The Total Synthesis of Vinigrol

Phil Baran, Thomas J. Maimone, Jun Shi, Shinji Ashida

*J. Am. Chem. Soc.* **2009**, *ASAP*

Current Literature - November 14th, 2009

Nolan Griggs
Vinigrol - Introduction

- Isolated by Ando and co-workers in 1987 from Virgaria nigra F-5408, a fungus strain found at the foot of Mount Aso, Japan.


- Tricyclic core contains 8 contiguous stereocenters around a bridged cis-decalin core.

- Core structure is similar to that of the taxane family:

Vinigrol has interesting biological activity including:

- Activity against human platelet aggregation with IC₅₀ values ~ 50 nM.

- Identified as a tumor necrosis factor (TNF) antagonist, which is useful in the treatment of AIDS.

- Other antiinflammatory properties and immunosuppressant antagonistic effects.

Efforts by Hanna and co-workers

All attempts to close the 8-membered ring failed. Among the different methods used are:

- Ring Closing Metathesis on many different variants of cis-decalin precursor.
- Barbier-type ring closures
- Variants of the McMurry Reaction
- Ring contraction strategies involving examples such as a Ramberg-Backlund Rearrangement

As a result, it was concluded that this strategy was not useful due to the equatorial nature of the sidechains, and therefore, no further attempts have been made.

Efremov, I. V. Ph.D. Thesis, The Ohio State University, 2001
Efforts by Corey and co-workers

Vinigrol $\Rightarrow$ 

\[ \text{OTMS} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{OMOM} \]

\[ \text{OTBS} \]

\[ \text{Me} \]

\[ \text{H} \]

\[ \text{OH} \]

\[ \text{OR} \]

\[ \text{OTMS} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{OMOM} \]

\[ \text{OTBS} \]

\[ \text{Me} \]

\[ \text{H} \]

\[ \text{OH} \]

\[ \text{OR} \]

\[ \text{OTMS} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{OMOM} \]

\[ \text{OTBS} \]

\[ \text{Me} \]

\[ \text{H} \]

\[ \text{OH} \]

\[ \text{OR} \]

\[ \text{OTMS} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{OMOM} \]

\[ \text{OTBS} \]

31% $\text{BF}_3\cdot\text{OEt}_2$

\[ \text{3 Steps} \]

\[ \text{3 Steps} \]

\[ \text{Carvone} \]

\[ \text{Limonene} \]

Goodman, S. N.; Ph.D. Thesis; Harvard University, 2000
Efforts by Barriault and co-workers

- DFT Calculations of gas-phase relative free energies at 298 K at the B3LYP level using 6-31G** basis set.


For other approaches by the same lab, see:

A similar strategy was disclosed later that year by Fallis and co-workers:
Initial Work Towards Vinigrol - Baran and co-workers

Initial Work Towards Vinigrol - Baran and co-workers

Completion of the Synthesis of Vinigrol - Baran and co-workers

Completion of the Synthesis of Vinigrol - Baran and co-workers

1. LiAlH₄ then HCO₂H,

2. 1. COCl₂, Et₃N
   2. AIBN, Bu₂SnH

3. 1. OsO₄, NMO
   2. NaOCl, TEMPO

Conclusions

• The first total synthesis of Vinigrol was accomplished in 23 steps with an overall yield of 3%

• The synthesis features a minimal use of protecting groups.

• Highlights include facile construction of the core utilizing an electron-neutral intramolecular Diels Alder reaction and subsequent Grob fragmentation, selective functionalization using an "unusual" dipolar cycloaddition, and a late stage Shapiro reaction.

• Despite the very concise, scaleable route, Baran states "obvious area for refinement" as "a minimalization of nonstrategic redox fluctuations and an enantioselective variant of the first step."