A Concise Approach to Vinigrol

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Vinigrol
Isolation & Biological Activity

Isolation: Novel diterpenoid isolated in 1987 by Ando and coworkers at Fujisawa Pharmaceutical Co. from fungal strain *Virgaria nigra*, isolated from soil collected at the foot of Mt. Aso, Japan:

*Virgaria nigra* also found in US, Canada and Cuba

Biological activity: antihypertensive, inhibition of platelet aggregation (rabbit and human), induces contraction of aortic smooth muscle (rat) through Ca$^{2+}$ ion channel agonist activity, TNF antagonist for possible treatment of endotoxic shock, inflammation, muscle atrophy, progression of ARC to AIDS, autoimmune diseases, arthritis...
Structural features

Figure: Carbogenic ring systems in terpene synthesis.

Scheme: Different topological viewpoints of vinigrol

- Decahydro-1,5-butanonaphthalene carbon skeleton.
- Presence of eight contiguous stereocenters.
- Multiple sites of oxygenation.
Studies directed towards vinigrol
(by L. A. Paquette *et al.*

Introduction

Previous approach

Baran’s approach

Conclusion
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- Different approach for construction of octalin core:

  - 8 steps
  - 5 steps
  - 6 steps

  ![Chemical structures and reactions]

  **Introduction**

  ✓ Previous approach
  Baran’s approach
  Conclusion

  ![Chemical structures and reactions]


Quantum Mechanical Study

Major conformer lacking the proximity needed for ring closure

![Chemical structure with energy values](image)

- $15.497 \text{ kcal/mol}$
- $\Delta E_{\text{strain}} = 28.172 \text{ kcal/mol}$
- $-92.083 \text{ kcal/mol}$
- $\Delta H_f = -79.408 \text{ kcal/mol}$
- $25.58 \text{ kcal/mol}$
- $\Delta E_{\text{total}} = 38.25 \text{ kcal/mol}$
Studies directed towards vinigrol (E. J. Corey IMDA Approach)

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S. N. Goodman, Ph. D. Dissertation Harvard University, 2000
Synthesis of the Complete Carbocyclic Skeleton of Vinigrol

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Important Features of Vinigrol

- Major conformer (4a) lacking the proximity needed for ring closure.
- C4 & C11 Carbons are unusually close.
Retrosynthetic analysis

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Synthesis of the vinigrol core (5). a) (E)-methyl 4-methyl-2-pentenoate (1.0 equiv), diene 8 (2.0 equiv), AlCl$_3$ (1.5 equiv), DCM, $-78$ °C, 1 h, 45 °C, 3 h, 65% (d.r.$\approx$2:1); b) LDA (1.2 equiv), Tf$_2$O (1.3 equiv), THF, 78 °C to $-23$ °C, 2 h, 87% (based on recovered starting material); c) vinyltributyl tin (1.2 equiv), LiCl (4.8 equiv), [Pd(PPh$_3$)$_4$] (0.1 equiv), THF, reflux, 3 h, 90%; d) DIBAL (2.5 equiv), DCM, $-78$ °C, 30 min, then DMP (1.25 equiv), DCM, 23 °C, 30 min, 80% over two steps; e) allylmagnesium chloride (1.0 equiv), PhMe, $-78$ °C to 105 °C, 90 min, then TBAF (4.8 equiv), 65 °C, 45 min, 75%;
Synthesis of the vinigrol core 5

f) DMP (1.1 equiv), DCM, 23 °C, 30 min, 92%; g) DIBAL (3.2 equiv), DCM, –78 °C, 30 min, then MsCl (1.25 equiv), Et₃N (1.5 equiv), 23 °C, 20 min, 79% over two steps (d.r.≈2.5:1); h) KHMDS (1.1 equiv), THF, 0 °C, 15 min, 93%; i) m-CPBA (1.5 equiv), NaHCO₃ (2.0 equiv), DCM, –15 °C, 45 min, 95%; j) DIBAL (3.2 equiv), DCM, –78 °C, 30 min, 96% (d.r.≈2.5:1); k) aqueous NH₄Cl, 23 °C, 81% (d.r.6:1).
Conclusion

- Tricyclic carbon skeleton 5 achieved in 9 steps 20% overall yield.

- Five out of eight stereocenters have been partially addressed in this sequence.

- Grob fragmentation followed by proximity induced intramolecular Diels-Alder reaction makes it possible to access this skeleton.

- Careful sequence choreography and redox accounting led to minimize the protecting group chemistry.