Comparative Syntheses of Taxol

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The players:

- Robert Holton, FSU, 1993
- K.C. Nicolaou, Scripps, 1994
- Sam Danishefsky, Columbia, 1995
- Paul Wender, Stanford, 1996
- Isao Kuwajima, Kansai Inst, 1999
- Tetsuaki Mukaigawa, Science Univ. of Tokyo, 1999

The game:

Structural Features of Taxanes

- Generally characterized by a common 6-8-6 tricyclic ring system, or related skeleton

Structure of Taxol elucidated 1971, but many others discovered both before and later

- Useful reviews:
**Proposed Biosynthesis of Taxanes**

- Biosynthetic studies are lacking, but synthesis presumed to go through geranylgeranyl pyrophosphate

![Chemical structures]

- Although this mechanism is generally accepted, attempts to convert Verticillane to taxanes have been unsuccessful; it is presumed particular oxygenations provide a conformational bias

**Biological Sources and Activity**

- Knowledge of the biological potency of the yew tree goes back millenia

![Yew tree image]

- While currently a massively successful drug, Taxol took many years to gain interest as a pharmaceutical agent

- Bioactivity of taxol discovered in 1962, but mode of action not found until 1979

- Taxol acts as a microtubule stabilizer, interrupting cell division (now known in the Epothilones, Rhazinilam, etc)

- Currently used against metastatic ovarian and breast cancers, and being tested against other indications
The Holton Approach

- Holton began on the premise of a ring expansion to make the required 8-ring.
- The remainder of the synthesis grapples with installation of the C- and D-rings.

Source of selectivity in the aldol not commented upon, some compounds are mixtures of conformations.

Starting from a natural source, this approach quickly accesses much of the requisite functionality.
**The Holton Approach**

**Functionalization of the C-ring proves lengthy**

1. O₃
2. KMnO₄
3. CH₂Al₂
4. TESO
5. TBSCO
6. 93% yield

- LDA
- TESO
- TBSCO
- 84% yield

- 1) pTSCH₂
- 2) PhSiK, 78°C; H₂
- TBSCO
- 92% yield

- 1) MeMgBr
- 2) SO₂Et₃N·OH
- TESO
- 59% yield


**Introduction of the D-ring is largely uneventful**

1. PhLi
2. TPAP, NMO
3. TBSO
4. 85% yield

- 1) DBU, 100°C
- 2) Ac₂O
- 3) HF·pyridine
- TBSO
- 56% yield

- 1) PhLi
- 2) TPAP, NMO
- TBSO
- 65% yield

The Holton Approach

An interesting oxidation sets up the endgame

\[
\begin{align*}
& \text{(oxidation)} \\
& \text{quantitative}
\end{align*}
\]

Completion of the synthesis is now readily achieved

\[
\begin{align*}
& \text{94\% yield} \\
& \text{93\% yield}
\end{align*}
\]

Taxol is completed in ca. 41 steps in 2\% overall yield from (-) patchino

The Nicolaou Approach

The plan calls for a late 8-ring formation and a convergent A- and C-ring union

The Nicolaou Approach

Formation of the A-ring precursor occurs in 7 steps

The Nicolaou Approach

- Formation of the C-ring precursor occurs in 13 steps

\[ \text{HO} \xrightarrow{1) \text{TPSCl}} \xrightarrow{2) \text{O}_2} \xrightarrow{3) \text{HWE olefination}} \xrightarrow{4) \text{TBAF}} \text{CO}_2\text{R} \]

\[ \xrightarrow{\text{PhB(OH)I}_2 \text{ 90°C}} \]

\[ \xrightarrow{1) \text{TBSOTf}} \xrightarrow{2) \text{LAI}} 89\% \text{ yield} \]

\[ \xrightarrow{1) \text{CSA}} \xrightarrow{2) \text{TPSCl}} \xrightarrow{3) \text{KOH, BnBr, n-BuLi}} 76\% \text{ yield} \]

\[ \xrightarrow{1) \text{LAI}} \xrightarrow{2) \text{CSA}} \xrightarrow{3) \text{TPAP, NMO}} 61\% \text{ yield} \]


The Nicolaou Approach

- Union of the two fragments allows access to a mostly-formed skeleton

\[ \xrightarrow{n-\text{BuLi}} \]

\[ \xrightarrow{\text{Nu}} 82\% \text{ yield} \]

\[ \xrightarrow{\text{VO(acac)}_2} \xrightarrow{\text{IBuOOH}} \]

\[ 87\% \text{ yield} \]

The Nicolaou Approach

- Closure of the B-ring proves...difficult

\[
\begin{align*}
\text{TB} & \xrightarrow{1) \text{LAH}} \text{TB}^* & \xrightarrow{2) \text{Phosgene}} & \text{TB}^* \quad \text{58\% yield} \\
\text{TB}^* & \xrightarrow{1) \text{TBAF}} \text{TB}^{**} & \xrightarrow{2) \text{TPAP, NMO}} & \text{TB}^{**} \quad \text{23\% yield}
\end{align*}
\]


- McMurry coupling, based perhaps on precedent of verticellene, is heavily optimized to no avail

The Nicolaou Approach

- Mechanistic divergence leads to a multitude of products

\[
\begin{align*}
\text{TB}^{**} & \xrightarrow{\text{TiCl}_4(\text{DME})} \text{TB}^{***} & \xrightarrow{\text{Zn-Cu, DME 70\degree C}} & \text{TB}^{***} \\
\text{TB}^{***} & \xrightarrow{\text{TiCl}_4(\text{DME})} \text{TB}^{****} & \xrightarrow{\text{Zn-Cu, DME 70\degree C}} & \text{TB}^{****} \\
\text{TB}^{****} & \xrightarrow{\text{TiCl}_4(\text{DME})} \text{TB}^{*****} & \xrightarrow{\text{Zn-Cu, DME 70\degree C}} & \text{TB}^{*****}
\end{align*}
\]

23\% yield \longrightarrow 10\% yield \longrightarrow 40\% yield \longrightarrow 15\% yield

The Nicolaou Approach

Resolution of the racemic intermediate is now performed

1) (-)-camphoric chloride
2) K$_2$CO$_3$

38% total use of material

1) Ac$_2$O
2) TPAP, NMO

88% yield

Hydroboration proceeds with 3:1 regioselectivity


The Nicolaou Approach

Completion of the synthesis centers on installation of the D-ring

1) H$_2$, Pd(OH)$_2$-C
2) TESCl
3) MsCl

60% yield


The synthesis of taxol is complete in 51 steps in .03% yield from butene diol (average 85% yield vs. 91% Holton)
The Danishefsky Approach

- Retrosynthesis focuses on exploitation of the Wieland-Miescher ketone

\[
\begin{align*}
&\text{AvO} \quad \text{OH} \\
&\text{RO}^+ \\
&\text{OTES} \\
&\text{OTBS} \\
&\text{MeO} \quad \text{OMe} \\
&\text{NC} \quad \text{OTMS} \\
&\text{MeO} \quad \text{OMe} \\
&\text{OTBS} \\
&\text{MeO} \quad \text{OMe} \\
&\text{OTBS}
\end{align*}
\]

*The sum of the components contain more than an ample number of carbons (20) to reach the ABC core (19)*

---

The Danishefsky Approach

- Functionalization of the starting ketone occupies the initial steps

\[
\begin{align*}
&\text{MeO} \quad \text{OTMS} \\
&\text{OTBS} \\
&\text{TBOS} \\
&\text{TBOS} \\
&\text{TBOS} \\
&\text{TBOS}
\end{align*}
\]

59% yield

The Danishefsky Approach

The integrity of the oxetane is maintained throughout the remainder of the route.

The inring of the A-ring resembles Nicolaou's approach.

The Danishefsky Approach

Coupling of the fragments provides one diastereomer, perhaps analogous to the Nicolaou precedent.

[Diagram showing the coupling process with yields indicated: 73% yield, 50% yield, 74% yield]


The Danishefsky Approach

Functionalization is then performed to set up an impressive Heck reaction.

[Diagram showing the functionalization process with yields indicated: 68% yield, 49% yield, 41% yield]

**The Danishefsky Approach**

- Completion of the synthesis relies on a few known methods

\[
\text{OTES} \rightarrow \begin{array}{c}
\text{H}_2, \text{Pd/C} \\ 2) \text{Ac}_2\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{OTES} \\ 1) \text{PhLi} \\ 2) \text{OsO}_4, 105^\circ \text{C} \\ 3) \text{Ph(OAc)}_3
\end{array} \rightarrow \begin{array}{c}
\text{55\% yield} \\ \text{56\% yield}
\end{array}
\]

- Danishefsky's synthesis requires 47 steps, 0.2\% yield from Wieland-Miescher ketone

**The Wender Approach**

- Wender's design relies upon manipulation of pinene

\[
\text{Verbenone} \leftrightarrow \begin{array}{c}
\text{TPSO}^* \\ \text{OTBS}
\end{array} \rightarrow \begin{array}{c}
\text{TPSO}^* \\ \text{OTBS}
\end{array}
\]

The Wender Approach

Starting from the air oxidation product of pinene, Wender attempts to introduce the A- and B-rings independently of the C-ring.

1. Pinene to Verbenone
   \[ \text{O}_2 \rightarrow \text{KOBu} \rightarrow \text{O}_3 \rightarrow \text{MeOH} \rightarrow \text{64\% yield} \]

2. 1,3 alkyl shift
   \[ \text{LDA, -78\°C} \rightarrow \text{TMSCl} \rightarrow \text{Me_2CuLi, -78\°C; AcOH, H_2O} \rightarrow \text{89\% yield} \]

Photochemical rearrangement occurs without loss of enantipurity.

The Wender Approach

An epoxide-opening ring expansion sets the B-ring in place.

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The Wender Approach

- The acetonide enforces a desirable conformation for stereochemical control

![Chemical reaction diagram](image1)

H₂CrO₇, Crabtree's catalyst
TMSCl, pyridine; Triphosgene

91% yield

![Chemical reaction diagram](image2)

98% yield

1) PCC
2) Ph₃P DMF
3) 1N HCl

79% yield


The Wender Approach

- The acetonide enforces a desirable conformation for stereochemical control

![Chemical reaction diagram](image3)

HO

1) TESCI
2) Dess-Martin; Me₃NCH₂I, TEA

90% yield

![Chemical reaction diagram](image4)

1) ZnCl₂
2) BIOMCl
3) NH₄Cl

82% yield

1) PhLi, Ac₂O
2) 

52% yield

The Wender Approach

- The intramolecular aldol reaction only proceeds without the carbonate

The Wender Approach

- Completion of the synthesis now requires oxetane formation

- Wender's synthesis involves 37 steps, 0.2% yield overall from verbenone
Conclusions

- While synthesis is not a practical approach to solve problems of Taxol's supply, fascinating chemistry has been discovered in pursuit of an optimal route.

- Taxol represents one of the greatest synthetic achievements in organic chemistry.