Total Syntheses of the Tetracyclic Cyclopiane Diterpenes Conidiogenone, Conidiogenol, and Conidiogenone B

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• Since 2002, a series of novel tetracyclic diterpenes of the cyclopiane class with some biologically important properties have been isolated and characterized, both from fermentation broths and marine-derived entophytic fungi of the *Penicillium* genus.

• Conidiogenone (1) and conidiogenol (2) exhibit potent conidiation-inducing activity (20 ng of 1 or 2 per milliliter of medium is enough for the total induction of conidiogenesis in the fermentation of *Penicillium cyclopium*).

• Conidiogenone (1) (0.64 mg) was isolated from a 300 L fermentation broth of *Penicillium cyclopium*. 
Semipinacol Rearrangement

Classical Pinacol Rearrangement

Original Definition of Semipinacol Rearrangement

The term “semipinacol” was first coined by Tiffeneau in 1923 to describe a special type of pinacol rearrangement in which the tertiary secondary 1,2-diol undergoes an unusual 1,2-migration toward the secondary center, rather than the tertiary one.
General Description of the Semipinacol Rearrangement

Mechanistically, all such processes share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C-C or C-H bond to terminate the process, generating a carbonyl group.
Type I Rearrangement

Refers to the rearrangement of 2-heterosubstituted alcohols and their derivatives. In this reaction, good leaving groups such as OMs, OTs, Cl, Br, I, N2, SR, and SeR are usually attached to the electrophilic carbon center.

Tsuchihashi’s Total Synthesis of Protomycinolide IV

Refers to rearrangements of allylic alcohols and their derivatives. The electrophilic carbon center is a carbocation that can be generated by the addition of an electrophile to a C=C bond. In contrast, oxocarbeniums, thiocarbeniums, and iminiums mainly undergo intramolecular ones. The latter case is now widely known as the Prins-pinacol rearrangement.

Tu’s Synthetic Studies toward Colchicine

Prins-pinacol rearrangement.

Overman’s Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo-[6.3.1.0]-dodecanes

Type III Rearrangement

Refers to rearrangements of epoxides. Investigations in this field have focused largely on the rearrangement of 2,3-epoxy alcohols and their derivatives. In this case, the electrophilic carbon center corresponds to either carbon of the oxirane, and the migration is driven by acid-promoted epoxide ring-opening.
Tu’s Formal Total Synthesis of Cephalotaxine

Type IV Rearrangement

Refers to rearrangements of tertiary α-hydroxy ketones and imines. This reaction is also known as the “acyloin rearrangement” or “α-ketol rearrangement”

McWhorter’s Synthesis of 8-Desbromohinckdentine A

Scheme 2. Retrosynthetic analysis of 1–3. TMS = trimethylsilyl.
NIBS 11

**Chemical Reaction Diagram**

- **Compound 10**
  - Reaction with **CuCl, TMSCl, LiOH**
    - 60% yield
  - **Compound 12**
  - Reaction with **(COCl)₂ then NEt₃**
    - 60% yield
  - **Compound rac-9**
  - Reaction with **L-selectride**
    - 90% yield
  - **Compound 11**
  - Reaction with **(1S, 4R)-camphanoyl chloride, DMAP**
    - 43% of 14
    - 45% of 15
  - **Compound rac-13**
  - Reaction with **K₂CO₃, MeOH**
    - 74%, 2 steps
  - **Compound 15**
  - Reaction with **IBX, EtOAc**
    - 54%, 2 steps

- **Compound 16, R = H**
  - Reaction with **TMSOTf, iPr₂NEt**
    - 92% yield

- **Compound 7, R = TMS**
  - Reaction with **BF₃·OEt₂**
    - 78% yield

- **Compounds 17, 6**
  - Reaction with **BF₃·OEt₂**
    - 80% yield

- **Compounds 18**
  - Reaction with **BF₃·OEt₂**
    - 92% yield

- **Compounds 8, 9a, 16a**
  - Reaction with **LDA, DMPU, PhSSPh**
    - 68% yield
  - Reaction with **tBuLi, 8 then 1 m HCl**
    - 60% yield
  - Reaction with **tBuLi, 9 then 1 m HCl**
    - 60% yield

- **Compounds 18, d.r. 1.2:1 (desired)**
  - Reaction with **BF₃·OEt₂**
    - 92% yield
  - Reaction with **sulfur-substituted tertiary carbon migration**

**Note:**
- **Me** represents methyl group.
- **OTMS** represents trimethylsilylmethyl group.
Scheme 4. Proposed mechanism for the formation of 18 from 7a. LA = Lewis acid.
Scheme 5. Synthesis of the key pentacyclic intermediate 21. Reagents and conditions: a) ethylene glycol, PTS, benzene, reflux (19, 45%; 19’, 41%; recovered material 18, 11%); b) allylmagnesium bromide, THF, 0°C (92%); c) O₃, CH₂Cl₂, −78°C, then PPh₃, 0°C, then 2 M HCl/H₂O, THF, 70°C (84%, one pot). PTS = p-toluenesulfonyl acid.
a) MsCl, NEt₃  
b) LiBr, Li₂CO₃  
c) Raney Ni

21  56%, 3 steps

22

23  72%, 2 steps

4  95%, 2 steps

d) SOCl₂, py  
e) PtO₂, H₂, then DMP

f) CH(OMe)₃  
g) Pd(OH)₂/C, tBuO₂H

i) LiAlH₄, THF  
then 1 m HCl

90%

(+)-3: proposed absolute configuration of conidiogenone B (ent-conidiogenone B)

h) LDA, MeI

78%

24

25  77%

j) Triton B, tBuO₂H

k) NaSePh

69%

(+)-1 (ent-conidiogenone)

l) L-selectride

77%

(+)-2 (ent-conidiogenol)
Summary

• total synthesis of the cyclopiane class tetracyclic diterpene conidiogenone B (3) in 24 steps

• Intramolecular [2+2] cyclization, a regioselective and diastereoselective cycloenlargement semipinacol-type rearrangement, and subsequent aldol cyclization.