Approaches Towards and Synthesis of Garsubellin A

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2/28/06
Isolation and Assignment

Isolated in 1997 by Fukuyama (Tokushima, Japan) from the wood of Garcinia subelliptica

Obtained 80.5 mg from the CH$_2$Cl$_2$ soluble portion (2.6g)

Highly substituted and oxygenated central [3.3.1] nonanone core

C$_{30}$H$_{44}$O$_5$

[$\alpha$]$_D^{20}$ = -21.3$^\circ$

Increases ChAT activity by 154%
(Alzheimer's)

Isolation and Assignment

Structure and relative stereochemistry assigned by NMR studies. Absolute configuration not known. 2 total syntheses, Shibasaki (2005) Danishefsky (2006). Both racemic. Some freedom as to which antipode is drawn. Drawn in this presentation as shown above. Can analogy be drawn to other molecules of similar structure?

Hyperforin: Anti-depressant found in St. John’s Wort
X-ray of p-Bromo benzoate in 1983 showed absolute configuration

Hyperforin
Paupaforin A
Aristophenone A
Guttiferone B

Retrosynthetic Analysis: Construction of the Core

Briefly, brainstorm a disconnection which may be used to construct the [3.3.1] nonanone
Biosynthesis of Hyperforin: Analogous to Garsubellin A?

Feeding studies with $^{13}$C glucose incorporation of 5 isoprenoid groups

Two Different Approaches to Construct the Core of Garsubellin A

In the synthetic work, 2 major approaches to the core stand out.

1. Formation of the B ring by annulation

2. Formation of the A ring by electrophilic cyclization
Shibasaki’s Model Study

a) KO\text{Bu} (3 equiv), -78°C, 100 min
b) LiClO\text{4}, (4.5 equiv), -78°C, 50 min
c) 1, (2 equiv), -78°C, 5.5 h
d) DMAP (5 equiv), 12-crown-4 (6 equiv)
   -78 to rt, 30h

76% yield
1:25 (natural:unnatural)

63% yield
1:5 (natural:unnatural)

70% yield
4:1 (natural:unnatural)

50% yield
1:2.6 (natural:unnatural)

Shibasaki’s Model Study

Other Annulation Approaches: Stoltz

![Reaction Scheme]

Other Annulation Approaches: Grossman

\[
\text{CO}_2\text{Me} \quad \text{O} \\
\text{CHO} \quad \text{SiEt}_3
\]

\[
\text{CO}_2\text{Me} \quad \text{O} \\
\text{SiEt}_3 \quad \text{HO}
\]

c) $\text{CO}_2(\text{CO})_8$, 87%

d) $\text{Et}_3\text{SiH}$, $\text{Me}_3\text{SiCCSiMe}_3$, 94%
e) 6N HCl, 72%

Other Annulation Approaches: Nicolaou

\[ \text{Acetonitrile} \rightarrow \text{CHO} \rightarrow \text{HO} \rightarrow \text{DMP} \rightarrow \text{KHMDS, PhSeBr} \]

63% 81% 71%, 98%
“the desired cyclization did not proceed, possibly due to the destabilization of the reactive conformation for this cyclization by the prenyl group.”

Cache calculations: Very little difference between the systems. Minor changes to bond lengths and dihedral angles in “transition structures”

One possible problem may be formation of acetal (pure speculation on my part)

Shibasaki: Back to the Drawing Board

What did he learn from the model study?

Shibasaki: First Total Synthesis of Garsubellin A

a) LDA; prenylBr, Bu$_4$NI, THF, -78°C 100%
b) MeLi LiBr; HCl, -78 to 0°C 100%
c) MeMgBr, Cul (22 mol%); iPrCHO, 61% THF, 4°C 92%
d) TIPSOTf, 2,6-lutidine, 92%
e) PhSiH$_3$, Co(acac)$_2$ (20 mol%); O$_2$, 73% THF, rt 96%
f) MOMCl, iPrEt$_2$N, Bu$_4$NI, 96%
g) KHMDS, prenylBr, Bu$_4$NI, THF, -78°C 98%
h) LDA, TMEDA; CH$_3$CHO, -78°C 94%
i) Martin sulfurane benzene, rt, 98%
j) AD-mix-α, CH$_3$SO$_2$NH$_2$, rt
k) Triphosgene, pyridine separation; 30%

>30:1 regioselectivity

1:1 dr before separation

Shibasaki: First Total Synthesis of Garsubellin A

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Nicolaou’s Model Retrosynthesis

Selenium Cyclization

**Ley’s studies**

\[
\text{CO}_2\text{Et} \quad \text{N-PSP, TsOH (0.05 equiv)} \quad -78 \text{ to } \text{rt, 66%}
\]

\[
\text{SnCl}_4 \quad (1 \text{ equiv}) \quad \text{rt, 17h, 79%}
\]

**Nicolaou’s studies**

\[
\text{CO}_2\text{Et} \quad \text{N-PSP, SnCl}_4 \quad 0 \text{ C, 88%}
\]

\[
\text{SnCl}_4 \quad (1 \text{ equiv}) \quad \text{no reaction (or TiCl}_4, \text{ ZnCl}_2, \text{ AlCl}_3, \text{ BF}_3\text{OEt}_2)
\]

\[
\text{CO}_2\text{Me} \quad \text{SnCl}_4 \quad 0 \text{ C, 88%}
\]

\[
\text{SnCl}_4 \quad (1 \text{ equiv}) \quad \text{no reaction (or TiCl}_4, \text{ ZnCl}_2, \text{ AlCl}_3, \text{ BF}_3\text{OEt}_2)
\]

\[
\text{CO}_2\text{Me} \quad \text{N-PSP, SnCl}_4 \quad -78 \text{ C, 94%}
\]

\[
\text{SePh}
\]

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¹ Reaction conditions: 1.1 equiv of N-PSP, 1.0 equiv of SnCl₄, CH₂Cl₂, -23 °C, 15 min. ² Isolated yield after purification unless otherwise noted. ³ Yield as a mixture of stereoisomers.

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Nicolaou: Synthesis of the Core

\[
\begin{align*}
\text{a) } & \text{DBU, BrCH}_2\text{CO}_2\text{Et, LiI, 65°C, 80%} \\
\text{b) } & \text{LiAlH(O-tBu)}_3, \text{THF, 0°C} \\
\text{c) } & \text{LiOH, rt} \\
\text{d) } & \text{DCC, DMAP, rt, 73%} \\
\text{e) } & \text{PDC, rt, 77%} \\
\text{f) } & \text{LHMDS, CNCO}_2\text{Me, THF, -78°C} \\
\text{g) } & \text{Ac}_2\text{O, DMAP, 70°C, 75%} \\
\text{h) } & \text{N-PSP, SnCl}_4, \text{CH}_2\text{Cl}_2, -23°C, 95%
\end{align*}
\]

Nicolaou: Elaboration of the Core

Nicolaou: Final Steps

Danishefsky: Retrosynthesis

Danishefsky’s Total Synthesis

\[ \text{OTIPS} \]
\[ \text{H}_3\text{CO} \]
\[ \text{OTIPS} \]
\[ \text{H}_3\text{CO} \]
\[ \text{OTIPS} \]
\[ \text{H}_3\text{CO} \]
\[ \text{OTIPS} \]
\[ \text{H}_3\text{CO} \]
\[ \text{OTIPS} \]
\[ \text{H}_3\text{CO} \]

\[ \text{a) } n\text{-BuLi; prenylBr} \]

\[ \text{MeO} \]
\[ \text{OMe} \]
\[ \text{TsOH, rt} \]
\[ \text{d) } \text{TBAF, rt, 70\%} \]

\[ \text{e) } \text{Pd(OAc)}_2, \text{PPh}_3, \text{Ti(PrO)}_4, 80\,^\circ\text{C, 62\%} \]

\[ \text{f) } \text{HClO}_4, \text{H}_2\text{O/dioxane, 60}\,^\circ\text{C} \]

\[ \text{C}_{16}\text{H}_{24}\text{O}_5 \]
\[ \text{C}_{16}\text{H}_{24}\text{O}_5 \]
\[ \text{C}_{15}\text{H}_{20}\text{O}_4 \]
\[ \text{C}_1\text{H}_4\text{O} \]

\[ \text{J. Am. Chem. Soc. 2006, 1048.} \]
Danishefsky: Stereocontrol

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{OCH}_3 \\
\text{O} & \quad \text{H}_3\text{CO} & \quad \text{OCH}_3
\end{align*}
\]

f) $\text{HClO}_4 \quad \text{H}_2\text{O/dioxane}, \quad 60 \text{ C} \quad \Rightarrow \quad \text{HO} \quad \text{H}_2\text{O} \quad \text{OCH}_3 \quad \text{HO} \\
\text{O} & \quad \text{H}_3\text{CO} & \quad \text{OCH}_3 \\
71\% \text{ after 12h}
\]
Danishefsky: Constructing the Core

g) Grubbs 2 (8 mol%), CH₂Cl₂, 40°C, 68%

h) KI, I₂, KHCO₃, THF/H₂O, 85%
i) I₂, CAN, CH₃CN, 50°C, 77%

j) i-PrMgCl, then LiCuCl₄, allyl bromide, THF, -78 to 0°C, 67%
k) TMSI, 1N HCl, CH₂Cl₂, 0°C, 98%

l) SnBu₃, AIBN, C₆H₆, 80°C, 82%
m) Grubbs 2 (15 mol%), CH₂Cl₂, 40°C, 73%

n) LDA, TMSCl, I₂, THF, -78 to 0°C, 25-36%

Danishefsky: Last Steps

\[ \text{I} \xrightarrow{o) \text{ } \text{iPrMgCl, isobutyraldehyde, THF, -78 to 0 C, 72\%} \text{TMSO}} \text{H} \]

\[ \text{O} \xrightarrow{p) \text{ } \text{DMP, CH}_2\text{Cl}_2, 0\text{C, 88\%}} \text{HO} \]

\[ \text{iPrMgCl, isobutyraldehyde, THF, -78 to 0 C, 72\%} \]

Several unique approaches to the construction of the hindered, functionalized core

Examples of overcoming the delicate balance between reactivity and non-reactivity due to hindrance (and subsequent modification of approach to complete the synthesis).

Due to the pharmaceutical interest, many synthetic routes may be needed for the selective construction of analogs.

The recent total syntheses (Shibasaki: Aug 12, 2005; Danishefsky: Oct 31, 2005) show interest is alive and well in this class of molecules.