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Total Synthesis of (±)-Maoecrystal V

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Jianxian Gong

Total Synthesis of (±)-Maoecrystal V

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Author
Dr. Jianxian Gong
School of Chemical Biology and Biotechnology
Peking University Shenzhen Graduate School
Shenzhen, Guangdong
People's Republic of China

Supervisor
Prof. Zhen Yang
College of Chemistry and Molecular Engineering
Peking University
Beijing
People's Republic of 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

Chapter 1
Research Background of Total Synthesis of Natural Product Maoecrystal V and Its Family

1.1 Introduction to the Research Background of Total Synthesis of Natural Products

Natural products refer to chemical components or metabolites produced by a living organism inside human beings and animals, plants, insects, marine lives and microorganisms [1]. Natural products are very important for drug discovery, because more than one third of the drugs in current clinical use come directly from natural products or derivatives developed with active ingredients of nature products as the lead compounds. China is famous for its massive land as well as its enrichment in natural product resources. Moreover, China has thousands of years' experience of using Chinese herbal medicine. Therefore, China has unique advantages on natural product research. In recent years, Chinese researchers have successfully isolated and extracted a large number of natural products, as well as identified their structures and realized the synthesis for the first time.

Total synthesis of natural products is an important part of organic chemistry. In principle, it starts with relatively simple small-molecule compounds through reasonable combination and application of the existing organic synthesis reactions, step by step to accomplish the construction of natural products with relatively complicated structures. In the early development process of organic chemistry, the primary mission of total synthesis was to confirm or correct the structures of natural products, check the applicability of existing methods as well as develop new methods for organic synthesis. Therefore, total synthesis of natural products is a powerful tool to promote the development of organic chemistry. In the early days, though limited by the available synthesis methods, organic chemists used their superb wisdom to come up with numerous total synthesis works through rigorous reasoning and clever design, these works are not only extremely high-valued in science but also reached a very high level of logical thinking and artistic design. Along with the development of synthetic and analytic methods and chiastopic fusion of various subjects, especially chemistry, biology, pharmaceutics and medicine, the mission of total synthesis has been changed to get the rare natural products, study the structure-activity relationship of important biological-

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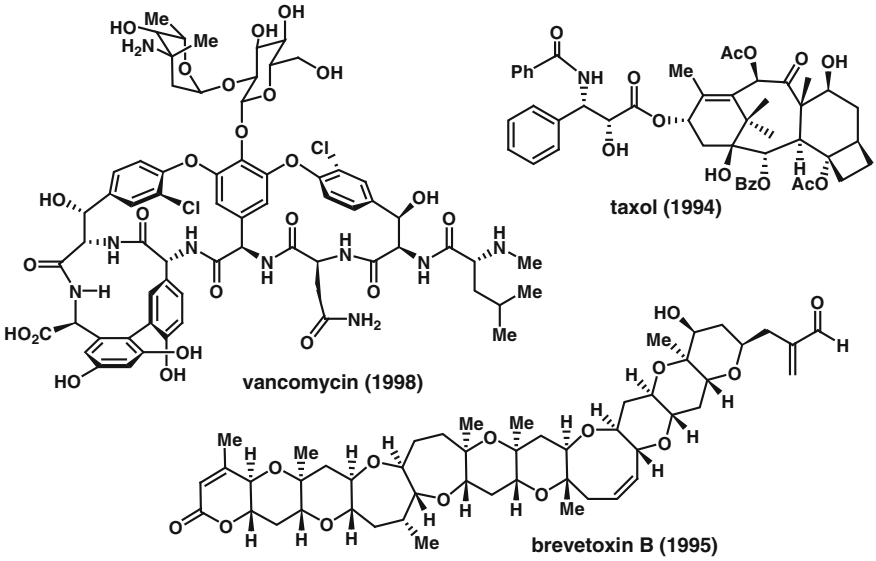

Fig. 1.1 Representative complicated natural products [1]

active natural products, and finally promote the research and development of natural product drugs and structure similar drugs. Certainly, the contribution of total synthesis is not only limited in the fields of chemistry and natural products, it has been also gradually applied to the development of new materials, new drugs, environmental science and so on. In addition, total synthesis research is able to help us to enlarge our scope of knowledge, cultivate the skill of conducting literature survey, develop the ability of organizing and allocating resources, foster the judgment and determination at critical moments as well as improve the anti-pressure ability and so on.

In 1828, German chemist Wöhler's success in the synthesis of urea marked the beginning of the modern organic synthesis [2]. Organic chemistry has made brilliant achievement in the following 180 years, and the syntheses of lots of complicated natural products have been conquered by organic chemists. The most representative ones in the recent 20 years (Fig. 1.1) are Taxol, Vancomycin, Brevetoxin A and B, palytoxin and so on.

Take palytoxin for example (Fig. 1.2), its structure has 64 chiral centers. In 1994, Kishi etc. first completed the total synthesis of this natural product [3], which made people realize how precise and complicated can the organic synthesis be. With outstanding wisdom and strong willpower, organic chemists showed their amazing creativity.

E.C Kornfeld from Eli Lilly and Company first separated vancomycin from the soil of deep forest in Borneo, which was collected by a churchman [4]. The bacteria producing vancomycin was named Amycolatopsis orientalis. Vancomycin was originally used to fight against the staphylococcus aureus which is resistant to

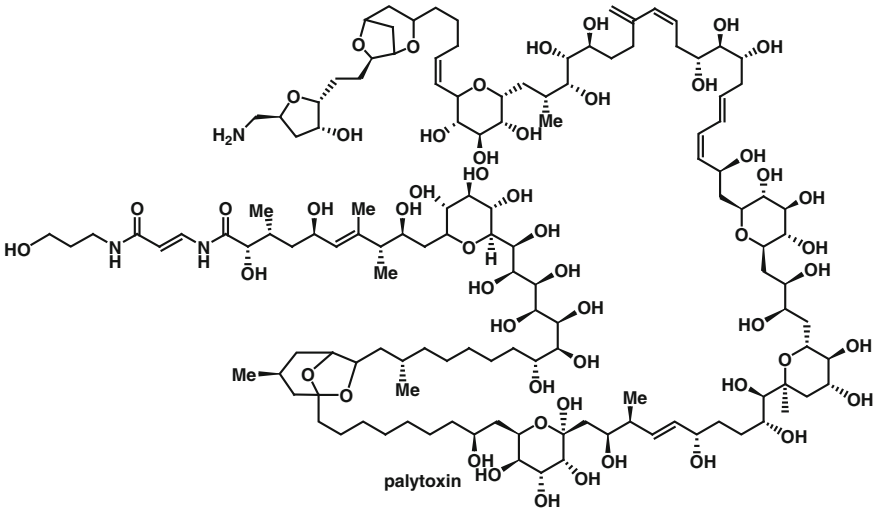

Fig. 1.2 The structure of palytoxin (Reprinted with the permission from Ref. [3]. Copyright 1994 American Chemical Society)

penicillin. With the follow-up research, people found that staphylococcus subcultured on medium containing Vancomycin didn't show obvious drug resistance even after many generations. Although Vancomycin obtained FDA's permission in 1958 [5], it didn't become the first-line anti-infection drug for two obvious flaws: (1) Isolation purity was not high enough in the early time, which led to obvious ototoxicity and renal toxicity. (2) It cannot be taken orally but has to be injected intravenously. However, when more and more staphylococcus developed drug resistance to penicillin antibiotics, Vancomycin became "the last line of defense" in fighting with infectious bacteria [4–6].

In view of the great value and potential of vancomycin in anti-infective field, it is very meaningful to develop a total synthetic route to improve the structure of Vancomycin (Fig. 1.3), reduce the toxicity as well as enhance the stability. So far as we know, several groups have been involved in the total synthesis of vancomycin, including K.C. Nicolaou and D. Boger from Scripps Research Institute, and D.A. Evans from Harvard University [7].

As time went on, there appeared 'super bacteria' such as Vancomycin-resistant enterococci. The activity of vancomycin against these bacteria has reduced nearly 1,000 times comparing to that in the old time. Boger discovered the analogs of Vancomycin through reforming the total synthesis route. These analogs have increased the anti-infective activity up to 40 times that of the ordinary vancomycin, which is the best result achieved so far, and this result can only be achieved by total synthesis. Therefore, we can say that total synthesis can make contributions to humanity in different ways in the new era.

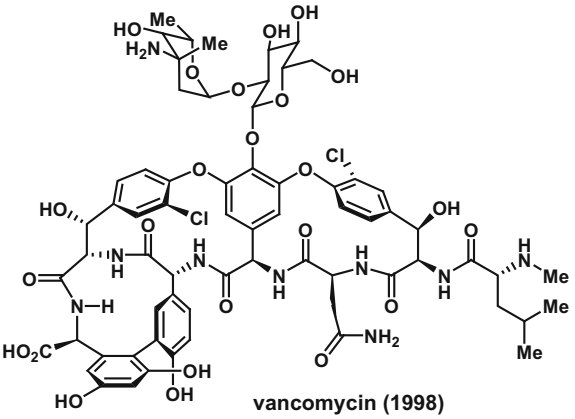

Fig. 1.3 The structure of vancomycin (Reprinted with the permission from Ref. [7]. Copyright 2011 American Chemical Society)

Nevertheless, no matter how fast the organic synthesis develops, there are still a lot of natural products chemists cannot conquer. The complexities of natural organisms are always beyond our imagination. The exploration of complicated natural products always challenges the wisdom and creativity of organic chemists. Furthermore, the cross fusion of various subjects in modern era put forward new requirements and challenges for chemists working in the field of total synthesis of natural products. It requires them to have not only excellent chemistry skills and visions but also open mind in the new era. It also requires chemists to be able to analyze problem in the views over various fields.

1.2 Terpenoids

Terpenoids, sometimes called isoprenoids, are a large and diverse class of naturally occurring organic compounds. Terpenoids derived from five-carbon isoprene units assembled and modified in thousands of ways. The word "Terpenoid" comes from "turpentine" (Latin: *balsamum terebinthinae*), which means "pine oil". Till now, the number of isolated terpenoids has reached more than 55,000 [8].

Terpenoids are widely distributed in nature; they mainly exist in plants, animals and microorganisms. Terpenoids are used extensively with a long history. The earliest application can be traced back to ancient Egypt, when people widely used this kind of compound in the manufacturing of spices, medicine, pigment and antiseptic. Many terpenoids have been proved to be the active components in Chinese medicinal herb. At the same time, terpenoids are essential basic raw materials in cosmetics and food industry. Even in the automobile and aircraft industry, terpenoids have found the applications such as terpenoids rubber and so on [9–11].

Terpenoids synthesis research made huge contributions to the development of organic chemistry. Although all terpenoids are constituted by single or multiple