Total Synthesis of (-)-Anisatin


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04/20/2012
1. Isolated as one of the toxic compounds from Japanese star anise in 1952.

2. Sesquiterpene: a) the oxabicyclo [3.3.1] skeleton; b) the spiro lactone; c) eight chiral centers; d) high oxidation states

3. Strong GABA$_A$ inhibition activity.
Retroynthetic analysis of (-)-anisatin by Fukuyama:

Scheme 1. Synthesis of precursor of Diels-alder reaction

1. Synthesis of precursor of Diels-alder reaction

\[
\begin{align*}
\text{6} & \quad + \quad \text{7} \\
\xrightarrow{[\text{Rh(cod)Cl}_2 \quad \text{NaOH}} \quad \xrightarrow{\text{THF/H}_2\text{O, rt}} \quad \text{8} \\
\text{9} \quad \xrightarrow{\text{NaBH}_4 \quad \text{KOH}} \quad \xrightarrow{\text{MeOH, 0°C}} \quad \text{10} \\
\end{align*}
\]

>99% ee

1) propargyl bromide
NaH, TBAI, THF/DMF
60°C, 88%

2) BH$_3$NH$_3$, n-BuLi
THF, 0°C, 80%

3) MsCl, Et$_3$N, CH$_2$Cl$_2$
0°C, 89%

\[
\begin{align*}
\text{11} & \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH, rt}} \quad \text{13} \\
\text{12} & \quad \xrightarrow{\text{Pb(OAc)}_4, \text{benzene, reflux, evaporation}} \quad \text{12} \\
\end{align*}
\]

\(\text{R}^*:\quad \text{D-Menthyl}\)
Scheme 2. Construction of key quaternary carbons on cyclohexane

\[ \text{OH} \quad \text{PhI(OAc)}_2 \quad \text{MeOH, rt} \quad \text{evaporation} \rightarrow \quad \text{OMe} \]

\[ \text{13} \quad \text{14} \]

\[ \equiv \left[ \begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{OMe}
\end{array} \right] + \left[ \begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{OMe}
\end{array} \right] \text{ 1 : 1} \]

toluene, reflux evaporation

\[ \text{OH} \quad \text{15a} \quad \text{15b} \quad \text{1 : 1} \quad \text{CAS, MeOH} \quad 50^\circ\text{C} \quad 76\% \text{ (three steps)} \]

\[ \text{1) (EtO)}_2\text{POCH}_2\text{CO}_2\text{Et} \quad \text{KHMDS, toluene reflux, 94\%} \rightarrow \quad \text{16} \]

\[ \text{2) LiAlH}_4, \text{ THF, 0}\circ\text{C} \]

\[ \text{1) Bu}_3\text{SnCH}_2\text{I, KH THF, 0}\circ\text{C to rt; BnBr, NaH, TBAI THF/DMF, rt 71\% (three steps)} \rightarrow \quad \text{17} \]

\[ \text{HMPA, MeLi, -78}\circ\text{C} \]

\[ \equiv \left[ \begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{OMe}
\end{array} \right] \rightarrow \quad \text{18} \]

\[ \text{BnBr, NaH, TBAI THF/DMF, rt 71\% (three steps)} \rightarrow \quad \text{19} \]

[2,3] wittig rearrangement
Scheme 3. Construction of C ring

1) AcOH, H₂O, THF, 30°C
2) I₂, imidazole, Ph₃P, THF, 0°C to rt, 90% (two steps)

1) t-BuLi, THF, -78°C
2) Burgess reagent, THF, 50°C, 62% (two steps)

1) MOMCl, NaH, THF/DMF, 0°C
2) TBAF, THF, rt, quant, 83%

BHT: butylhydroxytoluene, antioxidant properties
Scheme 4. Construction of A ring

1) MOMCl, NaI, iPr₂NEt, DME, reflux, 91%
2) O₃, Cl₂CHCH₃, -95°C; Me₂S

Bu₃SnH, AIBN, toluene, 100°C, quant

Pinnick oxidation

NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH-H₂O, rt, 73% (2 steps)
Scheme 5. Finish of anisatin

MNBA: 2–methyl-6-nitrobenzoic anhydride
DMAP: N,N-dimethyl-4-aminopyridine
Conclusion

• 39 total steps from 7
• The chirality was introduced by asymmetric 1, 4-addition.
• By using the steric or electronic character of the rings system, all of chiral centers were induced with high diastereoselectivities.
Thanks for your attention!
L: Ligand

[Rh(cod)Cl]$_2$:

(a) transmetallation;
(b) coordination to the electron-deficient alkene;
(c) alkene insertion into Rh-Ar bond;
(d) hydrolysis of rhodium-oxo-π-allyl intermediate
Oxidation of methylenedioxy with lead tetraacetate:

Oxidative dearomatization of Phenol:
Burgess dehydration:

2° or 3° alcohol + Burgess reagent (BR) → sulfamate ester → Alkene

(Elimination is syn-selective, but the syn-selectivity is higher for secondary alcohols. Tertiary alcohols tend to react faster and under milder conditions; E1 elimination products are observed when stabilized carbocations are formed. In most cases the elimination leads to the formation of the conjugated product, if conjugation with other C=C or C=O double bonds is possible. Primary alcohols are converted to the corresponding carbamates, which in turn give primary amines after hydrolysis.)
Chugaev elimination reaction

1. NaOH or KOH or NaH
2. R^4 = I

alkyl xanthate

alkene + O=S-SR^4 \rightarrow \text{CO}_2 + H\text{SR}^4

Pinnick oxidation

\text{ClO}_2 + \text{H}_2\text{PO}_4 \leftrightarrow \text{ClO}_2^+ + \text{H}_2\text{PO}_4^-

aldehyde + \text{ClO}_2 \rightarrow \text{HClO}_2 + \text{H}_2\text{O}

side reaction

2 \text{ClO}_2 + \text{Cl}^- + \text{OH}^- \rightarrow 2 \text{ClO}_2^- + \text{H}_2\text{O}

scavenging

2-methyl-2-butene + hypochlorous acid

Carboxylic acid