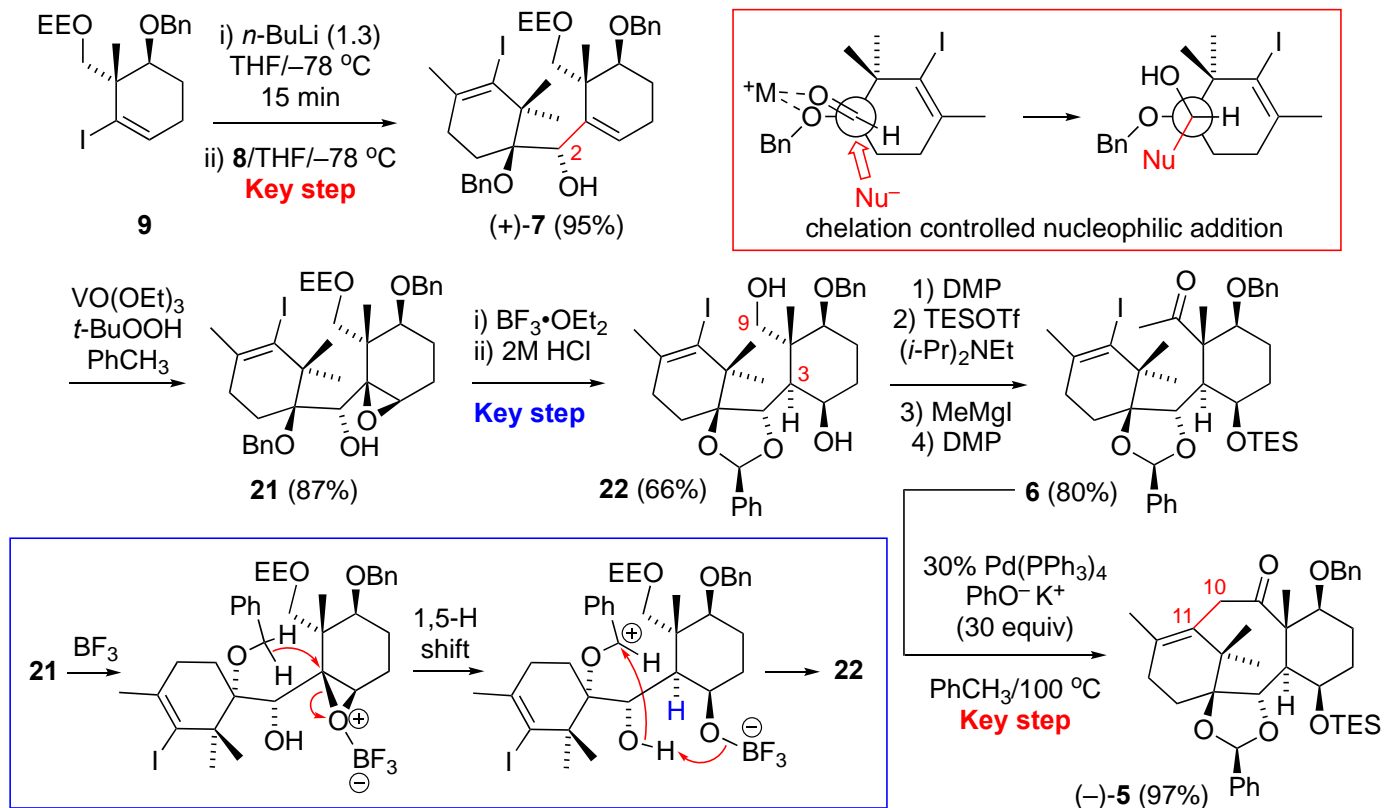
Preparation of the C ring fragment **9** commenced with Birch reduction of methyl 2,6-dimethoxybenzoate (**15**); alkylation of the product with LDA followed by methyl iodide gave diene **16** (Scheme 3).^{36,37} Reduction of the ester with DIBAL, protection of the resulting 1° alcohol as a benzyl ether and acid-catalyzed vinyl ether hydrolysis led to the achiral 1,3-cyclohexadione **17**. As was the case for preparation of the A ring fragment, Baker's yeast reduction of **17** proceeded in good yield and excellent enantioselectivity to give (+)-**18**. A protecting group swap yielded benzylidene acetal **19**. Transformation of **19** into the vinyl iodide **20** followed a procedure similar to previously used for **13** to **14**. Similar reductive cleavage of the benzylidene acetal at the less hindered oxygen and protection of the resultant 1° alcohol gave (+)-**9**.



Scheme 3. Synthesis of ring C fragment (+)-9.

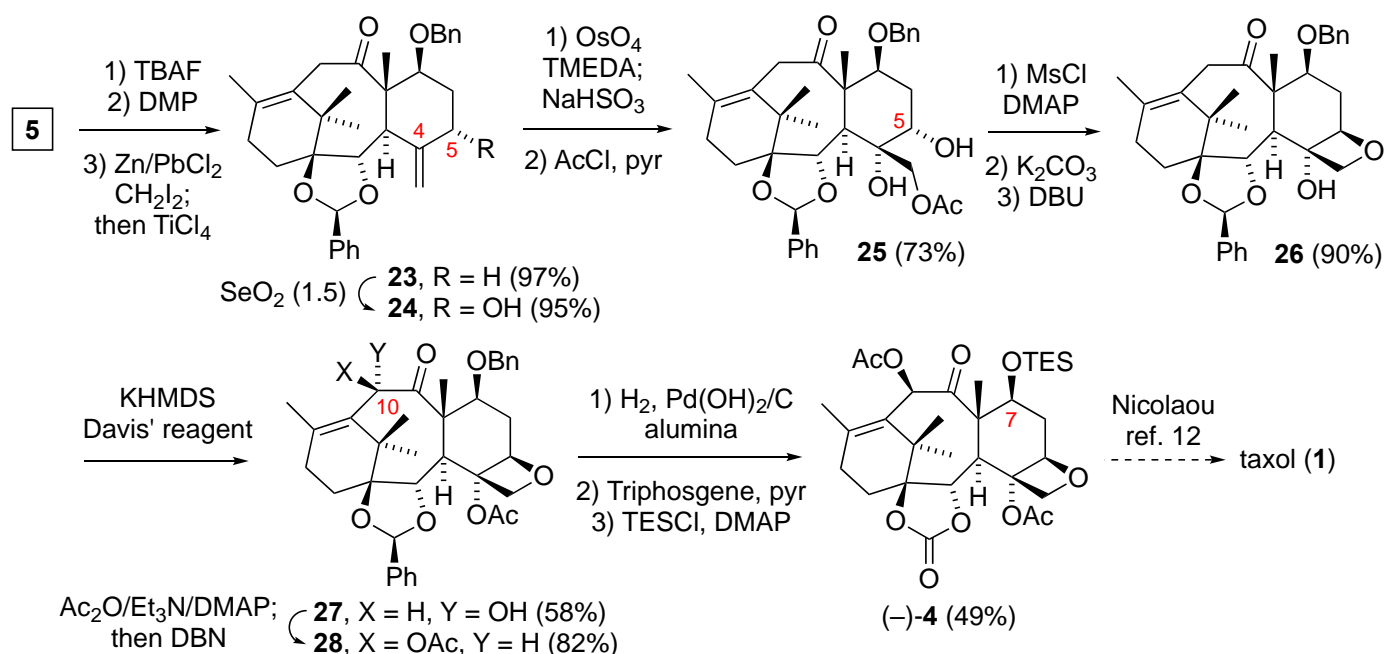
Lithium-halogen exchange of (+)-**9** and reaction with aldehyde (+)-**8** (R = I) gave (+)-**7** as a single diastereomer (Scheme 4).^{36,37} The stereochemical outcome was rationalized on the basis of a chelation-controlled addition (see red insert). Sharpless epoxidation of **7** catalyzed with VO(OEt)₃ gave epoxide **21** as a single stereoisomer. Attempted ionic reduction of **21** (BF₃-EtO₂/NaBH₃CN) led surprisingly to the cyclic benzylidene acetal **22**; the yield of this product could be improved by using only the Lewis acid. Nakada's group proposed that **22** is formed by a 1,5-hydride shift of the BF₃ complexed epoxide, followed by

deprotonation of the C2 hydroxyl group and nucleophilic attack on the benzyl cation (see blue insert). A sequence of oxidation of the C9 primary alcohol, protection of the C4 secondary alcohol, addition of methyl Grignard and oxidation afforded the methyl ketone **6**. Formation of the eight-membered B ring was achieved by Pd-catalyzed intramolecular alkenylation to give **5**. While this C–C bond formation proceeded in excellent yield, the catalyst loading (30%) was relatively high.



Scheme 4. Synthesis of the tricyclic core (–)-**5** of taxol.

The C4 exocyclic methylene was constructed by deprotection of the C4 silyl ether, Dess-Martin oxidation and a Takai methenylation (Scheme 5).^{36,37} Selenium dioxide allylic oxidation of the less substituted exocyclic olefin of **23** proceeded in a stereoselective fashion to give **24**. Transformation of **24** to the hydroxyoxetane followed a variation of the methodology utilized in Holton's synthesis.⁷ Thus, stereoselective dihydroxylation of allylic alcohol with stoichiometric OsO₄ and acylation of the 1° alcohol afforded **25**.



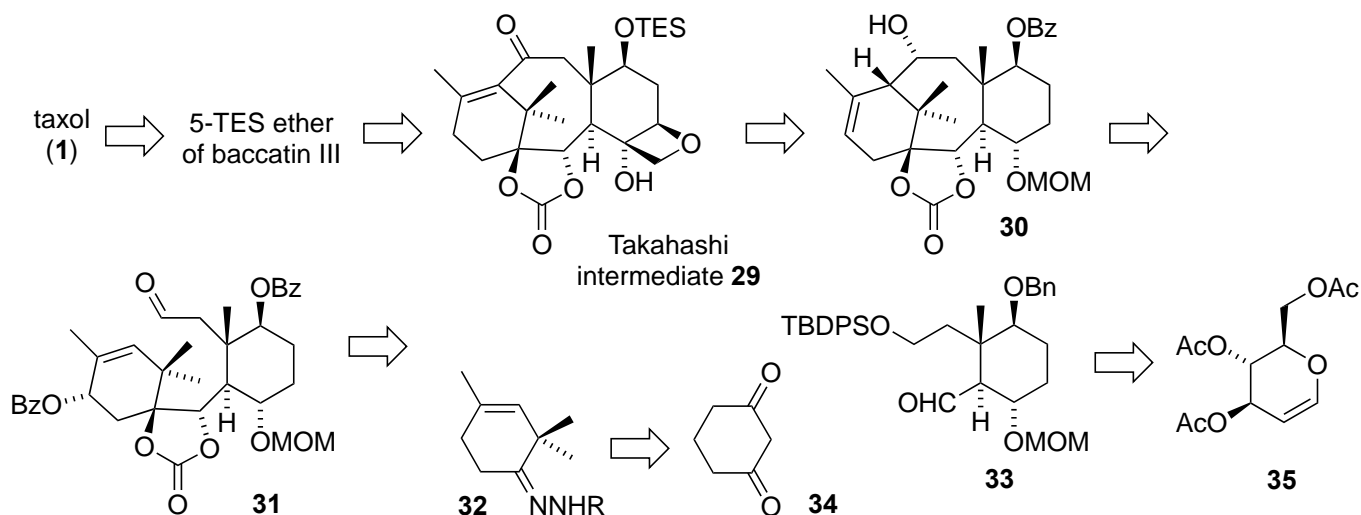
Scheme 5. Installation of the oxane ring and completion of the formal synthesis.

Mesylation of the C5 secondary alcohol, hydrolysis of the primary acetate and treatment with DBU afforded **26**. Treatment of the enolate anion of **26** with 2-(phenylsulfonyl)-3-phenyl-oxaziridine (Davis reagent) introduced a hydroxyl group at C10, however this possessed the opposite stereochemistry to that desired for taxol. Acylation of this alcohol and epimerization with DBN produced **28**. Reductive deprotection of the benzylidene acetal and the C7 benzyl ether was achieved using Pearlman's catalyst, reaction with triphosgene generated the cyclic carbonate ring and C7 hydroxyl protection as a TES ether rendered (–)-**4**, an intermediate in the Nicolaou total synthesis.¹²

The Nakada synthesis of chiral ABCD tetracyclic core of taxol required 49 steps from the commercially available achiral 2,2-dimethyl-1,3-cyclohexandione and 2,6-dimethoxy methyl benzoate resulting in ~0.91% overall yield. Approximately 1/3 of the steps involved protection or deprotection with approximately 1/6 of the steps utilized for oxidations or reductions.

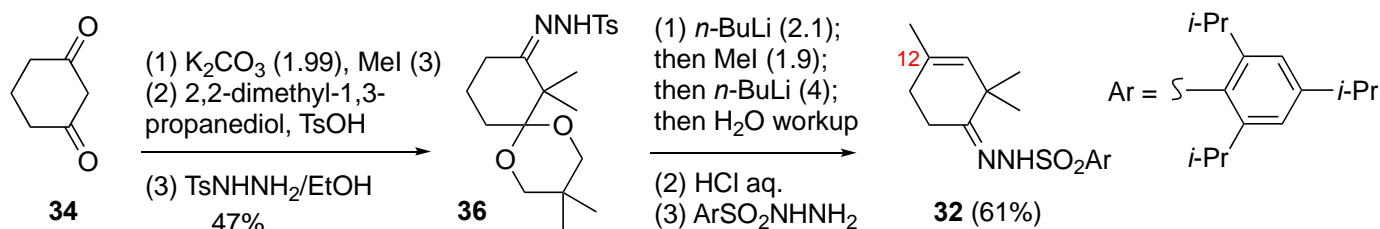
2.2. Chida formal synthesis (A + C → AC → ABC → ABCD)

Chida's group reported⁴¹⁻⁴³ a formal synthesis of taxol converging on a tetracyclic intermediate (**29**) in Takahashi's²³ formal synthesis (Scheme 6). A late-stage introduction of the oxetane ring was envisioned from tricyclic **30**. Generation of the eight-membered B ring would be accomplished by a SmI₂ mediated reductive cyclization of allylic benzoate **31**. Marriage of hydrazine **32** and aldehyde **33** utilized an intermolecular Shapiro reaction pioneered in the Nicolaou synthesis.^{8,10} The A ring fragment **32** and C ring fragment **33** would be synthesized from 1,3-cyclohexadienone **34** and tri-*O*-acetyl-D-glucal **35** respectively.



Scheme 6. Sato-Chida retrosynthetic analysis of taxol.

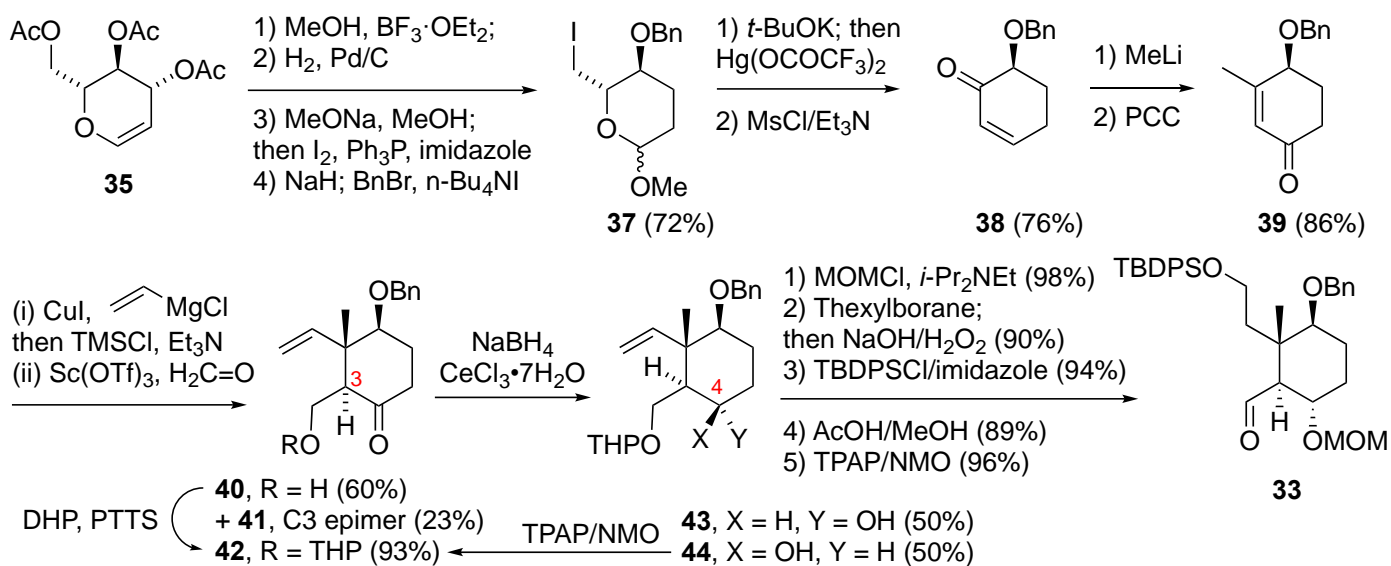
The preparation of hydrazone **32** from **34** (Scheme 7) followed a modification of Koskinen's procedure.⁴⁴ To this end, double methylation of **34**, followed formation of the mono ketal formation and reaction with tosylhydrazine afforded **36**. Alkylation of **36** introduced the requisite methyl group at C12; subsequent Shapiro reaction with protic work up gave the olefin. Deprotection of the ketal followed by hydrazone formation with 2,4,6-tri-isopropylbenzenesulfonylhydrazine gave **32**.



Scheme 7. Synthesis of ring A fragment **32**.

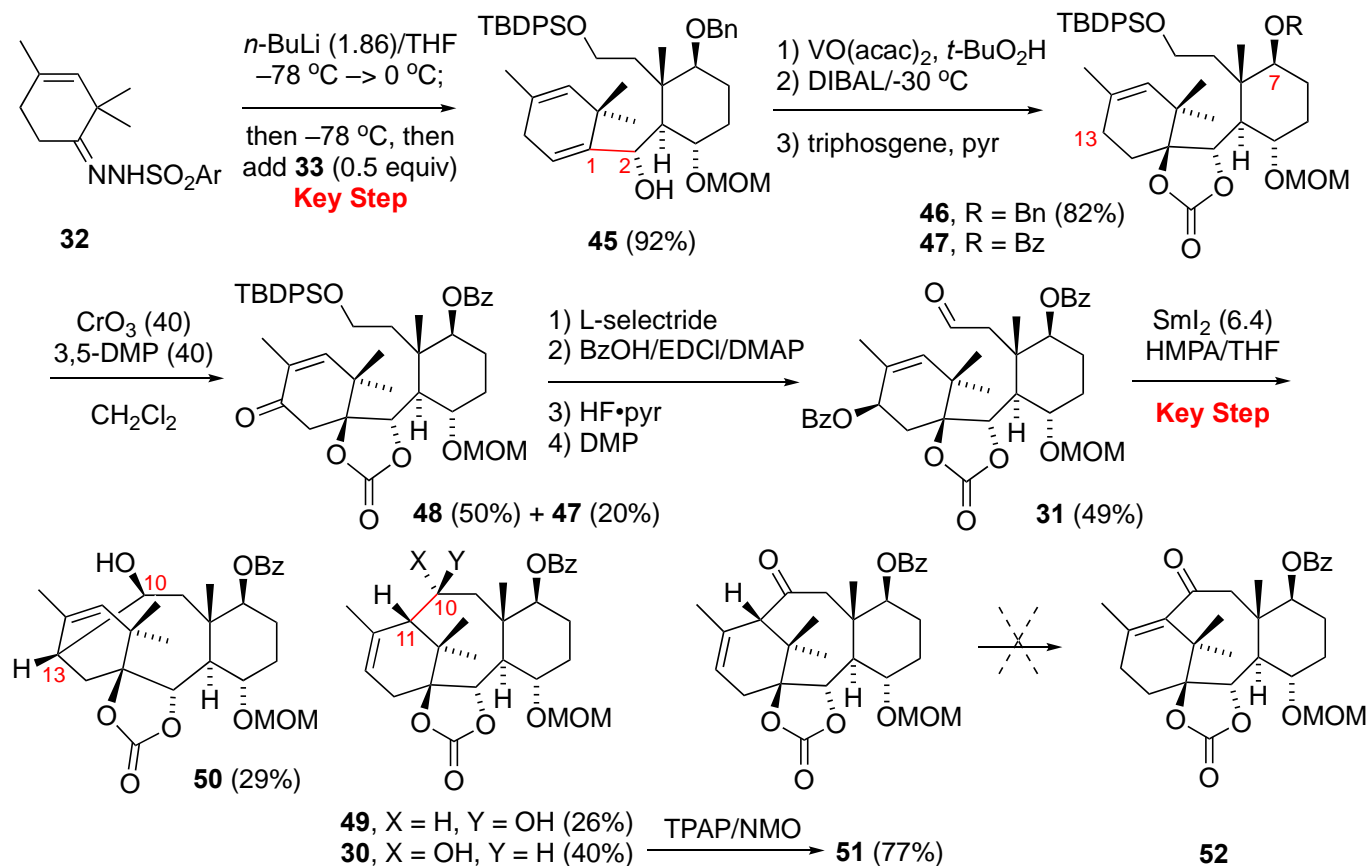
Ring C fragment **33** was synthesized from tri-*O*-acetyl-*D*-glucal **35** by Ferrier rearrangement with methanol, followed by catalytic hydrogenation, according to the literature procedure⁴⁵ (Scheme 8). Hydrolysis of the acetate groups, Appel iodination of the primary alcohol, and protection of the secondary alcohol gave **37**. Elimination with potassium *t*-butoxide, a carbo-Ferrier rearrangement,⁴⁶ and β -elimination with mesyl chloride/ NEt_3 gave 6(*S*)-benzyloxy-2-cyclohexenone (**38**). Carbonyl transposition⁴⁷ with methyl lithium followed by PCC oxidation generated **39**. Copper catalyzed 1,4-addition of vinyl magnesium chloride occurred on the face of the enone opposite to the 4-benzyloxy substituent. The resultant enolate was trapped *in situ* as the silyl enol ether; Lewis acid catalyzed aldol condensation with formalin gave a separable mixture of the desired **40** (60%) along with the C3-epimer (**41**, 23%, taxol numbering). Protection of the major diastereomer (**40**) as its THP ether, followed by Luche reduction gave an equimolar, but separable mixture of the desired secondary alcohol **43** and the diastereomer **44**. Oxidation of **44** under Ley conditions⁴⁸ regenerated **42**. Finally, protection of the secondary alcohol, regioselective hydroboration/oxidation, protection with *t*-butyldiphenylsilyl chloride, hydrolysis of the THP mixed acetal and Ley oxidation generated the requisite aldehyde **33**. While this route generated an optically pure fragment, drawbacks to this approach include

overall length (16 steps) and two steps with relatively low diastereoselectivity (**39** to **40/41** = 2.6:1 dr and **40** to **43/44** = 1:1 dr).



Scheme 8. Synthesis of the ring C fragment **33**.

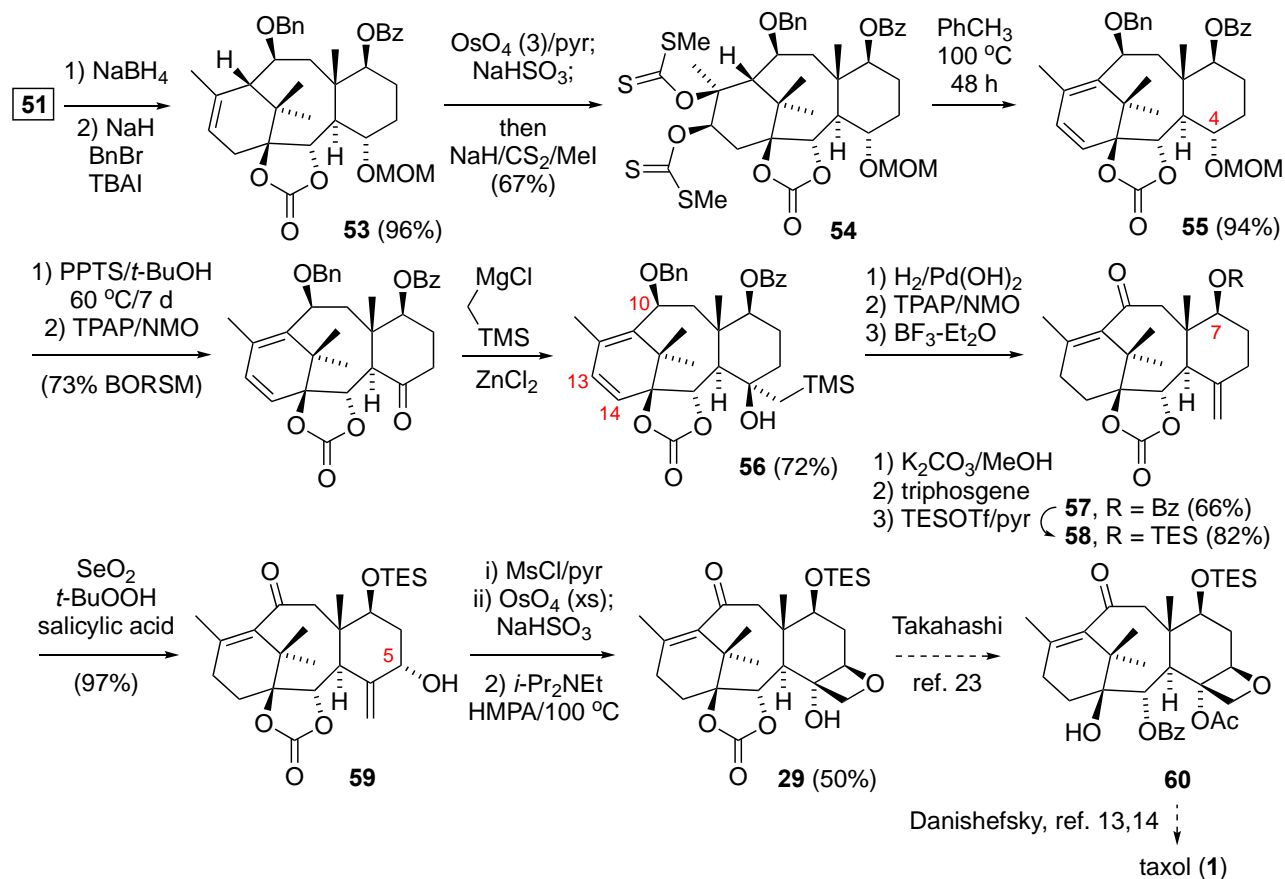
Coupling of **33** with a two-fold excess of the vinyl anion generated from hydrazine **32** gave the allylic alcohol **45** as a single diastereomer (Scheme 9).^{42,43} The stereochemical outcome is similar to that observed in the syntheses of Nicolaou,^{8,11} Danishefsky^{13,14} and Kuwajima^{17,18} where a Shapiro reaction was utilized to generate the C2-C3 bond. Stereoselective epoxidation catalyzed by $\text{VO}(\text{acac})_2$, followed by regioselective reduction gave the *vic*-diol which was protected as the cyclic carbonate **46**. Oxidation of **46** with a large excess of chromium trioxide in the presence of 3,5-dimethylpyrazole proceeded predominantly at both the C13 allylic position as well as at the C7 benzyl ether to generate **48**, along with a lesser amount of partially oxidized **47**. Subjecting **47** to further treatment with CrO_3/DMP gave additional **48**. Stereoselective reduction of **48** at C13, protection of the resultant secondary alcohol as the benzoyl ester, deprotection of the silyl ether and oxidation of the primary alcohol afforded **31** and set the stage for the final key step. Cyclization was achieved using an excess of SmI_2 to afford a mixture of diastereomeric homoallylic alcohols **30** and **49** (66%, 1:1.5 ratio). The structural assignments of **30** and **49** were confirmed by X-ray crystallography. An additional byproduct (**50**) resulted from formation of a C–C bond between C10 and C13. Formation of product **50** is reminiscent of the challenges faced by the Nicolaou group in their McMurry coupling to generate the C9-C10 bond.^{8,11} Chida found that use of HMPA as a co-solvent was crucial for the success of this reaction, as THF alone led to simply reduction of the aldehyde. Oxidation of **49** gave **51**; all attempts to isomerize the olefin into conjugation failed. DFT calculations of simplified models of **51** and **52** indicated that the conjugated olefin (**52**) was less stable than the skipped enone (**51**).



Scheme 9. Sato-Chida coupling of fragments **32** and **33** and closure of ring B.

Since isomerization of **51** to **52** failed, an alternative route to converge with Takahashi's intermediate was devised (Scheme 10).^{42,43} Stereoselective reduction of **51**, and protection of the resultant alcohol gave the benzyl ether **53**. Dihydroxylation of **53** with an excess of OsO₄, followed by reaction with sodium hydride, carbon disulfide and iodomethane gave the bis-xanthate **54**. Thermal double elimination of **54** led to the conjugated diene **55**. Deprotection of the C4 methoxymethyl ether and oxidation to the ketone set the stage for eventual introduction of a C4 exocyclic methylene via an interrupted Peterson olefination. To this end, addition of the Grignard reagent from (chloromethyl)trimethylsilane yielded the tertiary alcohol **56**. Reduction of **56** with hydrogen in the presence of Pearlman catalyst proceeded via addition at the less substituted C13-C14 olefin as well as cleavage of the C10 benzyl ether; the resultant secondary alcohol was oxidized to a ketone, and elimination of the β-silyl alcohol rendered the exocyclic olefin (**57**). The C7 benzoate ester was exchanged for a triethylsilyl ether over a three-step sequence to afford **58**. Selenium dioxide allylic oxidation of the less substituted exocyclic olefin proceeded in a stereoselective fashion to give **59**. Transformation of **59** to the hydroxyoxetane followed a variation of the methodology utilized in Holton's synthesis.⁷ Thus, mesylation of the C5 hydroxyl, stereoselective dihydroxylation of the exocyclic olefin and treatment with Hunig's base afforded **29**. As an intermediate in Takahashi's formal synthesis,²³ the cyclic carbonate present in **29** was opened with phenyl lithium, followed by acetylation of the C4 tertiary alcohol to generate **60**, which is itself an intermediate in the Danishefsky total synthesis.^{13,14}

The Chida synthesis of chiral ABCD tetracyclic core of taxol required 31 steps from the commercially available achiral 1,3-cyclohexandione and chiral tri-*O*-acetyl-D-glucal resulted in ~0.12% overall yield. Approximately 1/3 of the steps involve protection or deprotection while approximately 1/6 of the steps were utilized for oxidations or reductions.

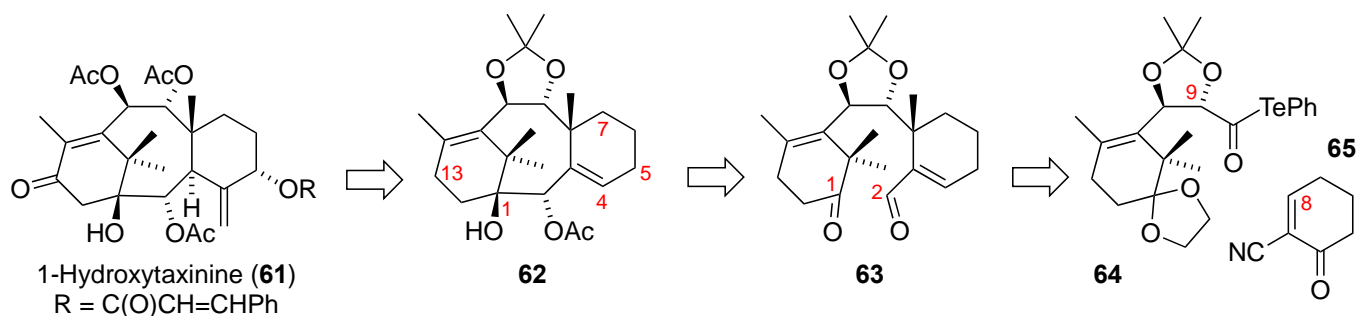


Scheme 10. Final steps of the Chida formal synthesis.

3. Total Syntheses

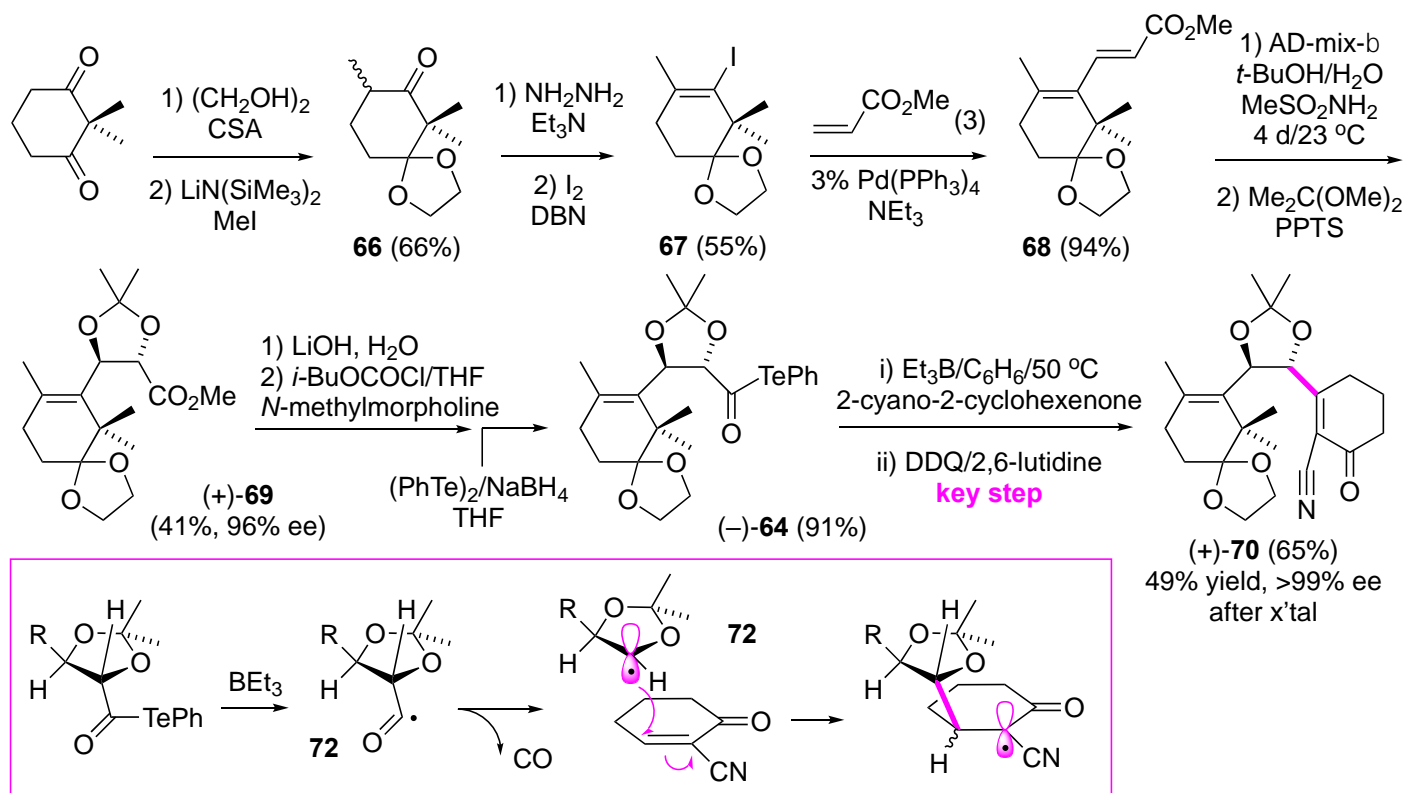
3.1. Inoue total synthesis of 1-hydroxytaxinine (A + C > AC → ABC)

Inoue's group reported the first total synthesis of 1-hydroxytaxinine (**61**, Scheme 11).⁴⁹ Their retrosynthetic analysis required the introduction of oxygen functionality at C5, C7 and C13 of a nearly complete carbon skeleton (**62**). They envisioned generation of the C1-C2 bond in the B ring by a pinacol coupling of the keto-aldehyde **63**. This approach is relatively unique, as many of the other syntheses create the C1-C2 bond prior to formation of the central eight-membered ring. Precursor **63** would be accessed by a decarbonylative radical coupling of fragments **64** and **65**.



Scheme 11. Inoue retrosynthetic analysis of 1-hydroxytaxinine.

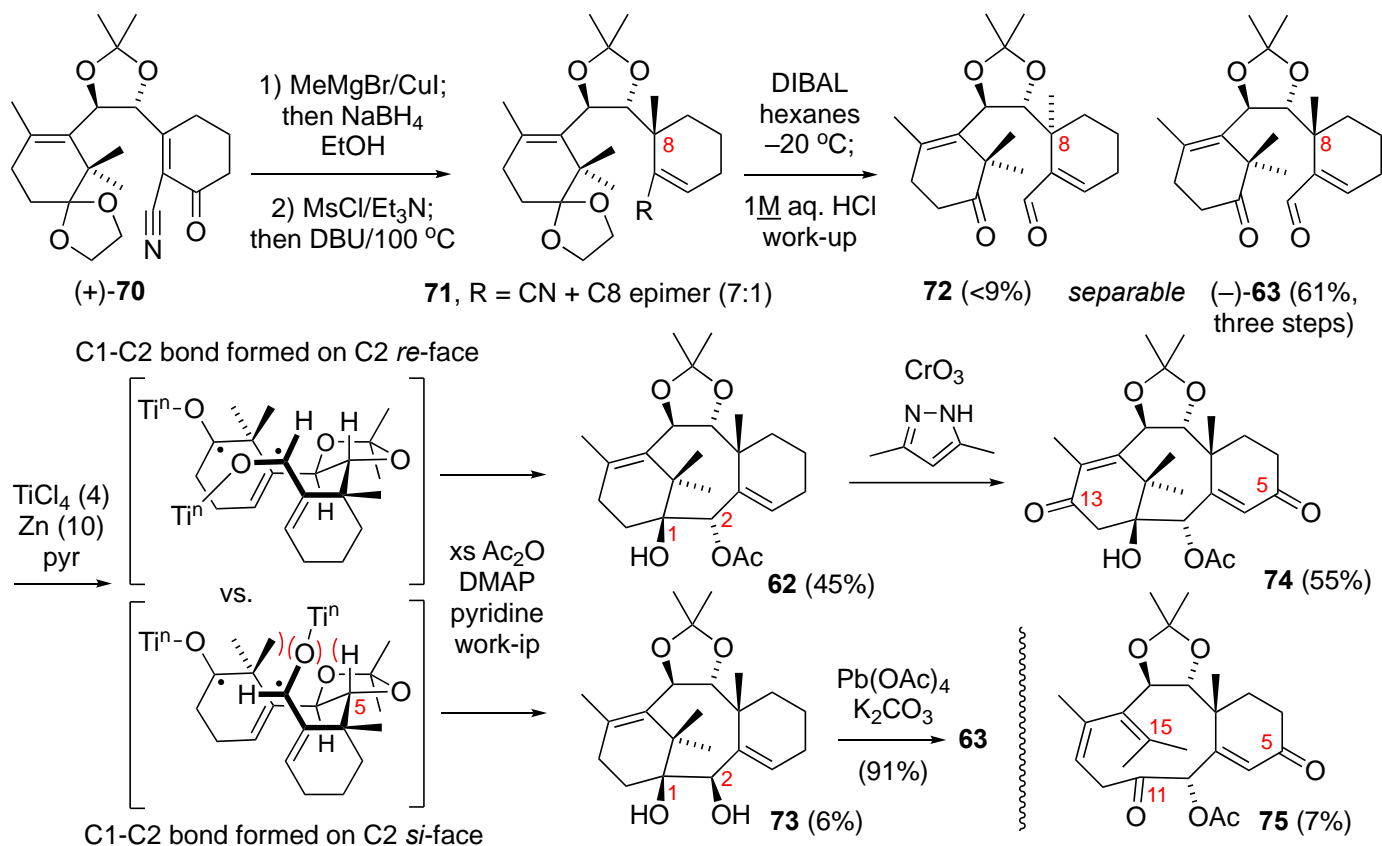
The initial steps for preparation of the A ring fragment are similar to those utilized by Nakada^{36,37} (c.f. Scheme 2). Thus, mono-protection of 2,2-dimethyl-1,3-cyclohexadione followed by α -methylation generated **66**; hydrazone formation and treatment with iodine/DBU gave vinyl iodide **67** (Scheme 12). Heck reaction of **67** with an excess of methyl acrylate led to **68**. Sharpless asymmetric dihydroxylation of dienoate **68** proceeded at the less substituted, albeit more electron-deficient olefin. Since the diol was not completely separable from methyl sulfonamide, the crude mixture was directly protected as acetonide derivative **69**. Conversion of methyl ester **69** to an acyl telluride **64** required saponification, activation with *i*-butyl chloroformate, and reaction with phenyltelluride (prepared by reduction of diphenyl ditelluride). Reduction of the acyl telluride with triethylborane in an open-air reaction, proceeded with formation of the C8–C9 bond in a stereoselective fashion; oxidation of the product with DDQ restored the 2-cyano-2-cyclohexenone ring (**70**). The reductive decarbonylation of **64** proceeded via the acyl radical **71**, and while decarbonylation of **72** immolated the C9 stereocenter, addition of the α -alkoxy radical **72** proceeded from the less sterically hindered face with apparent stereo-retention (see magenta insert).



Scheme 12. Formation of precursor **70** via decarbonylative radical coupling reaction.

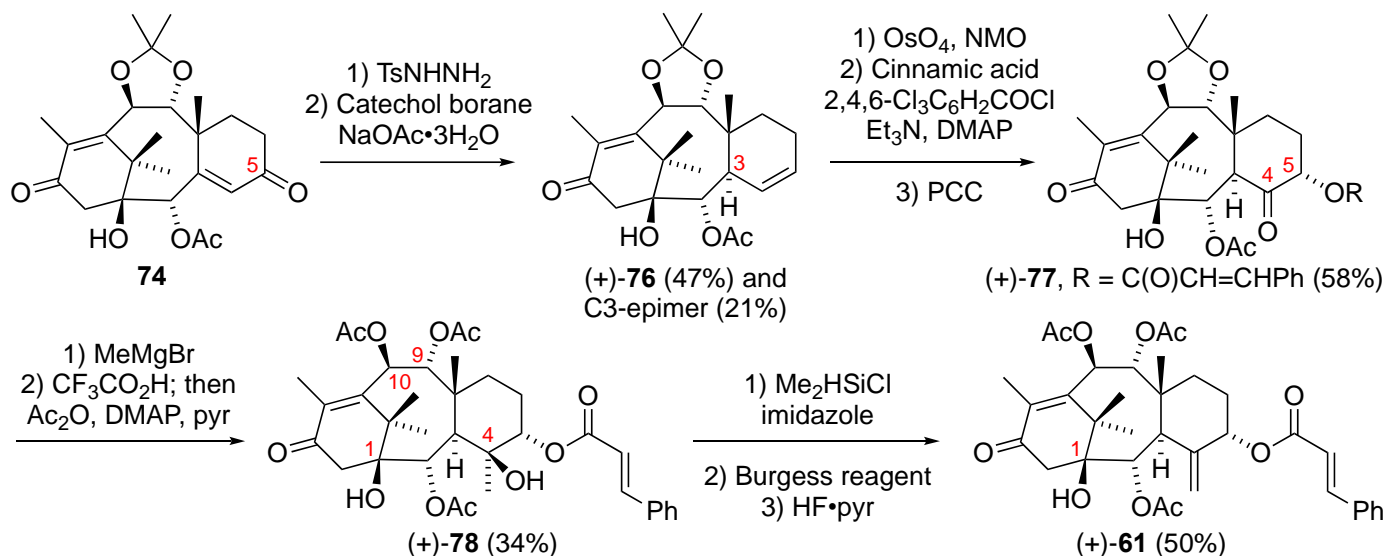
Conjugate addition of methyl Grignard in the presence of CuI to **70** proceeded predominantly on the β -face (Scheme 13).⁴⁹ Reduction of the resultant α -cyano cyclohexanone, mesylation of the secondary alcohol and elimination with DBU gave the corresponding α,β -unsaturated nitrile **71** as an inseparable mixture of diastereomers at C8. Reduction of the nitrile, followed by aqueous acidic work-up (for hydrolysis of the imine and cyclic ketal) led to a separable mixture of the desired stereoisomer (-)-**63** and **72**. A TiCl_4/Zn mediated pinacol coupling of **63**, after work-up with excess acetic anhydride, provided mono-acetate **62** as the major product along with minor amounts of diol **73**. The structure of **62** was corroborated by X-ray crystal structure. The stereochemical outcome was rationalized by proposing that the transition state for C1-C2 bond formation

on the *si*-face of C2 would be higher in energy (compared to the *re*-face) due to steric interactions between the Ti–O moiety with one of the gem-dimethyl groups at C15 as well as with the C5 hydrogen. The undesired diol **73** could be recycled to (–)-**63** by glycol cleavage with Pb(OAc)₄. Exhaustive allylic oxidation at both C5 and C13 was achieved with CrO₃/3,5-dimethylpyrazole to give **74** as the major product along with minor amounts of a product reflecting cleavage of the C1–C15 bond (**75**).



Scheme 13. Closure of B ring by pinacol coupling.

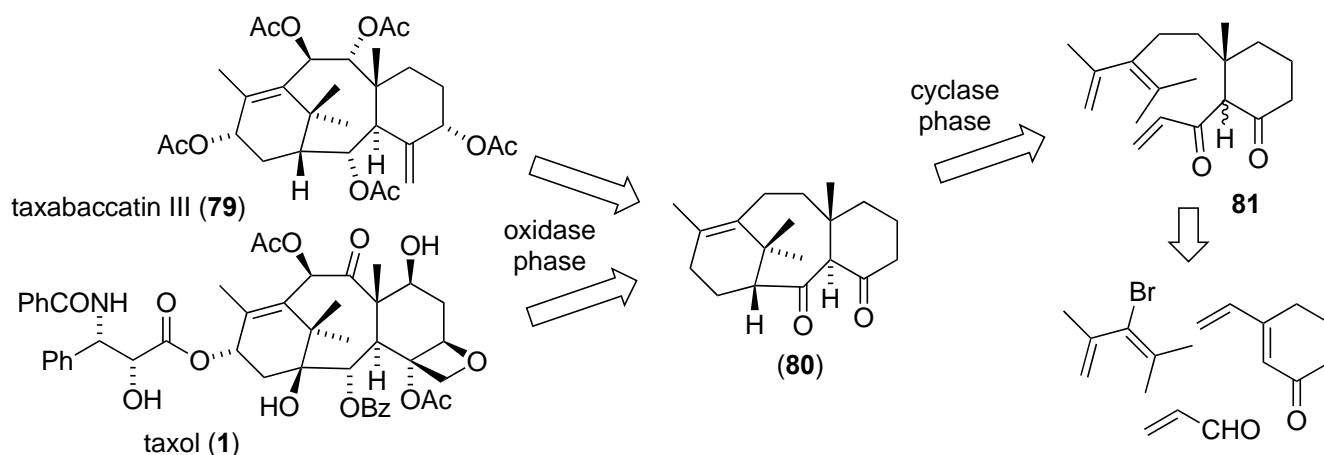
While the oxidation of **62** to **74** introduced oxygen functionality at the desired C5 position, establishment of the C3 stereocenter remained to be accomplished (Scheme 14). To this end, reaction of **74** with tosylhydrazine occurred at the less hindered C5 ketone. Catecholborane reduction took place predominantly on the less hindered *re*-face to generate an allylic diazine that undergoes [3,3]-sigmatropic rearrangement to afford the desired (3*R*)-stereocenter present in **76**. Catalytic osmium dihydroxylation in a stereofacial fashion, esterification of the more accessible C5 alcohol with cinnamic acid and oxidation of the C4 alcohol yielded ketone **77**. Chemo- and stereoselective nucleophilic addition of methyl Grignard to the C4 ketone gave the corresponding tertiary alcohol. Acetonide hydrolysis and chemoselective acetylation of the C9 and C10 secondary alcohols in the presence of the C1 and C4 tertiary alcohols afforded **78**. Attempted dehydration of **78** with Burgess reagent was plagued by rearrangement to afford a 5/7/6 skeleton of the abeotaxane family along with **61**. In order to avoid this rearrangement, the tertiary C1 alcohol of **78** was protected as the dimethylsilyl ether, followed by dehydration of the C4 alcohol with Burgess reagent and cleavage of the silyl ether yielded 1-hydroxytaxinine (+)-**61**.



Scheme 14. Generation of the C3 stereocenter and completion of the synthesis.

3.2. Baran total synthesis of taxabaccatin III (A + C > AC → ABC → oxidase phase)

Baran's approach for taxol synthesis is inspired by the biosynthesis of terpenes via a two-phase process⁵⁰ which his group has applied to other target molecules⁵¹⁻⁵⁴ including taxabaccatin III (**79**),⁵⁵ and most recently taxol.^{56,57} Retrosynthetically, the oxidase phase introduces oxygens onto the taxendione skeleton **80**, which was assembled through Diels-Alder cycloaddition of **81** (Scheme 15). The Diels-Alder precursor was prepared from 3-bromo-2,4-dimethyl-1,3-pentadiene, 3-vinyl-2-cyclohexenone and acrolein.

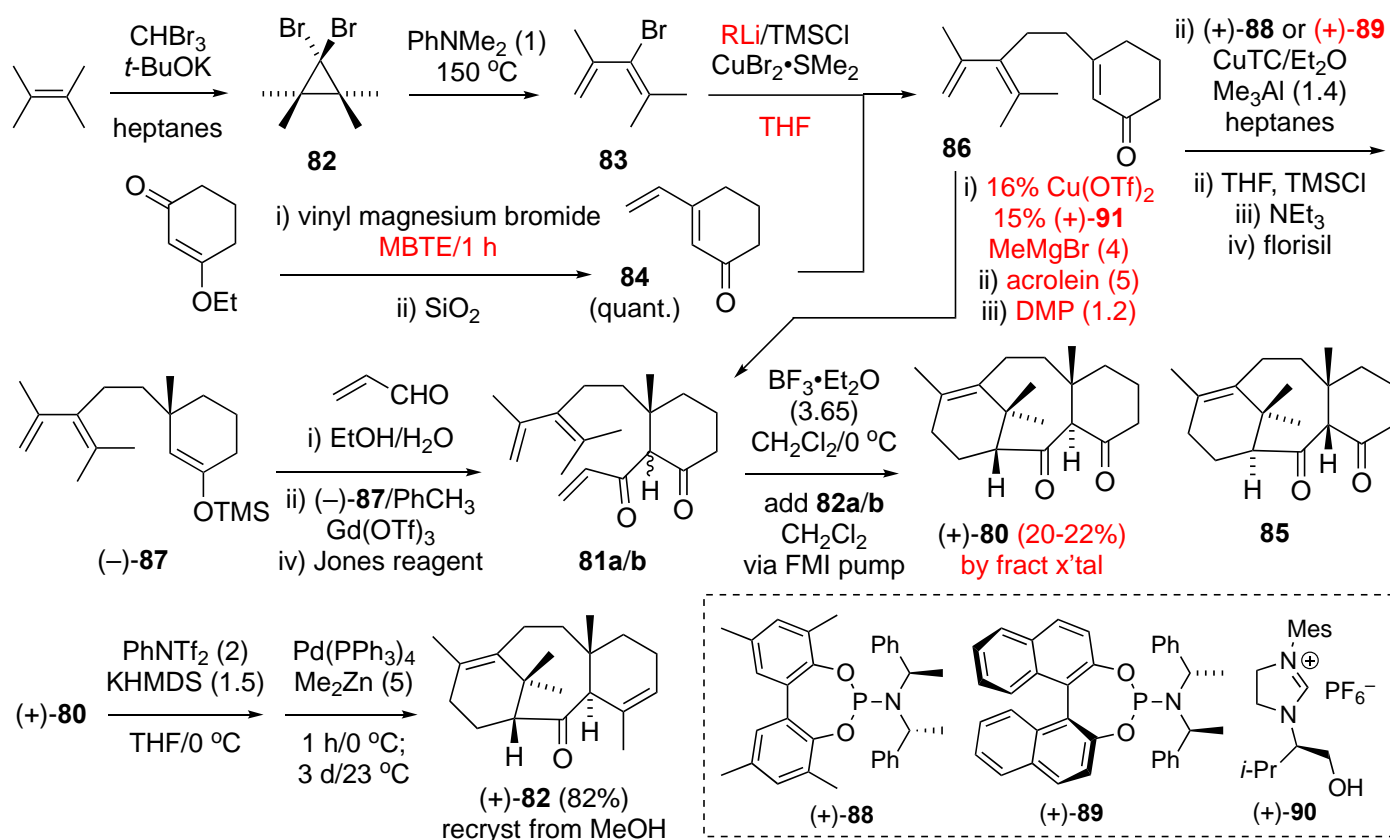


Scheme 15. Retrosynthetic analysis of tax according to Baran's approach.

3.2.1. Process improvements to the synthesis of taxadienone. Refinements of the original⁵⁸ Baran synthesis of (+)-taxadienone (**80**) have followed the same sequence of reactions, however with improvements for scale-up (Scheme 16). Due to concern for highly energetic nature for the ring opening/elimination of *gem*-dibromocyclopropane (**82**) to 3-bromo-2,4-pentadiene (**83**), the process research group at Albany Molecular Research Institute established a continuous flow process for this transformation with a 12.5 min residence time at 150 °C.⁵⁹ Additionally, the AMRI group established a crystallization protocol for separation/purification

of (+)-**80** (20-22% isolated yield) from the ~2:1 mixture of diastereomers **80** and **85** resulting from the intramolecular Diels–Alder cyclization.

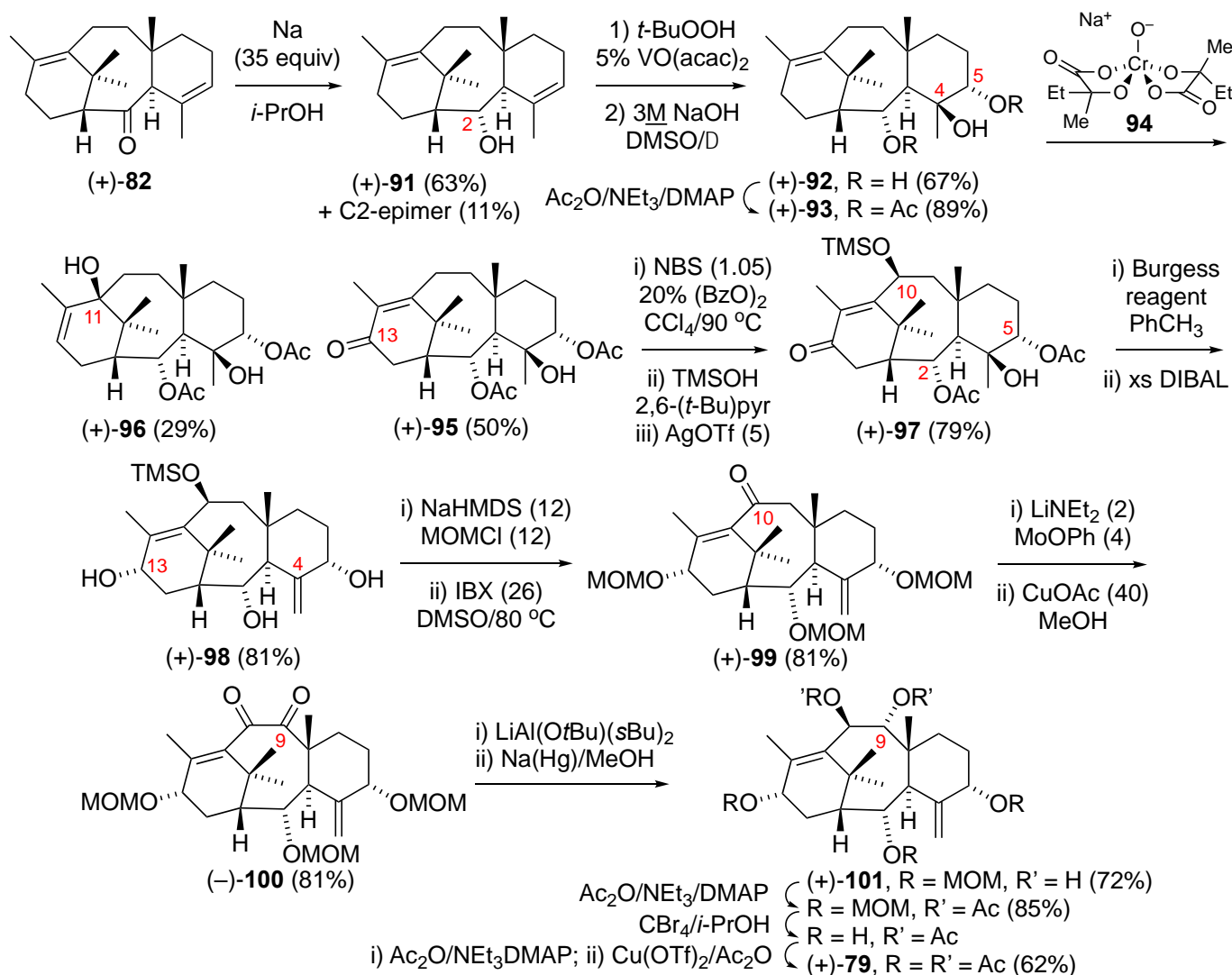
In their recent synthesis of taxol,^{56,57} Baran's group reported using *n*-butyl lithium (in place of *s*-butyl lithium used in their original⁵⁸ synthesis) for the lithium halogen exchange of **83**. A further improvement reported in the recent Baran synthesis concerned a telescoping of the cuprate addition/aldol condensation/oxidation sequence from **86** to the Diels-Alder precursor **81a/b**. This improvement utilized *N*-heterocyclic carbene ligand (+)-**90** (15 mol%) instead of phosphoramidite (+)-**88** for the cuprate addition and the *in situ* aldol condensation with acrolein, followed by a DMP oxidation (in place of Jones reagent). Conducting these reactions also avoided the unstable trimethylsilyl enol ether **87** and shortened overall process time from 3 days to 1 day.



Scheme 16. Synthesis of taxadienone (+)-**82** (CuTC = copper(I)-thiophene-2-carboxylate, process improvements in red).

3.2.2. Oxidase phase synthesis of taxabaccatin III. Baran's group utilized taxadienone (+)-**82** as the starting point for their oxidase phase synthesis of taxabaccatin III (Scheme 17).⁵⁵ Bouveault-Blanc reduction of **82** with sodium in isopropanol gave **91** along with a minor amount of the C2-epimer. Directed epoxidation with VO(acac)₂ followed by alkaline hydrolysis afforded the triol **92**, which was protected as the bis-acetate **93**. Introduction of the C13 and C10 oxygen atoms was informed by the lessons which were learned in their synthesis of taxuyunnanin D.⁵⁴ Thus, allylic oxidation of **93**, using the Cr(V) reagent **94** pioneered in the Baran synthesis of proceeded to give a separable mixture of the desired enone **95** along with minor amounts of the tertiary allylic alcohol **96**. Additionally, oxidation at C10 utilized the radical-mediated protocol with NBS/benzoyl peroxide followed by solvolysis with trimethylsilyl alcohol to yield **97**. Dehydration of **97** with

Burgess reagent and subsequent treatment with excess DIBAL effected reduction at C13 as well as removal of the acetate groups at C2 and C5. The resultant triol was protected as the tris-MOM ether, followed by selective oxidation of the C10 silyl ether to generate the ketone **99**. Introduction of the C9 ketone relied on treatment of the enolate anion of **99** with “MoOPh”,⁶⁰ and CuOAc oxidation of the resultant α -hydroxyketone led to **100**. A sequential application of $\text{LiAlH}(\text{O}t\text{-Bu})(s\text{-Bu})_2$ and sodium amalgam generated diol **101**, which embodied all of the oxygen functionality in the correct positions with the correct stereochemistry. The synthesis was completed by acetylation of the C9 and C10 alcohols, mild removal of the three MOM protecting groups and acetylation of the C2, C5 and C13 alcohols.



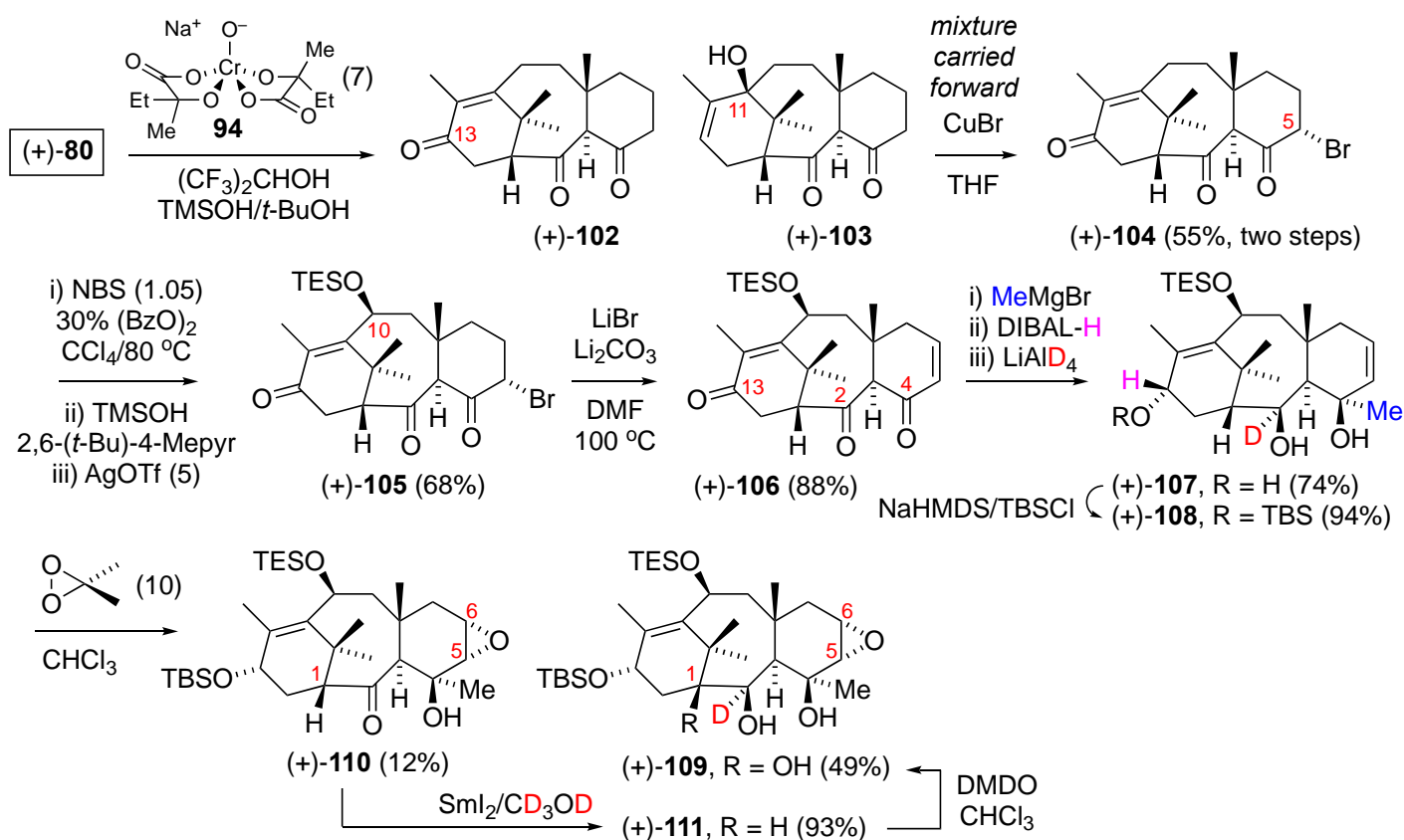
Scheme 17. Baran oxidase phase synthesis of taxabaccatin III.

3.3. Baran oxidase phase synthesis of taxol

While the Baran oxidase phase syntheses of (–)-taxuyunnanine D⁵⁴ and (+)-taxabaccatin III⁵⁵ proceeded in relatively short order from taxadienone (+)-**82** (5 and 13 steps respectively), application of this strategy to the total synthesis of taxol presented considerable challenge. This is due not only to the need to introduce six oxygen atoms but also two of these sites are the secondary neopentyl carbon (C7) and the bridgehead quaternary carbon (C1). The supporting information for the Baran synthesis outlines numerous unsuccessful

attempts at directed C–H oxidation at these two positions. Due to these failures, it was necessary to introduce a C5–C6 olefin to facilitate oxidation at C7.

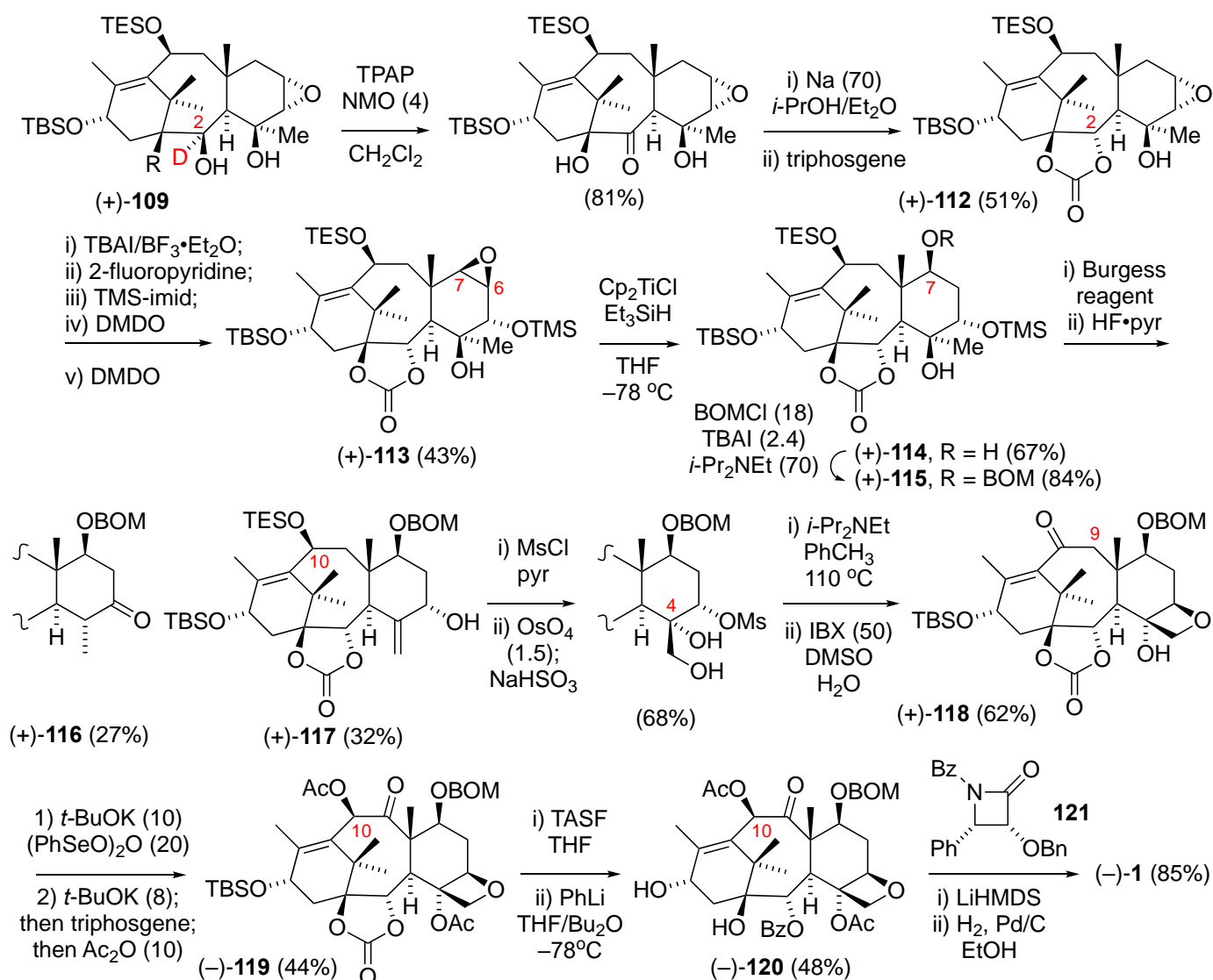
The oxidase phase commenced from the diketone (+)-**80** (Scheme 18),^{56,57} and utilized oxidation protocols at C13 and C10 similar to those pioneered in the (–)-taxuyunnanine D⁵⁴ and (+)-taxabaccatin III⁵⁵ syntheses. Thus, allylic oxidation using the Cr(V) oxidant **94** proceeded at both C13 as well as at C11 to generate a mixture of **102** and **103**; regio- and enantioselective bromination of this mixture using CuBr₂ gave **104** after purification. Radical allylic bromination of **104** followed by silver mediated substitution by triethylsilananol generated **105**. Elimination of HBr introduced the C5–C6 olefin which would eventually be crucial for oxidation at C7. The differential reactivity of the three carbonyl groups in **106** allowed for sequential reaction with methylmagnesium bromide, then DIBAL and finally LiAlD₄ to give triol **107**, which was protected at the secondary allylic alcohol. Oxidation using excess dimethyldioxirane (DMDO) proceeded predominantly at the bridgehead C1 and the less hindered C5–C6 olefin to generate **109**, along with minor amounts of the keto epoxide **110**. Deuterium labelling at C2 of **108** was necessary, since attempted oxidation of the protio-version of **108** with DMDO proceeded predominantly via C2 alcohol oxidation instead of C1 hydroxylation. Thus, deuterium labelling at C2 suppressed this alcohol oxidation via a kinetic isotope effect. The keto epoxide **110** could be further processed into additional **109** by Sml₂ mediated reduction of the C2 ketone, followed by treatment of **111** with excess DMDO.



Scheme 18. Synthesis of taxaepoxide **109**.

Notably, at this stage the stereochemistry at C2 of **109** is opposite to that desired in taxol. The stereochemistry was corrected by an oxidation/reduction sequence, followed by reaction with triphosgene to give the cyclic carbonate **112** (Scheme 19). Lewis acid activated epoxide opening with tetrabutylammonium

iodide, separating the boron salts with 2-fluoropyridine, and protection of the resultant iodohydrin as the TMS ether was followed by iodine oxidation with DMDO leading to a *syn*-elimination. The resultant C6-C7 olefin was epoxidized with further application of DMDO. Titanium mediated epoxide ring opening of **113** in the presence of triethylsilane proceeded regioselectively at the less hindered C6 carbon to give **114**; the C7 alcohol was protected as a BOM ether. Sequential treatment of **115** with Burgess reagent followed by HF-pyridine gave a nearly equimolar, but separable, mixture of ketone **116** along with allylic alcohol **117**; this latter product closely resembled an intermediate in the Holton synthesis⁷ except that it possessed the opposite stereochemistry at C10. Introduction of the oxetane D ring closely followed the precedent set by the Florida State group (as well as that in the Chida formal synthesis^{42,43}). To that end mesylation, followed by dihydroxylation with stoichiometric OsO₄, treatment with Hunig's base and oxidation of the C10 TES ether gave ketone **118**. Oxidation at C9 with selenic anhydride in the presence of water, followed by redox-isomerization, regeneration of the cyclic carbonate and exhaustive acetylation yielded the diacetate **119**. Finally, cleavage of the C13 TBS ether and opening of the carbonate with phenyl lithium yielded **120**. Esterification with lactam **121** followed by hydrogenolysis of the BOM ether completed the total synthesis of taxol [(-)-**1**].

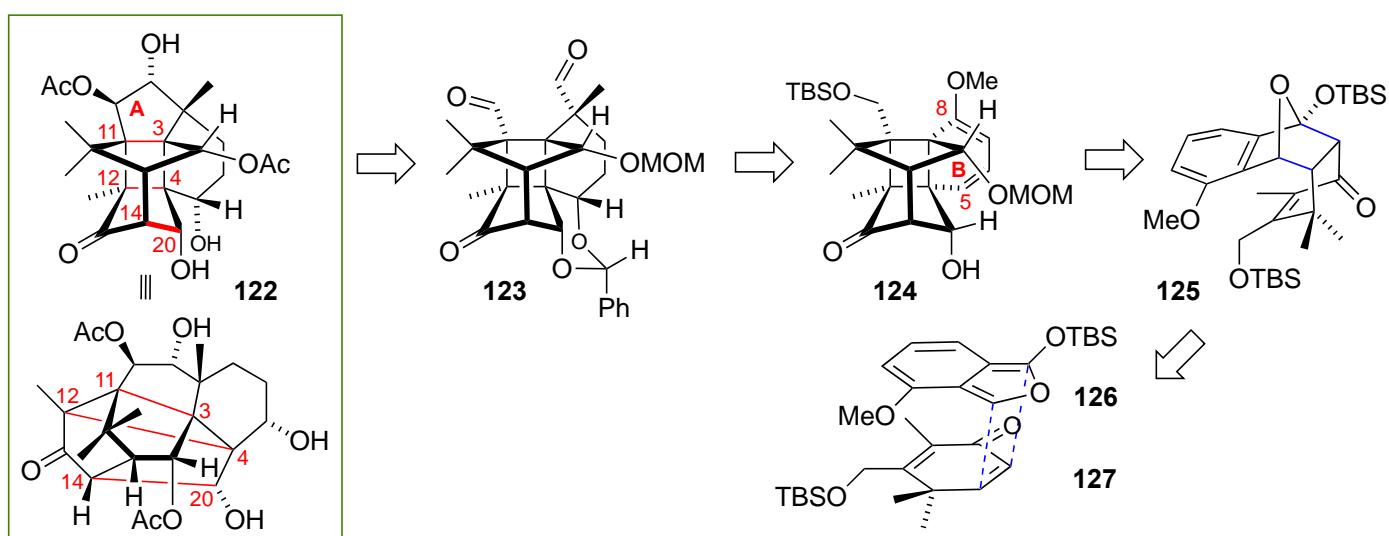


Scheme 19. Baran taxol synthesis end-game.

The Baran two phase enantioselective synthesis of taxol required 27 steps from commercially available achiral tetramethylethylene and 3-ethoxy-2-cyclohexenone resulted in ~0.005% overall yield. Approximately 1/3 of the steps involved protection or deprotection with approximately 1/5 of the steps were utilized for oxidations or reductions. At the time of their report, a total of 35.2 mg of (–)-**1** was produced, representing a 2.5-fold increase in the next greatest quantity produced by prior total syntheses.¹² While the Baran synthesis stands as a significant example of the two-phase approach, there are notable downsides. These include a low yield of the key intramolecular Diels-Alder product (**80**, 20-22%), low yield for formation of **117** from **115** (32%), and relatively low conversion of 5,6-epoxide **112** to C7-alcohol **114** (29%).

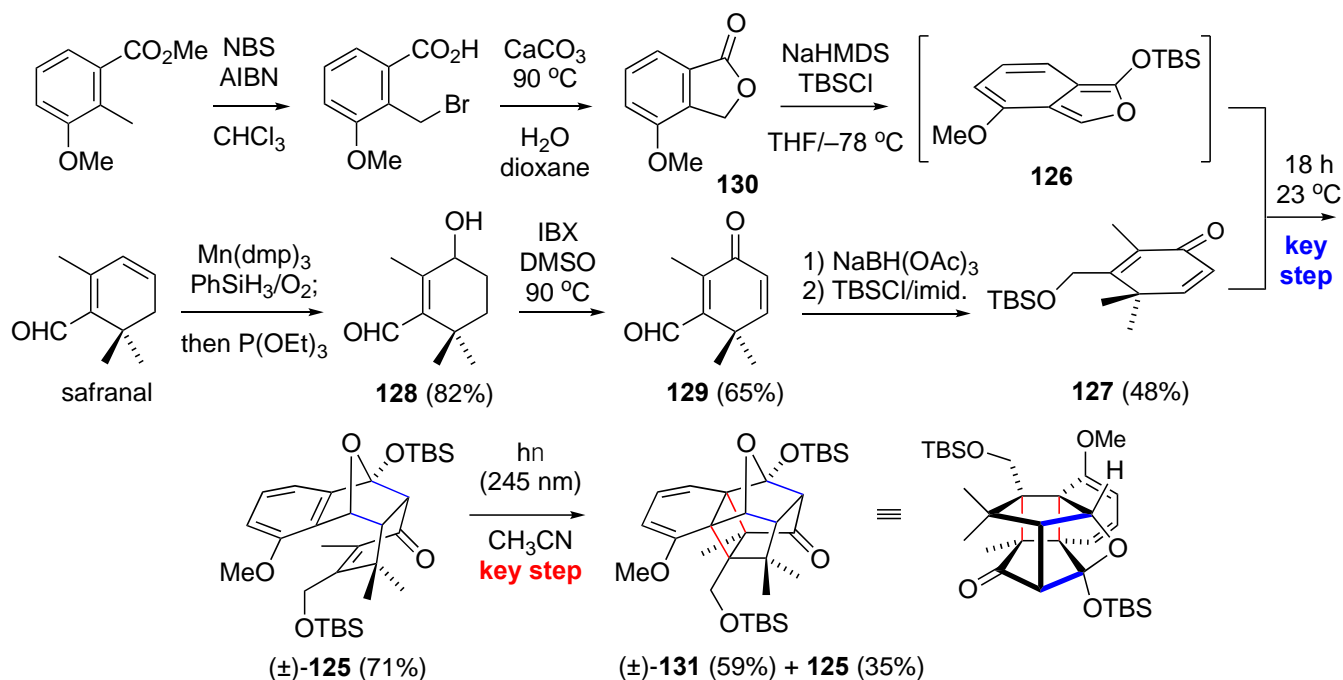
3.4. Gaich synthesis of (±)- and (–)-canataxpropellane

Canataxpropellane (**122**, Scheme 20) is a highly oxidized, heptacyclic diterpene isolated from *Taxus canadensis*, the Canadian yew.⁶¹ It is related to the more common taxoids by virtue of three additional C–C bonds, between C3-C11, C4-C12, and C14-C20. The structure of **122** was assigned on the basis of extensive NMR spectral analysis. The authors proposed⁶¹ that **122** exists as an undefined mixture of interconverting conformers (3:1 ratio), based on an appearance of an additional set of signals in the NMR spectra which they stated showed chemical exchange correlation. No biological data were reported for this compound. Very recently, Gaich's group in Konstanz, Germany reported a total synthesis of both racemic and optically active canataxpropellane.^{62,63} Their retrosynthetic analysis envisioned generation of the cyclopentane A ring by a pinacol coupling of dialdehyde **123**. This dialdehyde can be accessed from **124** by B-ring functionalization at C8 and C5 positions via singlet oxygen cycloaddition. Synthetic intermediate **124** would be generated from an intermediate which resulted from a photochemical [2+2] cyclization of **125** which would itself be constructed via Diels-Alder reaction between isobenzofuran **126** and dienophile **127**.



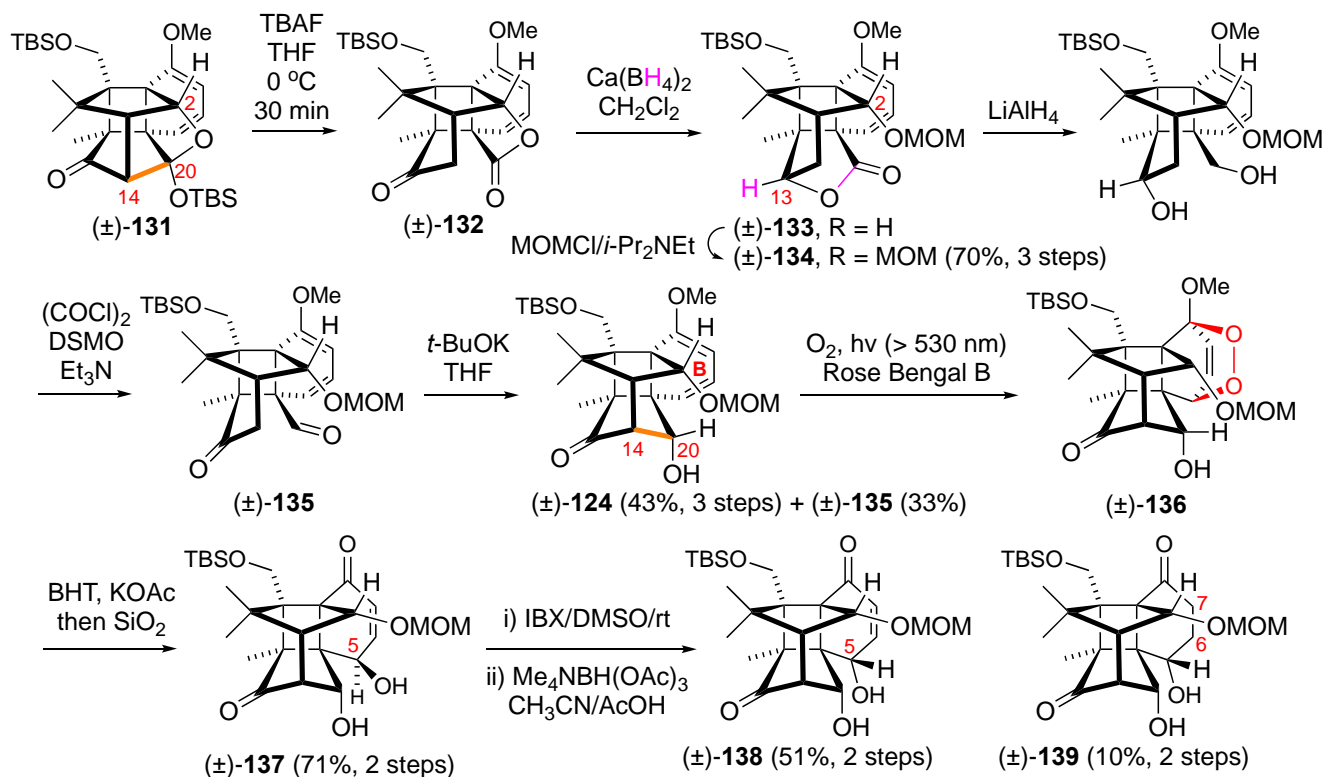
Scheme 20. Gaich retrosynthetic analysis for canataxpropellane.

Dienophile **127** was prepared in three steps from the terpene safranal, by hydration of the distal olefin and oxidation of the γ -hydroxyenal **128** to give the 2,5-cyclohexadienone **129** (Scheme 21).⁶² Reduction with triacetoxyborohydride, and protection of the primary allylic alcohol afforded **127**. Benzylic bromination of methyl 3-methoxy-2-methylbenzoate, followed by lactone formation in the presence of CaCO_3 led to **130**.



Scheme 21. Preparation of hexacyclic intermediate **124** by Diels-Alder and [2+2] photochemical cyclization.

Treatment of lactone **130** with base followed by quenching with *t*-butyldimethylsilyl chloride gave the isobenzofuran **126** which was not isolated but instead immediately reacted with **127** to give (\pm)-**125** with excellent endo-selectivity. Irradiation of a degassed solution of **125** at 254 nm afforded (\pm)-**131** along with recovered starting material. Recovered **125** could be recycled to eventually give 71% of the desired **131**.

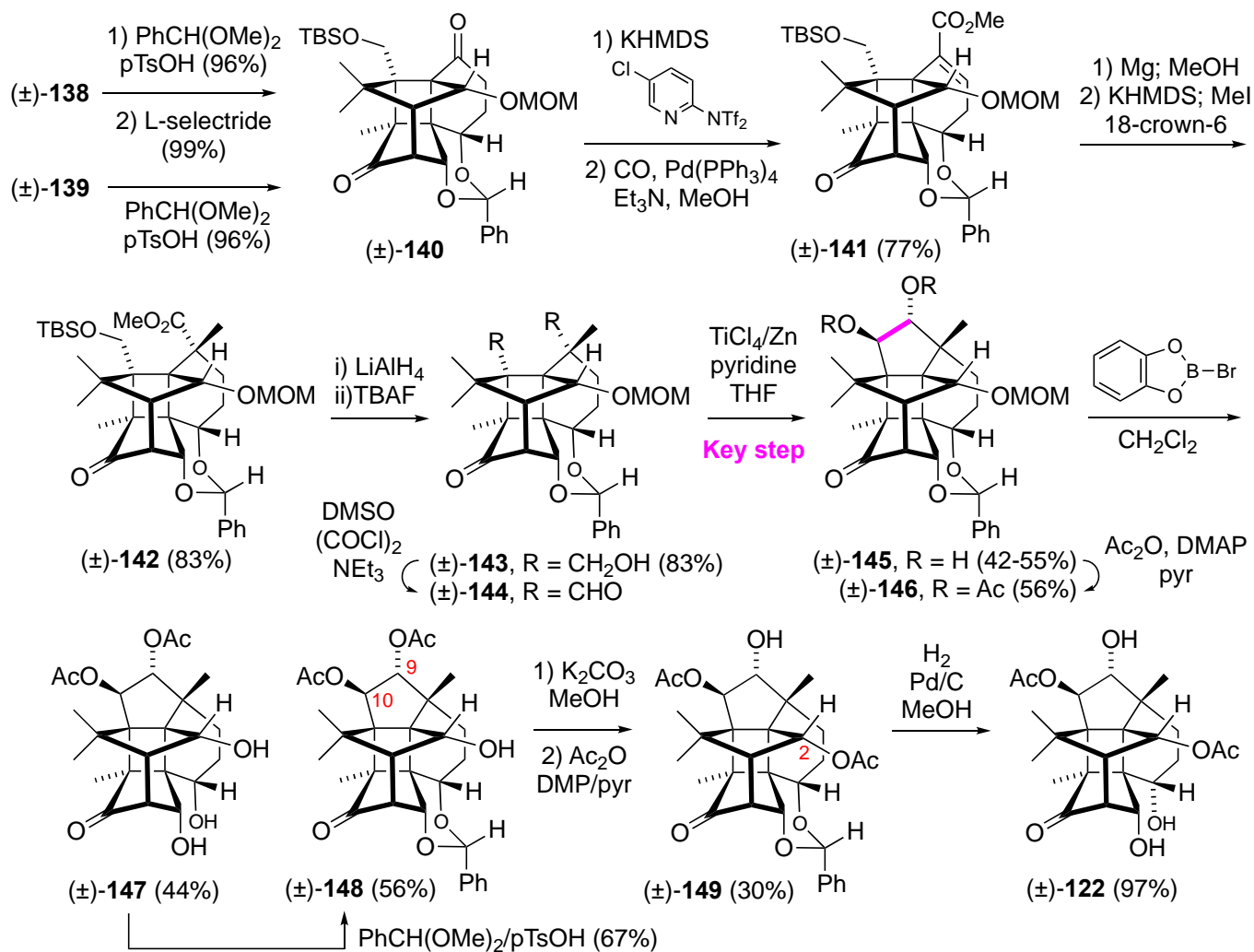


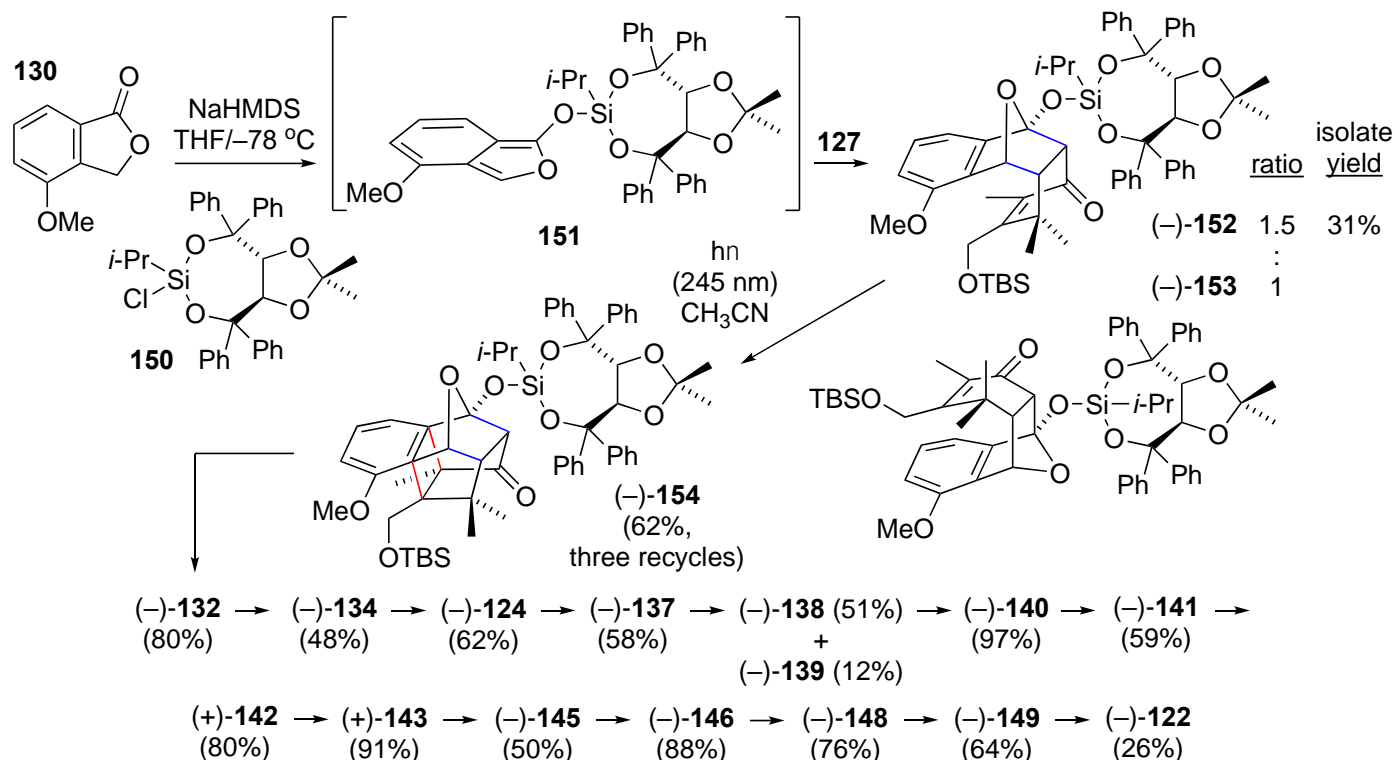
Scheme 22. Generation of the cyclic core of cataxpropellane skeleton via cycloaddition.

While **131** contains six of the required seven rings present in the target structure along with oxygenation at C2 with the appropriate stereochemistry, cleavage of the C20-bridging oxygen bond required a sequence of 6 steps. To this end, treatment of **131** with TBAF initiated a retroaldol reaction cleaving the C14-C20 bond (Scheme 22). Stereoselective reduction of the resultant ketone **132** resulted in a *trans*-lactonization to give **133**; the C2 alcohol was protected as a MOM ether. Reduction of **134** followed by Swern oxidation and base-mediated aldol condensation reinstalled the C14-C20 bond with appropriate stereochemistry at C20. Attention was next turned to elaboration of the methoxycyclohexadiene B ring. Singlet oxygen cycloaddition gave a single endoperoxide (**136**) which was immediately reduced with 2,6-di-tert-butyl-4-methylphenol (BHT) to yield hydroxyenone **137** in a good yield. Attempted reduction with other standard endoperoxide reducing agents (thiourea; H₂, catalyst; L-selectride; HN=NH) resulted in considerably lower yields. Since the stereochemistry at C5 of **137** was opposite to that required for the target molecule, an oxidation/reduction sequence was used to generate the desired hydroxyenone **138**, along with a minor amount of the product resulting from reduction of the C6-C7 olefin (**139**). The structure of **138** was secured by X-ray crystallographic analysis.

Either **138** or **139** could be converted into the benzylidene acetal **140** (Scheme 23). Vinyl triflate formation from **140** using Comin's reagent to convert the carbonyl to an enol triflate, set the stage for Pd-catalyzed carboxymethylation. Reduction of the resultant enoate **141** with Mg in methanol produced a saturated ester which underwent deprotonation and α -methylation with iodomethane to afford **142**. Reduction of **142** with LiAlH₄ and treatment with TBAF led to diol **143**. Bisaldehyde **144**, generated by Swern oxidation of **143**, was subjected to a pinacol coupling with TiCl₄/Zn metal to yield diol **145** as a single stereoisomer, which comprises the complete carbon skeleton and oxidation level of the target, cantaxpropellane. To complete the synthesis, **145** was peracetylated, before deprotection of the MOM ether with 2-bromo-1,3,2-benzodioxaborole gave a separable mixture of alcohol **148** and triol **147**; this latter product could be recycled into additional **148** by reintroducing the benzylidene acetal. The less sterically hindered C9 acetate underwent selective methanolysis and the resulting diol was selectively acetylated at the C2 alcohol. Finally reductive removal of the benzylidene acetal gave *rac*-cantaxpropellane (\pm)-**122**. Notably, the NMR spectral data for synthetic **122** matched the major set of signals from the isolation work reported by Kiyota's group.⁶¹ For this reason, Graich suggested⁶² that the second set of signals found in their isolation product may be due to a related derivative of **122** rather than a conformer.

Since the cycloaddition of achiral components **126** and **127** generates racemic **125**, a synthesis of (–)-**122** would require either an enantioselective Diels-Alder reaction, or separation of enantiomers or diastereomers at some early stage. Attempts to use Lewis or Bronsted acid catalysts for the Diels-Alder reaction led to decomposition of the cycloadduct **125**. Reaction of the anion generated from lactone **130** with a TADDOL based silyl chloride **150** yielded chiral isobenzofuran **151**, which upon reaction with the cyclohexadienone **127** generated a separable mixture of diastereomers (–)-**152** and (–)-**153** (~3:2 ratio) from which pure (–)-**152** was isolated in 31% yield (Scheme 24). Photocycloaddition of **152** gave (–)-**154** and treatment with TBAF gave the optically active synthetic intermediate (–)-**132**, which was assessed as >98% ee by chiral HPLC. The absolute configuration of (–)-**132** was established by X-ray crystal structure analysis [Flack $x = -0.11(7)$; Hooft $y = -0.030(18)$] as well circular dichroism. Lactol (–)-**132** was processed by the same sequence of reactions as in the racemic synthesis to subsequently yield optically active (–)-canataxpropellane.

Scheme 23. Completion of the synthesis of *rac*-cataxpropellane.



Scheme 24. Synthesis of (-)-canataxpropellane [(-)-122] via separation of Diels-Alder diastereomers.

Conclusions

While the first syntheses of taxol⁷⁻¹² were reported more than 25 years ago, it is clear from the work of the last 5 years that there is continued interest in this and related targets. Since the industrial preparation of taxol is a semisynthetic route, the value of these total synthesis efforts lies in the development of novel synthetic transformations which might be applied to different targets. Baran's two-phase approach reveals the particular challenge involved in selective C–H oxidation at unfunctionalized sites. It might be anticipated that the next frontier to be advanced may focus on the synthesis of other taxoid natural products as represented by the Gaich synthesis of canataxpropellane.

Abbreviations used

BHT = 2,6-di-tert-butyl-4-methylphenol

BOM = benzyloxymethyl

DBN = 1,5-diazabicyclo[4.3.0]non-5-ene

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone

DIBAL = diisobutylaluminum hydride

DMDO = dimethyldioxirane

DMP = Dess-Martin periodinane (3-oxo-1,3-dihydro-1λ⁵,2-benziodoxole-1,1,1-triyl triacetate)

3,5-DMP = 3,5-dimethylpyrazole

FDA = Food and Drug Administration

HMPA = hexamethylphosphoramide

LDA = lithium diisopropylamide

MOM = methoxymethyl

MoOPH = oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)

NMR = nuclear magnetic resonance

PCC = pyridinium chlorochromate

TADDOL = $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

TBAF = tetra-*n*-butylammonium fluoride

TBS = *t*-butyldimethylsilyl

TES = triethylsilyl

THP = tetrahydropyran

TMS = trimethylsilyl

References

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.
<https://doi.org/10.1021/ja00738a045>
2. Wang, Y.-F.; Shi, Q.-W.; Dong, M.; Kiyota, M.; Gu, Y.-C.; Cong, B. *Chem. Rev.* **2011**, *111*, 7652-7709.
<https://doi.org/10.1021/cr100147u>
3. Kim, S. H.; Kim, M.-J.; Kim, Y. J.; Chang, H.; Kim, J. W.; Lee, J.-O.; Lee, K.-W.; Kim, J. H.; Bang, S.-M.; Lee, J. S. *Medicine (Baltimore)* **2017**, *96*, e8176.
<https://doi.org/10.1097/MD.00000000000008176>
4. Li, Q.; Ma, Z.; Liu, Y.; Kan, X.; Wang, C.; Su, B.; Li, Y.; Yang, Y.; Wang, P.; Lou, Y.; Na, D.; Wang, L.; Zhang, G.; Zhu, X.; Wang, L. *FEBS J.* **2016**, *283*, 2836-2852.
<https://doi.org/10.1111/febs.13767>
5. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665-667.
<https://doi.org/10.1038/277665a0>
6. Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598.
<https://doi.org/10.1021/ja00083a066>
7. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599-1600.
<https://doi.org/10.1021/ja00083a067>
8. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634.
<https://doi.org/10.1038/367630a0>
9. Nicolaou, K. C.; Nantermet, P. B.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633.
<https://doi.org/10.1021/ja00107a006>

10. Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634-644.
<https://doi.org/10.1021/ja00107a007>
11. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645-652.
<https://doi.org/10.1021/ja00107a008>
12. Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chada, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 653-659.
<https://doi.org/10.1021/ja00107a009>
13. Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 1723-1726.
<https://doi.org/10.1002/anie.199517231>
14. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859.
<https://doi.org/10.1021/ja952692a>
15. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciari, T. P.; Muhlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tommoda, D. *J. Am. Chem. Soc.* **1977**, *119*, 2755-2756.
<https://doi.org/10.1021/ja9635387>
16. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1977**, *119*, 2757-2758.
<https://doi.org/10.1021/ja963539z>
17. Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980-12981.
<https://doi.org/10.1021/ja963539z>
18. Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811-3820.
<https://doi.org/10.1021/ja9939439>
19. Mukaiyama, T.; Shina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad. Ser. B* **1997**, *73B*, 95-100.
<https://doi.org/10.2183/pjab.73.95>
20. Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1-2.
21. Shiina, I.; Saitoh, K.; Frechard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3-4.
<https://doi.org/10.1246/cl.1998.3>
22. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *1*, 121-161.
[https://doi.org/10.1002/\(SICI\)1521-3765\(19990104\)5:1<121::AID-CHEM121>3.0.CO;2-O](https://doi.org/10.1002/(SICI)1521-3765(19990104)5:1<121::AID-CHEM121>3.0.CO;2-O)
23. Doi, T.; Fuse, S.; Miyamoto, S.; Nakai, K.; Sasuga, D.; Takahashi, T. *Chem. Asian J.* **2006**, *1*, 370-383.
<https://doi.org/10.1002/asia.200600156>
24. Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558-6560.
<https://doi.org/10.1021/ja00227a043>

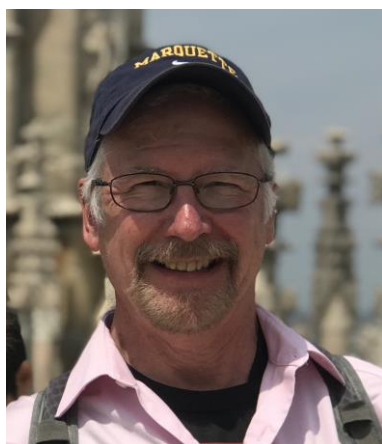
25. Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203-5212.
<https://doi.org/10.1021/ja9805371>
26. Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213-5225.
<https://doi.org/10.1021/ja980538t>
27. Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186-9187.
<https://doi.org/10.1021/ja9610949>
28. Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072-3082.
<https://doi.org/10.1021/ja984250f>
29. Mukaiyama, T. *Tetrahedron* **1999**, *55*, 8609-8670.
[https://doi.org/10.1016/S0040-4020\(99\)00437-8](https://doi.org/10.1016/S0040-4020(99)00437-8)
30. Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. *Prog. Chem. Org. Nat. Prod.* **2002**, *84*, 53-225.
https://doi.org/10.1007/978-3-7091-6160-9_2
31. Xiao, Z.; Itokawa, H.; Lee, K.-H. *Med. Arom. Plants Indust. Profiles* **2003**, 245-297.
32. Zefirova, O. N.; Nurieva, E. V.; Ryzhov, A. N.; Zyk, N. V.; Zefirova, N. S. *Russ. J. Org. Chem.* **2005**, *41*, 315-351.
<https://doi.org/10.1007/s11178-005-0168-0>
33. Wilson, R. M.; Danishefsky, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1207-1226.
<https://doi.org/10.1039/b611967k>
34. Urabe, D.; Asaba, T.; Inoue, M. *Chem. Rev.* **2015**, *115*, 9207-9231.
<https://doi.org/10.1021/cr500716f>
35. Borah, J. C.; Boruwa, J.; Barua, N. C. *Curr. Org. Chem.* **2007**, *4*, 175-199.
<https://doi.org/10.2174/157017907780598899>
36. Hirai, S.; Utsugi, M.; Iwamoto, M.; Nakada, M. *Chem. Eur. J.* **2015**, *21*, 355-359.
<https://doi.org/10.1002/chem.201404295>
37. Utsugi, M.; Iwamoto, M.; Hirai, S.; Kawada, H.; Nakada, M. *J. Synth. Org. Chem., Jpn.* **2017**, *75*, 1102-1114.
<https://doi.org/10.5059/yukigoseikyokaishi.75.1102>
38. Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487-5493.
[https://doi.org/10.1016/S0040-4020\(01\)91348-1](https://doi.org/10.1016/S0040-4020(01)91348-1)
39. Utsugi, M.; Kamada, Y.; Miyamoto, H.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 6868-6872.
<https://doi.org/10.1016/j.tetlet.2007.07.179>
40. Hirai, S.; Urushizako, N.; Miyano, M.; Fujii, T.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 1888-1892.
<https://doi.org/10.1016/j.tetlet.2013.01.115>
41. Momose, T.; Setoguchi, M.; Fujita, T.; Tamura, H.; Chida, N. *Chem. Commun.* **200**, 2237-2238.
42. Fukaya, K.; Tanaka, Y.; Sato, A. C.; Kodama, K.; Yamazaki, H.; Ishimoto, T.; Nozaki, Y.; Iwaki, Y. M.; Yuki, Y.; Umei, K.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2570-2573.
<https://doi.org/10.1021/acs.orglett.5b01173>
43. Fukaya, K.; Kodama, K.; Tanaka, Y.; Yamazaki, H.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2574-2577.
<https://doi.org/10.1021/acs.orglett.5b01174>
44. Tormakangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron* **202**, *58*, 2175-2181.
[https://doi.org/10.1016/S0040-4020\(02\)00089-3](https://doi.org/10.1016/S0040-4020(02)00089-3)
45. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570-575.
<https://doi.org/10.1039/J39690000570>

46. Koto, S. *Glycoscience* Ed. Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. Springer-Verlag, Berlin, Germany, **2001**, *1*, 785-874.
https://doi.org/10.1007/978-3-642-56874-9_24
47. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682-685.
<https://doi.org/10.1021/jo00424a023>
48. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.
<https://doi.org/10.1055/s-1994-25538>
49. Imamura, Y.; Yoshioka, S.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 12159-12163.
<https://doi.org/10.1002/anie.201906872>
50. Ishihara, Y.; Baran, P. S. *Synlett* **2010**, 1733-1745.
<https://doi.org/10.1055/s-0030-1258123>
51. Foo, K.; Usui, I.; Gotz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11491-11495.
<https://doi.org/10.1002/anie.201206904>
52. Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59-63.
<https://doi.org/10.1126/science.1230631>
53. Jorgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878-882.
<https://doi.org/10.1126/science.1241606>
54. Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4909-4912.
<https://doi.org/10.1021/ja501782r>
55. Yuan, C.; Jin, Y.; Wilde, N. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8280-8284.
<https://doi.org/10.1002/anie.201602235>
56. Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020**, *142*, 10526-10533.
<https://doi.org/10.1021/jacs.0c03592>
57. Kanda, Y.; Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293-10320.
<https://doi.org/10.1021/acs.joc.0c01287>
58. Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nature Chem.* **2012**, *4*, 21-25.
<https://doi.org/10.1038/nchem.1196>
59. Krasutsky, S. G.; Jacobo, S. H.; Tweedie, S. R.; Krishnamoorthy, R.; Filatov, A. S. *Org. Process Res. Dev.* **2015**, *19*, 284-289.
<https://doi.org/10.1021/op500314c>
60. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188-196
<https://doi.org/10.1021/jo00396a002>
61. Huo, C.-H.; Su, X.-H.; Wang, Y.-F.; Zhang, X.-P.; Shi, Q.-W.; Kiyota, H. *Tetrahedron Lett.* **2007**, *48*, 2721-2724.
<https://doi.org/10.1016/j.tetlet.2007.02.063>
62. Schneider, F.; Samarin, K.; Zanella, S.; Gaich, T. *Science* **2020**, *367*, 676-681.
<https://doi.org/10.1126/science.aay9173>
63. Reuss, F.; Heretsch, P. *Angew. Chem. Int. Ed.* **2020**, *59*, 10232-10234.
<https://doi.org/10.1002/anie.202002118>

Authors' Biographies



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William A. Donaldson was born near Philadelphia, Pennsylvania. He received his B.A. degree in Chemistry from Wesleyan University (1977), and his Ph.D. in Organometallic Chemistry from Dartmouth College (1981) working with Prof. Russell Hughes, before conducting postdoctoral research with the late Prof. Myron Rosenblum at Brandeis University (1981-1982). He joined the faculty at Marquette University in 1983, rising through the ranks to full professor in 1996. He held an Alexander von Humboldt research fellowship at Philipps Universitat-Marburg (1990-1991) and was a Visiting Professor at the University of Strathclyde (2015). His research has centered on the application of organoiron complexes to organic synthesis, synthesis of hydropyran natural products and generation of molecular complexity from simple hydrocarbons. More recently, his research has focused on the development of estrogen receptor- β selective agonists. He is a co-

founder and President of a start-up company, Estrigenix Therapeutics. Upon retiring from formal teaching and service from Marquette he will be employed with managing and directing the synthetic efforts at Estrigenix.

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