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Jianxian Gong

Total Synthesis of (±)-Maoecrystal V

Doctoral Thesis accepted by
Peking University, Beijing, China

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Supervisor's Foreword

The field of total synthesis of natural products is practiced in a scientific and artistic way. The strategy should be balanced based on the dimensions, geometries, and symmetries of the molecules. During the pursuit of total synthesis, the artistic taste was exercised in the way combining chemical reactions to arrive at a strategy that will lead to the target molecule. The powerful methodology and sophisticated instrumentation available today have profoundly affected the way in which organic molecules are synthesized and characterized. In spite of the great advances that have enormously facilitated our operations, the synthesis of organic molecules even of medium levels of complexity still faces practical, theoretical, and logical challenges.

This thesis focuses on the total synthesis of Maoecrystal V. Maoecrystal V, a natural product with potent biological activity, is a novel diterpenoid which was isolated from the leaves of Chinese medicinal herb, Isodon eriocalyx, by Prof. Handong Sun and co-workers. The synthesis challenge exists in the novel pentacyclic ring system and six chiral centers, including four continuous chiral centers, three all quaternary carbon centers.

Many distinguished synthetic groups have carried out the total synthesis toward Maoecrystal V due to the complexity of the structure and the importance of its bioactivity. The thesis mainly focuses on two aspects: the first part is the stereoselective construction of the tetracyclic model system and the second part is the first total synthesis of natural product Maoecrystal V. Based on the model study, the total synthesis of Maoecrystal V is accomplished in 17 steps, 1.2 % yield.

In such an exciting field, only a tip of the iceberg in terms of molecular diversity from nature has been just touched by the synthesis. With the development of organic synthesis, I strongly believe that we are going to see a lot of creative and efficient strategies for the synthesis of complex molecules. As Prof. K. C. Nicolaou said "It's rather complicated to even define art, science, and technology. There is a triangle of art, which is the pursuit of something new, usually associated with esthetics; science, the pursuit of something new, perhaps the understanding of nature; and technology, the application of science." Keeping ourselves busy inventing and discovering new generations of medicine used in the pharmaceutical and biotechnology industries will always be our unremitting pursuit.

Beijing, March 2013 Zhen Yang

Contents

Abbreviations

Ac	Acetyl
AVMA	Asymmetric vinylogous Mukaiyama aldol
Bn	Benzyl
Boc	*t*-butoxycarbonyl
BOM	Benzyloxymethyl
i-Bu	*i*-butyl
n-Bu	*n*-butyl
t-Bu	*t*-butyl
Bu	Butyl
CAN	Cerium(IV) ammonium nitrate
Cp	Cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide
dr	Diastereoselective ratio
EA	Ethyl Acetate
EE	2-ethoxyethyl
Et	Ethyl
eq.	Equivalent
HMPA	Hexamethylphosphoramide
i-Pr	*i*-propyl
LDA	Lithium Diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide
NaHMDS	Sodium Hexamethyldisilazide
Me	Methyl
MEM	(2-methoxyethoxy) Methyl
MES	Mesityl
MOM	Methoxymethyl

MS	Molecular Sieves
OTf	Triflate
PE	Petroleum Ether
PG	Protective Group
Ph	Phenyl
Piv	Pivaloyl
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
RCM	Ring Closing Metathesis
RT	Room Temperature
SM	Starting Material
TBAF	Tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TIPS	Triisopropylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
Ts	*p*-toluenesulfonyl