Formal asymmetric synthesis of Echinopine A and B

\[
\begin{align*}
&\text{R = H \rightarrow Echinopine A} \\
&\text{R = Me \rightarrow Echinopine B}
\end{align*}
\]
Introduction:

- Isolation of these two new sesquiterpenes from *Echinops spinosus* in 2008 by Kiyota et al.

- No real interesting biological activities but unprecedent architectures....

- Represent an enticing challenge for the synthetic community because of their unique carbocyclic framework characterized by a [3,5,5,7] ring system

5 stereogenic centers
2 quaternary carbons

R = H → Echinopine A
R = Me → Echinopine B

Precedent on the subject

- **Proposed biosynthetic pathway:**

  ![Diagram of a biosynthetic pathway involving guaiiane-type precursor](image)

- **Already two total synthesis of these compounds:**

  **The first**
  
  ![Chemical structures](image)


  **The second**
  
  ![Chemical structures](image)

A one pot preparation of a [5,6,7] system and its conversion to the [5,5,7] framework system

His strategy

R = H -> Echinopine A
R = Me -> Echinopine B

Ring contraction

Biosynthetic pathway

Cascade process

Hosomi-Sakurai reaction
Synthetic pathway:

1°) n-BuLi, CuI then acrolein, TMSI
2°) Lindlar catalyst quinoline, H₂

1°) n-BuLi then TMSCH₂I
2°) n-BuLi then OHC~TMS

TiCl₄ (1 equiv) CH₂Cl₂

R₁ = H, R₂ = TBS, R₃ = TMS

C₁₀ ca. 3:1 d.r

1°) Et₃N, TBSOTf, CH₂Cl₂
2°) p-TsOH, CH₂Cl₂/MeOH
3°) K₂CO₃, MeOH

C₁₀ ca. 3:1 d.r

1°) NaHCO₃, DMP
2°) Pinnick oxdation
3°) KHCO₃, MeI

TBSO₉

75 %

Dibal-H then P(Ο₂, H₂)

160°C

Pd(QAc)₂ (0.1 equiv)

TBSO₉

PPH₃ (0.2 equiv)

Toluene, 80 °C

Pd

TBSO₉

TBSO₉

TBSO₉

TBSO₉
Final steps...

1) NEt₃, MsCl then NaI
2) DBU, THF
3) OsO₄, NMO then Pb(OAc)₄

1) LDA, PhSeBr then H₂O₂
2) NaOH, H₂O₂

ring contraction
montmorillonite K10
benzene, 80°C then NaOH
71 %

Enantioselective synthesis

1) ρ-TsOH, MeOH
2) Martin's sulfuran

only one diastereoisomer
10 étapes
Elegant formal synthesis of Echinopine A and B thanks to 3 key steps

18 steps to synthesise key compound in 12 % overall yield

Conceptually contrasting sequence involving a one pot preparation of a [5,6,7] system and its conversion to the [5,5,7] ring framework