Total Synthesis of (+)-Yohimbine via an Enantioselective Organocatalytic Pictet–Spengler Reaction

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Liming Cao
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Indole alkaloids: (+)-Yohimbine

- the principal alkaloid found in the bark of evergreen *Pausinystalia yohimbe*, *Rubiaceae* family, with 31 other yohimbane alkaloids, mostly in South Africa

- well-known indole alkaloid in the medicinal history:
  - traditionally used as aphrodisiac
  - treatment of sexual dysfunction (HCl salt)
    - over-the-counter dietary supplement in herbal extract form
    - prescription medicine in pure form
  - remedy for type 2 diabetes in animal and human models carrying polymorphisms of the α₂A- adrenergic receptor gene

General Strategies Employed in Previous Syntheses of Yohimbine and Related Alkaloids

- generation of the DE-ring system, followed by cyclization to form the C ring
  - difficult control of C(3) stereogenic center

- formation of the ABC-ring system, followed by annulation of DE rings
  - lack of methods for:
    - preparation of enantioenriched ABC-rings
      - H8 BINOL PA catalyzed Pictet–Spengler Reaction
    - diastereoselective formation of DE-rings
      - IMDA

Pictet–Spengler Reaction

Previous Work

Tamelen and co-workers: the first total synthesis of the racemic compound

![Chemical structure and reaction scheme](image)

**Previous Work**

**Szantay and co-workers:** enantiopure form by a second-order asymmetric transformation step in the resolution of an intermediate

Diastereomeric salt formation with (+)-tartaric acid

Previous Work

Momose and co-workers: the first asymmetric synthesis of (+)-yohimbine

Synthetic Strategies toward (+)-Yohimbine


First catalytic enantioselective total synthesis of (+)-yohimbine
Relative energies of IMDA transition structures

- D-ring: chairlike over boatlike (a-e vs f).
- C3 substituent: equatorial over axial (a vs e).
  - High dienophile facial selectivity, C3-C15 cis.
- N4 substituent: equatorial over axial (a,c vs b,d).
- Negligible endo/exo preference with equatorial N4 substituent (c vs a).
- Significant endo preference with axial N4 substituent (d vs b).
  - Model not good

- B3LYP/6-311+G-(d,p)//B3LYP/6-31G(d) level of density functional theory
- c and d lead to a cycloadduct with the relative configuration of (+)-yohimbine

Relative energies of IMDA transition structures

- N4 substituent: equatorial over axial (a,c vs b,d).
- Small endo preference with equatorial N4 substituent (c vs a).
- Significant endo preference with axial N4 substituent (d vs b).
- Axial N4 substituent TS more accessible
  - Carbamate C=O coplanar with indole, repulsive nonbonding interactions
  - A basis for high diastereoselectivity

**Previous Work**

\[
\text{Pyrrrole} + \text{Acetone} + \text{Catalyst (2 mo \text{ %})} \rightarrow \text{Product}
\]

\[
\begin{align*}
&\text{Product} \\
&\text{4 Å MS,} \\
&\text{toluene,} \\
&\text{70 °C, 24h}
\end{align*}
\]

<table>
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<th>ee(%)\textsuperscript{b}</th>
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</tr>
<tr>
<td>2</td>
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</table>

\textsuperscript{a.} Determined by 1H NMR spectroscopy. \textsuperscript{b.} Determined by HPLC on a chiral column (Chiralcel OD).

Previous Work

Total Synthesis of (+)-Yohimbine

The selectivities and overall yield leave much to be desired.

Total Synthesis of (+)-Yohimbine


(+)-Yohimbine
Other applications

Sato and co-workers:


Four steps, 51% overall yield.
Conclusion

• Key steps include:
  o The enantioselective organocatalytic Pictet–Spengler reaction
  o Intramolecular Diels-Alder reaction

• Total synthesis involved nine steps from tryptamine (only six pots) and gave an overall yield of 16%.

• It also worked well for N-alkyltryptamines as was proven in the key chirality introducing step of the total syntheses of arboricine and corynantheidine.