Total Synthesis towards Maoecrystal V


- structure was determined by comprehensive NMR and MS spectroscopic analysis and confirmed by single-crystal X-ray diffraction study.

- exhibits highly selective antitumor activity, HeLa cells with IC$_{50}$ = 60 nM (cis-platin: IC$_{50}$ = 0.99 µg/mL).

- belongs to the family of C$_{19}$ diterpenoid, specifically *ent*-kauranoids.

- Contain highly congested polycyclic core. 7 stereocenters, 3 of which are quaternary stereocenters.

- 1 total synthesis and 6 partial synthesis have been reported till now.

*Org. Lett.*, 2004, 6 (23), pp 4327-4330

www.eFloras.org
EDUCATION
Ph. D. in Chemistry                  The Chinese University of Hong Kong (1989 – 1992)
M.S. in Medicinal Chemistry    Shenyang College of Pharmacy, P. R. China (1983-1986)
B.S. in Medicinal Chemistry     Shenyang College of Pharmacy, P. R. China (1978-1982)

EXPERIENCE
2001.9-present       Changjiang Professor
                    College of Chemistry, Peking University, Beijing, China
                    Research Interest:
                    Total Synthesis of Natural Product and Organometallic Chemistry
                    Diversity Oriented Synthesis and Chemical Biology

2005.9-present       Director of Chemistry
                    XTL Biopharmaceutical, New York, USA
                    Research Interest:
                    Medicinal Chemistry and Combinatorial Chemistry

2001.5-2005.9        Co-Founder and Director of Chemistry
                    VivoQuest. Inc. New York, USA
                    Research Interest:
                    Anti-Viral Drug Discovery

1998.5-2001.5        Institute fellow
                    Harvard Institute of Chemistry and Cell Biology,
                    Harvard University
                    Research Interest: Diversity Oriented Synthesis

1995.6-1998.5        Assistant Professor
                    The Scripps Research Institute
                    Research Interest: Total Synthesis of Complex Natural Products

1992.5-1995.5        Postdoctoral Fellow
                    The Scripps Research Institute
                    Topic: Total Syntheses of Taxol, Brevetoxin A and Epothilone A

HONORS AND AWARDS
2000’s Young Investigator Award (abroad), NSF of China
2001’s Glaxo-Smith-Kline Drug Discovery and Development Award (USA)
2004’s Young Investigator Award, NSF of China
2005      Eli Lilly Scientific Excellence Award (China)
          Research Interests: Development of synthetic methods for the synthesis of complex natural

1993-1999, 23 papers and 4 patents with Nicolaou

Yang Zhen, Ph.D.
Changjiang Professor
College of Chemistry
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Chuang-chuang Li, Ph.D.
Associate Professor
Yang’s Total Synthesis of Maoecrystal V

16 steps, 2% overall yield

Yang’s Total Synthesis of Maoecrystal V

1. tBuOK, (HCHO)n, THF, 0 °C, 95%
2. TFA, CH₂Cl₂, rt, 90%

Yang’s Total Synthesis of Maoecrystal V

1. NBS, (PhCO₂)₂
   CCl₄, reflux, 2 h
   90%
2. Bu₃SnH, TEMPO
   PhH, reflux, 2 h
   75%

1. Zn, AcOH, THF, H₂O
   70 °C, 2 h
   85%
2. SmI₂, THF, MeOH
   rt, 10 min
   88%

Lindlar cat. MeOH, THF
rt, 2 h
92%

DBU, toluene, 100 °C, 1 h
48% (90% brsm)

DMP, CH₂Cl₂, rt, 1 h
88%

Baran’s Synthesis towards Maoecrystal V

Baran’s Synthesis towards Maoecrystal V

1. Li(t-BuO)$_3$AlH, 72%
2. OCl
   dr = 7:3, 67%

OCl

165 °C
79%

H$_2$, Pd/C
97%

Nicolaou’s Synthesis towards Maoecrystal V

Chem. Commun., 2010, 46, 70-72
Danishefsky’s Synthesis towards Maoecrystal V

Tetrahedron Letters 50 (47), 25, 2009, 6586-6587
Danishefsky’s Synthesis towards Maoecrystal V

1. Pd(OAc)$_2$, K$_3$PO$_4$, THF
   $80 ^\circ C$, 12 h
   91%

2. TMSCHN$_2$, Hünig’s base
   CH$_3$CN/MeOH = 9:1, 6 h
   100%

1. Bu$_3$SnCH$_2$OMOM, BuLi
   THF, -78 $^\circ$C to -40 $^\circ$C
   30 min, 0.5% HCl work-up
   75%

Stork-Danheiser protocol

1. HCl/MeOH, 50 $^\circ$C
   75%

2. PivCl, Py, DCM, 12 h
   96%

1. NaBH$_4$, CeCl$_3$
   MeOH, 0 $^\circ$C, 2 h
   93%

2. MOMCl, Hünig’s base
   DCM, 12 h
   95%

1. DIBAL-H, -78 $^\circ$C
   DCM, 30 min
   95%

2. KH, 18-crown-6
   ICH$_2$SnBu$_3$
   0 $^\circ$C, THF, 6 h
   90%

n-BuLi, -78 $^\circ$C to -20 $^\circ$C
   THF, 6 h
   88%

Witting-Still rearrangement

Tetrahedron Letters 50 (47), 25, 2009, 6586-6587
Danishefsky’s Synthesis towards Maoecrystal V

Tetrahedron Letters 50 (47), 25, 2009, 6586-6587
Trauner’s Synthesis towards Maoecrystal V

Org. Lett., Article ASAP
DOI: 10.1021/ol102446u
Trauner’s Synthesis towards Maoecrystal V

Open book effect

LDA, CH₂O, -40 °C, 92%

1. DMP, 90%
2. NaBH₄, 92%

LDA, CH₂O, -40 °C
65%

O₃, Me₂S, 46%
Trauner’s Synthesis towards Maoecrystal V

1. O₃, Me₂S  
   94%

2. HCl, 56%  
   3. TBSCI, ImH  
   73%

dr = 7:1

1. LDA, CH₂O, -40 °C  
   49%

2. Me₂CO, p-TSA  
   43%

1. DIBAH, 99%  

2. NaOH, 96%

Org. Lett., Article ASAP  
DOI: 10.1021/ol102446u
Trauner’s Synthesis towards Maoecrystal V

1. **TMSA, BuLi**
   - Reaction with TMSA and BuLi
   - 75% yield
   - dr = 7:1

2. **NaH, 40 °C**
   - Reaction with NaH at 40 °C
   - 82% yield

3. **H₂, Pd/CaCO₃, Pyr**
   - Hydrogenation with Pd/CaCO₃ and Pyr
   - 96% yield

4. **LDA, CH₂O**
   - Reaction with LDA and CH₂O
   - -40 °C to rt
   - 12% yield

5. ****
   - Reaction with unknown reagent
   - 54% yield

**Org. Lett., Article ASAP**
**DOI: 10.1021/ol102446u**
Thomson’s Synthesis towards Maoecrystal V

Lots of FGIs

DA

Nazarov

Org. Lett., 2010, 12 (13), 3010–3013
Thomson’s Synthesis towards Maoecrystal V

1. LDA/TMScI, m-CPBA
2. TBSCI, ImH
70% over 2 steps

1. NaH, OMe
2. OMe
73 % over 2 steps

FeCl₃
72%

1. KOH
2. Pd/C, H₂
86%

Necessary for following DA

1. DIBAL-H
2. O₂
44% over 2 steps

Baeyer-Villiger

TMSI/HMDS m-CPBA
88%

CF₃COOOH
52%

Grob fragmentation
PhI(OAc)₂/I₂, hv
95%
Thomson’s Synthesis towards Maoecrystal V

Org. Lett., 2010, 12 (13), 3010–3013