Synthesis of Alkaloid (−)-205B via Stereoselective Reductive Cross-Coupling and Intramolecular [3+2] Cycloaddition


(−)-205B

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Current Literature
6 October 2012
(-)-205B Isolation, Structure, and Biological Activity

- Isolated in 1987 by Daly and co-workers from the skin extracts of the Panamanian frog *Dendrobates pumilio*
- The structure was first reported as 1 and revised in 1998 by Daly and co-workers based on extensive FTIR, NMR, and HRMS
- The absolute sterochemistry was reported in 2003 by Toyooka and co-workers based on their total synthesis of (+)-205B
- (-)-205B possesses an unusual and unique 8b-azaacenaphthylene ring system containing 5 asymmetric centers
- Target of interest due to intriguing structure and the discovery that the unnatural enantiomer, (+)-205B, blocks the 7α nicotinic acetylcholine receptor in a selective fashion

Toyooka and Co-Workers: (+)-205B

- 30 steps (longest linear)
- Determined the absolute stereochemistry of the natural product to be (−)-205B
- Key features:
  - Stereocontrolled Michael-type additions to enaminoesters

Smith and Co-Workers: (-)-205B

- 19 steps (longest linear)
- 5.6% overall yield
- Key features:
  - Dithiane three-component linchpin coupling
  - One-pot sequential construction of the indolizidine ring

Comins and Co-Workers: (-)-205B

- 11 steps (longest linear)
- 8% overall yield
- Key features:
  - Asymmetric N-acylpyridinium reaction
  - Tsuji-Trost allylic amination of a vinylogous amide

Title Paper: Retrosynthesis of (−)-205B

Control of reaction pathway dictates stereochemistry of the heterocyclic product

(E)-anti-Homoallylic Primary Amines

- Chelation-controlled addition reactions of chiral crotylsilanes for the synthesis of (E)-anti-homoallylic carbamates

\[
\text{Ph} \quad \text{Me} \quad \text{H} \\
\text{N} \quad \text{SiMe}_3 \\
\text{Ph} \quad \text{NH}_2
\]

92% ee, 96% de


- Asymmetric crotylation and allylation reactions of imines and oximes

\[
\text{Ph} \quad \text{H} \\
\text{N} \quad \text{SiMe}_3 \\
\text{Ph} \quad \text{NH}_2
\]

78%

92% ee, 96% de


- Iminine propargylation

\[
\text{Me} \quad \text{H} \\
\text{O} \quad \text{P(O)(OEt)}_2 \\
\text{Ti(O\(\text{i-Pr}_4\))} \\
\text{i-PrMgCl} \\
\text{H} \quad \text{Me} \\
\text{TiL}_3 \\
\text{Me} \quad \text{TMS} \\
\text{N} \quad \text{Bn} \\
\text{R} \quad \text{NH} \quad \text{Bn} \\
\text{TMS} \\
\text{Me}
\]

87% (9:1 dr)

Methodology: Stereodefined Homoallylic Hydroxylamines

- Reaction proceeds with aromatic and aliphatic aldehydes
- Delivers stereodefined \((E)\)-anti-homoallylic amines as single diastereomers

\[
\begin{align*}
\text{R}^1 & \quad \text{H} \\
\text{O} & \\
\text{LiHMDS} & \quad \text{Et}_2\text{O} & \quad \text{TMS} & \quad \text{N} \\
\text{R}^1 & \quad \text{H} \\
\text{N} & \\
\text{Ti(Oi-Pr)}_4 & \quad \text{s-BuLi} & \quad \text{TMS} & \quad \text{N} \\
\text{R}^1 & \quad \text{H} \\
\text{TMS} & \quad \text{N} & \quad \text{Ti(Oi-Pr)}_4 & \quad \text{R}^2 \\
\text{O} & \\
\text{R}^1 & \quad \text{H} \\
\text{NH}_2 & \\
\text{R}^1 & \quad \text{H} \\
\text{R}^2 & \quad \text{R}^3 & \quad \text{R}^4
\end{align*}
\]

Methodology: 1-Aza-7-oxabicyclo[2.2.1]heptanes

**Reactions:**

\[
\text{Ph-CH} = \text{CH-CH} = \text{CH-Ph} \quad \text{toluene, 50 °C} \quad 84\%
\]

\[
\text{Ph-CH} = \text{CH-N} = \text{O-Ph} \quad \text{toluene, 120 °C} \quad 74\%
\]

**Yield and Diastereomeric Ratio:**

- Product A: 67%
- Product B: 20%
- Product C: 17% (B:C = 2.5:1)

**Diastereomeric Ratio:**

- D: ds ≥ 20:1

**References:**

Methodology: 1-Aza-7-oxabicyclo[2.2.1]heptanes

\[
\begin{align*}
\text{NH}_2 & \quad \text{R}^1 \quad \text{R}^3 \\
\text{R}^2 & \\
\text{H} & \\
\text{O} & \\
\text{OEt} & \\
\text{toluene} & \text{4Å mol. sieves} \\
\text{rt to 120 °C} & \text{2-12 h} \\
\text{R}_1^6 & \text{N}_2 \text{CO}_2\text{Me} \\
\text{R}_5^4 & \\
\text{R}_3^4 & \\
\text{2,3-} \text{anti; 3,4-} \text{syn; 4,5-} \text{anti; 5,6-} \text{anti} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^3 & \text{O} \\
\text{EtO}_2\text{C} & \\
\text{[3+2]} & \\
\end{align*}
\]

major product

\[
\begin{align*}
\text{R}^3 & \text{O} \\
\text{EtO}_2\text{C} & \\
\text{[3+2]} & \\
\end{align*}
\]

not observed

\[
\begin{align*}
\text{R}^3 & \text{O} \\
\text{EtO}_2\text{C} & \\
\text{[3,3]} & \\
\end{align*}
\]

Ti-Mediated Reductive Cross-Coupling

\[
\text{MeO-CH-CH-CHO} + \text{Me-OH} \xrightarrow{\text{reductive coupling}} \text{MeO-CH-CH-CO-Me}
\]

\[
\text{A, LiHMDS, Et}_2\text{O; then Ti(O-i-Pr)}_4, \text{s-BuLi; then B}
\]

57%

B (91% ee)

(91% ee)

\[
\text{low conversion}
\]

\[
\text{poor steroselection}
\]

Stereochemical Analysis of Reductive Cross-Coupling

Asymmetric Synthesis of (−)-205B

1. LAH, THF
2. DMP, CH$_2$Cl$_2$
3. NaH, C, DME

51%

MeO
\[\text{O}^{\text{P}}\]
\[\text{TMS}\]
\[\text{OMe}\]
\[\text{O}\]
\[\text{TMS}\]
\[\text{OMe}\]
\[\text{E:Z = 2:1}\]

1. DIBAL, CH$_2$Cl$_2$
2. NBSH, PPh$_3$, DIAD
3. NMM, -15 °C to rt

55%

55%

Cationic Annulation: Aza-Sakakurai vs Aza-Cope

\[ R = \text{CH}_2\text{TMS} \]

Completion of (−)-205B

1. KOt-Bu, 18-crown-6  2. TCDI, 4-DMAP  59%

1. AIBN, Bu₃SnH  2. p-TsOH, benzene  61%

Conclusion

- Completed the asymmetric total synthesis of \((-\)-205B in 17 steps
- Successfully employed two stereoselective synthetic methods developed in their laboratories
  - Ti-mediated reductive cross-coupling of allylic alcohols with aldehydes
  - Path-selective intramolecular [3+2] cycloaddition of glyoxylate-based homoallylic nitrones