Highlights from the Synthesis of Gibberellins: a 30 Year Odyssey

A Friday Afternoon Seminar
6 February 2004

Jonathan R. Scheerer
Highlights from the Synthesis of Gibberellins:

Outline of Presentation:
I. Introduction to Gibberellins: History, Ubiquity, and Biology
II. Biosynthesis
III. Gibberellic Acid: Structure and Reactivity
IV. Conversion of Gibberellic Acid into other Gibberellins
V. Total Synthesis
VI. Partial Synthesis / Strategy

Relvant Reviews:
A Brief History of Gibberellin Research:

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1828</td>
<td>First reports of &quot;bakanae&quot; disease in rice plants (foolish seedling; stupid rice crop)</td>
</tr>
<tr>
<td>1898</td>
<td>First research paper, links disease to fungal infection</td>
</tr>
</tbody>
</table>
| 1912 | Kurosawa found that filtrates from infected dried rice seedlings also causes disease  
     Concludes that bakanae is caused by discrete chemical               |
| 1935 | First use of term "gibberellin" in scientific literature            |
| 1938 | Crystalline compound (mix of three gibberellins) isolated from fungal filtrate |
| 1945 | Research expands to U.S. and U.K.                                  |
| 1955 | Compound isolated. Termed "gibberellic acid"                        |
| 1958 | Correct structure proposed (stereochemical ambiguities remain)      |
| 1961 | Structure verified by X-ray                                         |
| 1978 | First total synthesis (Corey)                                       |
C₂₀ and C₁₉ Gibberellins: Structure and Nomenclature

C₂₀-Gibberellin Skeleton

ent-gibberell-16-ene-7,19-dioic acid

C₁₉-Gibberellin Skeleton

ent-norgibberell-16-ene-7,19-dioic acid 19,10-lactone
Gibberellic Acid (GA$_3$)

Fermented from Gibberellia fujikuroi (a fungus) on ton scale

Bioactive at low concentrations ((sub-nanomolar common for applications)

Widely investigated and applied for commercial uses

Retail prices: $10 / g

Current yields: 15-30 g / L culture

Also bio-available in decent quantity:
A Brief History of Gibberellins:

Representative Biological Functions of Gibberellins:

- Stimulate stem elongation by stimulating cell division elongation
- Breaks seed dormancy in plants which require winter freezing
- Stimulates flowering/budding in response to lengthening days
- Can induce seedless fruit development (parthenocarpic)
- Can delay senescence (ripening) in leaves and fruit
- Induces maleness (sex expression) in dioecious flowers
- Other growth effects on fruit and budding
Gibberellin Biosynthesis: Three Stages

Stage A

mevalonic acid (MVA)

Stage B

ent-kaur-16-ene

Stage C

GA_{12}-aldehyde

C_{19}-gibberellins and C_{20}-gibberellins
**Gibberellin Biosynthesis: Stage A**

- mevalonic acid (MVA)
- *ent*-CCP
- ent-kaur-16-ene
- *ent*-copalyl pyrophosphate
- ent-CCP geranyl-geranylpyrophosphate
- Dimethylallyl pyrophosphate (DMAPP)
- Geranylgeranylpyrophosphate (GGPP)
- Dimethylallyl pyrophosphate (GPP)
- Farnesylpyrophosphate (FPP)

Chemical structures and reactions involved in gibberellin biosynthesis are illustrated. The image shows the conversion of mevalonic acid (MVA) to ent-kaur-16-ene, which is then converted to ent-CCP geranyl-geranylpyrophosphate (GGPP) through various intermediates such as IPP (Isopentenyl pyrophosphate), DMAPP (Dimethylallyl pyrophosphate), GPP (Geranylpyrophosphate), and FPP (Farnesylpyrophosphate).
Gibberellin Biosynthesis: ent-CCP to ent-kaurene
**Gibberellin Biosynthesis: Stage B**

- **ent-kaur-16-ene**
- **ent-kaur-16-en-19-ol**
- **ent-kaur-16-en-19-al**

*Stage B*

GA$_{12}$-aldehyde

*biosynthetic progenitor of all gibberellins*

*same biosynthesis for fungal or higher order plants*
Gibberellin Biosynthesis: Ring Contraction

Stage B

ent-kaur-16-ene

1,2-radical shift

radical trapping

GA_{12}-aldehyde
Gibberellin Biosynthesis: Stage C

GA_{12}-aldehyde

and/or early or late oxidations of C3, C13

R = H, OH

-very complex
-parallel pathways
-organism dependent (fungal or higher order plants)
-converge to common GA

many complex, as yet incompletely defined, oxidative processes

oxidative decarboxylation
Rearrangements of Gibberellic Acid in Basic Media

GA$_3$

Gibberellic Acid

via

retrograde aldol / aldol

favored equatorial C3 configuration

isolable transformation can be effected by palladium
Rearrangements on Gibberellic Acid in Acidic Media

...gibberellic acid has enjoyed a significant notoriety for instability and rearrangement. This view appears to be exaggerated." L.Mander
C11 oxidation: Bishydroboration

BH₃•SMe₂ → BH₃

H₂O₂, NaOAc

e.g. GA₃₅
C12 oxidation of Gibberellin Skeleton

\[
\text{Pb(OAc)}_4, \text{I}_2 \quad \rightarrow \quad \text{Zn, HOAc}
\]
C14 Hydroxylation of Gibberellin Skeleton

1) DMDO
2) TBAF

C18 Hydroxylation of Gibberellin Skeleton

Conversion of $C_{19}$ Gibberellins into $C_{20}$ Variants

C$_{20}$ gibberellins: e.g. GA$_{19}$
Radical Cascade: Attempted Deoxygenation at C3

Barton, McCombie, JCS Perkin I, 1975, 1574.
*synthetic application: Sherburn, JACS, 2003, 12108.
Dismantling and Reconstituting the A-Ring

methyl gibberellate

Corey-Carney Acid

Corey Synthesis of GA₃: Hydronaphthalene Approach

\[ \text{o-allyl eugenol} \rightarrow \text{7 steps} \rightarrow \text{THPO} \rightarrow \text{PhH, 80°C} \rightarrow \text{Oxidation Products:} \]

"...quenching reactions involving 50g of potassium can provide moments of great drama, as well as piquant stimulation for the experimentalist."

Contraction of B-Ring; A-Ring Formation through Cycloaddition


1) OsO₄, NMMO
2) Pb(OAc)₄

Bn₂NH₂⁺-TFA⁻

1) Ph₃PCH₂
HMPA, 65
°
C
2) AcOH

nBuLi;

Cl

O

Cl

O

Cl

O

Me

89%

78%

57%

72%

70%

55%

**Gibberellic Acid Endgame: Corey**

1. **ZnBr₂**
2. KOH, Na₂RuO₄

   95%

---

**Corey-Carney Acid**

1. mCPBA
2. NaOH
3. I₂, NaHCO₃

---

**GA₃**

1. TFAA, pyr
2. Zn
3. PrSLi

---

Alternative Route to Key Tricyclic Intermediate: The Hammer and Tongs Approach


3 steps 7 steps

67% 60%

KO\textsubscript{t}Bu

93%

3 steps

46% 4 steps

6 steps

48%

67% 60%

46% 4 steps

48%
Cope Rearrangement for B/C Ring Junction

1) BuLi; 2) DBU

9 steps saved over original synthesis

1) \( \text{Bu}_2\text{CuLi} \); 2) MEMCl, iPr\(_2\)NEt

Enantioselective variant has appeared

\( [3,3] \)

160°C, DMSO, H\(_2\)O, NaCl

71%
Mander: Fluorene Approach

1) Li, NH₃
2) \( \text{MeO} \)\( \text{CO}_2\text{Me} \)
   \[\text{MeO} \text{CO}_2\text{Me} \]

88%

PPA
36%

1) HCN; NaOH
2) \( \text{ClCH}_2\text{CO} \)\( \text{O} \)
3) \( \text{ClCO} \)\( \text{O} \); CH\( \text{N}_2 \)

64%

TFA
35%

1) Na\( _2 \)CO\( _3 \), MeOH
2) H\( ^+ \), (HOCH\( \text{2} \))\( \text{2} \)
3) MOMCl, iPr\( _2 \)NEt
4) tBu(chx)NLi; CO\( _2 \)
5) H\( _2 \), Pd/C

68%

Mander: A-Ring Assembly through Birch Reduction/Alkylation

1) KOtBu, K, NH₃; Mel  
2) CH₃CHN₂

66%  

KHCO₃, KBr₃

86%  

C7 ester controls alkylation

Mander, JACS. 1980, 6626.  
**Mander: Gibberellic Acid**

1) OsO$_4$, NMMO
2) PhCHO, H$^+$

1) DBU
2) H$_2$O, H$^+$

3) TMSCl

90%

1) OsO$_4$, NMMO
2) PhCHO, H$^+$

1) Ph$_3$PCH$_2$, ClCH$_2$CH$_2$OTMS
2) K$_2$CO$_3$, MeOH
3) nPrSLi, HMPA

75%

Mander: A-ring Aldol Approach (GA₁)

Mander, JACS. 1980, 6626.
Yamada: Intermolecular [4+2] Ring A Construction

1) K, NH₃
2) Swern
3) MOMCl, iPr₂NEt
4) Ph₃PCH₂

1) Na, NH₃
2) AcOH, H₂O
3) K₂CO₃, MeOH

1) AlCl₃
2) mCPBA

49%


80%

53%

86%

57%

971.

Yamada: Synthesis of Gibberellic Acid

8 steps
1) I₂, NaHCO₃
2) DBU

6 steps (Corey et al)
MOM-protected Corey-Carney Acid

91% from tri-MOM-ether

30% from tri-MOM-ether

Synthesis of GA₅ via Furan [4+2]: DeClercq

DeClercq, Tet. Lett. 1986, 1731.
GA₁₂ Synthesis from Dehydroabietate: Tahara

1) CH₂N₂
2) H₂SO₄
3) mCPBA; NaOH

Wenkert, JACS, 1958, 211.

1) H₂, RuO₂
2) H₂CrO₄
3) Ph₃PCH₂
4) BH₃/H₂O₂

epimerization at C6

epimerization at C6

37-GA12-Tahara-total.cdx 2/5/04 3:00 PM

Tahara, JCS Perkin I, 1972, 320.
Tahara, TL, 1976, 1515.
GA$_{12}$ Formal Synthesis: Mori

(±)- from synthesis of steviol Tet, 1966, 879.

Cross, Hanson, JCS, 1963, 2944.

Mori, Tet, 1976, 1497.
**GA_{12} Formal Synthesis: Ihara**

1) Bu$_3$SnH, AIBN
2) SiO$_2$

93% (1:18 mix)

1) 200°C
2) TBAF

72% (4 steps)

3:1 at C7

88%

1) s-BuLi
2) Ac$_2$O

5 steps

37%

Cross, Hanson, JCS, 1963, 2944.

Ihara, JACS, 2001, 1856.
Stork D-ring Approach: Reductive Cyclization

Three Routes to Bicycle:

Total Synthesis of Antheridic Acid: Corey

Total Synthesis of Antheridic Acid: Corey

Antheridic acid original structure proposed as 3β-OH

Total Synthesis of Antheridic Acid: Corey

Total Synthesis of Antheridic Acid: Corey

Total Synthesis of Antheridic Acid: Corey
Proposed Biomimetic Synthesis of Antheridic Acid Investigated

C9,10-epoxygibberellin

Epoxide initiated 1,2 bond migration

Desired Bond Migration could not be Effected

A) Im$_2$CO, H$_2$O$_2$ intramolecular delivery
B) mCPBA ($k_{rel} < 10^{-2}$) intermolecular

antheridic acid
original structure proposed as 3β-OH

Mander, JACS, 1987, 6839.
Conversion of GA₇ into Antheridic Acid

1) LiN(chx)iPr; Et₃NHCl
2) SeO₂, tBuOOH
3) Me₂BBr
4) LiOH

Mander, JACS, 1987, 6839.
Synthesis of Antheridiogens: Mander

1) h\textnu, MeOH
2) PDC
3) H\textsubscript{2}, Pd
18 h, rt
added in situ
75%

1) PhI(OAc)\textsubscript{2}, I\textsubscript{2}
2) Hg(OAc)\textsubscript{2}, HOAc
75%
75%

1) PhI(OAc)\textsubscript{2}, I\textsubscript{2}
2) Hg(OAc)\textsubscript{2}, HOAc
75%

71%

Formal synthesis
antheridic acid

Mander, JACS, 1997, 3828.
**Aldol C/D Ring Strategies Not Discussed**

Ireland, *JOC, 1966*, 2530. (toward kaurenes)


Ziegler, *JOC, 1971*, 3707. (model system)
Acylation C/D Ring Strategies Not Discussed


Alkylation C/D Ring Strategies Not Discussed

Nagata, JACS, 1972, 4654.


Barco, Tet., 1989, 3935.
Rearrangement C/D Ring Strategies Not Discussed

Cross, MacMillan, JCS, 1958, 2520.

Ziegler, Tet., 1977, 373.


Mori, Tet., 1972, 3217.
A Summary of General C/D Ring Strategies

I) Reductive Ring Closure

II) Alkylation / Acylation

"The problem of the synthesis of gibberellic acid has provided the impetus for the development of many new synthetic methods . . . " Corey

III) Aldol

IV) Carbenoid

V) Rearrangement / Fragmentation