Maoecrystal V: A formidable synthetic challenge

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Abstract. Nature continues to be a rich source of bio-active compounds that often provide the lead for drug development. Isolation and characterization of maoecrystal V, a C19 terpenoid, having potent and selective cytotoxicity towards HeLa cells was recently reported. Unusually complex pentacyclic molecular structure, presence of spirofused rings and several stereogenic centres posed a great synthetic challenge. In this short review, efforts made towards synthesis of maoecrystal V are presented.

Keywords. Maoecrystal V; synthesis; Diels–Alder reaction; dearomatization.

1. Introduction

There is continuing search for biologically active compounds from various types of natural sources as it often provides a lead or inspiration for drug discovery and development.^{1–4}

Investigations on plants and shrubs that are used in folk medicine often lead to isolation of interesting compounds with potent biological properties. *Isodon eriocalyx* (Dunn.) Hara, a herb widely distributed in China and used as folk medicine for treatment of various kinds of ailments, is known to be a rich source of biologically active diterpenoids.⁵ Maoecrystal V (figure 1) was isolated from the leaves of this plant by Sun and co-workers.⁶ The structure of maoecrystal V was established by detailed spectroscopic methods and confirmed with the help of a single-crystal structure determination.⁶ Maoecrystal V exhibits a highly remarkable inhibitory activity towards HeLa cells at very low concentrations ($IC_{50} = 0.02$ mg/ml; *cis*-platin $IC_{50} = 0.99$ mg/mL). Potent biological activity and unusually complex structure of maoecrystal V has stimulated intense interest in its synthesis.

Presence of a bridged bicyclo[2.2.2]octanone ring annulated with a lactone ring that is spiroannulated with a six-membered enone and a strained five-membered ether in a highly unusual fashion, and several quaternary centres in molecular structure of maoecrystal V

poses a formidable synthetic challenge. Several leading research groups undertook this challenge,^{7–20} however, only two groups have succeeded in the synthesis of maoecrystal V since its isolation a decade ago. Yang and co-workers reported the first total synthesis of **1** in 2010.¹⁹ Danishefsky and co-workers unravelled synthesis of maoecrystal in 2012.²⁰

We wish to highlight the synthetic approaches and studies directed towards synthesis of maoecrystal V in this short review in order to give an overview that would provide further stimulation to generate new ideas and chemistry. We would first summarize various approaches and model studies; total synthesis will be presented towards the end.

2. Studies towards synthesis of maoecrystal V

Yang and co-workers reported synthesis of tetracyclic framework of maoecrystal-containing lactone ring.⁷ Oxidative dearomatization and intramolecular Diels–Alder reaction are the key features of their design and approach.⁷ They employed aryl lead compound **3**, prepared from aryl boronic acid **2**, for coupling with active methylene compound. Thus, treatment of **2** with $Pb(OAc)_4$ and $Hg(OAc)_2$ gave aryl lead compound **3**, which upon oxidative arylation²¹ with 2-carboethoxycyclohexanone followed by acid catalysed removal of methoxymethyl (MOM) ether furnished tricyclic compound **4**. Reduction of the ester group and subsequent esterification with acrylic acid gave hemiketal **5**. Wessely oxidation²² of **5** with $Pb(OAc)_4$ gave a diastereomeric mixture of embellished cyclohexa-2,4-dienone **6** that underwent intramolecular Diels–Alder

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Figure 1. Structure of maoecrystal V.

reaction to furnish a mixture of adduct **7a,b**. Reduction of **7a,b** with H_2 , Pd-C followed by SmI_2 furnished tetracyclic compounds **8a,b**, respectively (scheme 1).

Subsequently, Baran's group disclosed their approach towards maoecrystal V that features oxidative

dearomatization via Wessely oxidation and intramolecular Diels–Alder reaction as key steps.⁸ Coupling of keto-enol **9** with aryl bismuth chloride **10** gave the precursor **11** that was converted into **12** having dienophilic moiety. Hydrolysis of MOM group led to the formation of lactol **13**. Interestingly, oxidative dearomatization of **13** with lead tetracetate gave the dienone acetate **14** as a mixture of diastereoisomers. Intramolecular Diels–Alder reaction in **14** furnished tetracyclic adduct **15** that upon hydrolysis of tert-butyl dimethylsilyl (TBS) group gave alcohol **16**. Reduction of the double bond and acetate group gave **17** (scheme 2) having tetracyclic framework of maoecrystal V (scheme 2).⁸

Danishefsky and co-workers described their approach towards creation of tetracyclic network of maoecrystal V that involved reductive dearomatization and intramolecular Diels–Alder reaction as key elements.⁹ Palladium-catalysed arylation²³ of 4,4-dimethylcyclohexane-1,3-dione **18** with *m*-bromoanisole **19** followed by o-alkylation gave compound **20** that was elaborated into stannate **21**. Treatment of **21** with BuLi furnished

Reagents/conditions: i, $Pb(OAc)_4$, $Hg(OAc)_2$, $CHCl_3$, 60°C ; ii, Pyridine, $CHCl_3$, then H^+ ; iii TMSCl, imidazole, CH_2Cl_2 , 0°C ; iv, DIBAL-H, CH_2Cl_2 , -78°C to rt, then HCl (85%); v, acrylic acid, EDCI, DMAP (70%); vi, $Pb(OAc)_4$, acetic acid (92%); vii, 130°C , Toluene (**7a**: 88%, **7b**: 82%); viii, Pd-C, H_2 (92% from **7a**, 90% from **7b**); ix, SmI_2 , THF, *t*BuOH (68% from **7a**, 65% from **7b**).

Scheme 1. Yang's approach to tetracyclic core.

Reagents/conditions: i, Ar_3BiCl_2 , DBU, toluene (67%); ii, $\text{Li}(\text{tBuO})_3\text{AlH}$, THF (72%); iii, acryloyl chloride, DIEPA, DMAP, CH_2Cl_2 , -78°C (69%); iv, Trifluoroacetic acid (65%); v, $\text{Pb}(\text{OAc})_4$, AcOH (81%); vi, 165°C , DCB, BHT (79% for **15a**, 69% for **15b**); vii, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 (82%); viii, H_2 , Pd-C (93%); ix, Sml_2 , MeOH, THF 0°C (76%).

Scheme 2. Synthesis of tetracyclic core by Baran's group.

compound **22**. Birch reduction of **22** followed by hydrolysis of enoether and isomerization gave bicyclic compound **24** that was elaborated into the intermediate **25** containing diene and dienophilic moieties for the subsequent intramolecular Diels–Alder reaction. Heating **25** furnished tetracyclic compound **26** containing spiro-annulated lactone ring. The *endo*-selectivity during cycloaddition was however, governed by carbomethoxy group. Hydrolysis of enol ether moiety gave the ketone **27** having tetracyclic core of maoecrystal V (scheme 3).

Nicolaou and co-workers reported the synthesis of a highly functionalized maoecrystal V core structure, wherein intramolecular Diels–Alder reaction has been employed to generate bridged tetracyclic structure having five-membered ring ether and oxidative dearomatization of phenol to create functionalized cyclohexane ring and the lactone moiety (scheme 4).¹⁰ Thus, palladium-mediated decarboxylative coupling²⁴ of **28** with cyclohexenone gave the arylated enone **29** that was converted into **30**. Reaction of **30** with **31** followed by

elimination led to compound **32** that upon treatment with tert-butyldimethylsilyltriflate (TBSOTf) generated the triene **33**. Intramolecular Diels–Alder reaction in **33** followed by hydrolysis of TBS ether gave tetracyclic keto-ester **34** containing major structural features of maoecrystal V. Oxidative dearomatization of phenolic ring in **34** followed by hydrogenation gave the keto-acetal **35**. Hydrolysis of the ester group and subsequent treatment of the resulting carboxylic acid with chloriodomethane in presence of KOtBu furnished the pentacyclic compound **37** in a neat manner (scheme 4).

Singh and co-workers developed a route to tricyclic framework having a lactone ring.¹¹ They relied on oxidative dearomatization of o-hydroxymethylphenol and intramolecular cycloaddition of 6,6-spiroepoxycyclohexa-2,4-dienone (scheme 5).¹¹ Thus, o-hydroxymethylphenol **39** containing acryloyl moiety, readily available from **38**, was oxidized with aq. NaIO_4 ²⁵ to give the adduct **42** as a result of intramolecular cycloaddition in **40** and the dimer **41** arising due to intermolecular reaction between cyclohexadienone moiety of **40**.

Scheme 3. Danishefsky's approach to tetracyclic compound **27**.

Alternatively, adduct **42** was also obtained in excellent yield by thermal activation of dimer **41** via a tandem retro Diels–Alder/Diels–Alder cycloaddition. Adduct **42** was readily manipulated to give tricyclic compound **44** that upon hydrogenation afforded **45** containing tricyclic core of maoecrystal V (scheme 5).

Thomson and co-workers devised an approach to tetracyclic framework of maoecrystal V that employed Nazarov cyclization²⁶ to make tetracyclic precursor-containing diene moiety and intermolecular Diels–Alder reaction to create bridged ring system of maoecrystal V as shown in scheme 6. Thus, treatment of compound **46** with FeCl₃ generated spiroannulated dienone **47** that upon reduction of ketone followed by cycloaddition of the resulting alcohol with nitroethylene gave tetracyclic compound **48**. Treatment of **48** with KOH followed by Jones oxidation gave compound **49** that upon oxidation of methylene group of the five-membered ring afforded keto-alcohol **50**. Reduction of enone **50** to generate saturated ketone proved to be unpredictable. However, reduction of **50** with H₂ on Pd-C gave highly unexpected compound **51** containing cyclopropane ring as a result of displacement of nitro group. Oxidative cleavage of keto-alcohol followed by reduction with NaBH₄ furnished pentacyclic compound **52** (scheme 6).¹²

Trauner's approach to tetracyclic framework of maoecrystal V is depicted in scheme 7.¹³ Intramolecular aldol condensation in **53** followed by protection of the resulting alcohol gave **54** having bridged bicyclo[2.2.2]octane ring system of maoecrystal. Bicyclic compound **54** was elaborated into aldehyde **55** with the hope to introduce a prenyl chain. Unfortunately, attempts to perform reverse prenylation using various reagents failed. Therefore, **54** was treated with lithiated trimethylsilyl acetylene that furnished the adduct **56** which was converted into vinyl lactone **57**. Further elaboration of **57** led to the diol **58** that upon ozonolysis furnished tetracyclic compound **59** (scheme 7).

In continuation of their studies towards synthesis of maoecrystal V, Danishefsky and Peng reported synthesis of pentacyclic core **68** (scheme 8).¹⁴ Alkylation of diene **60** with 3-chlorocyclohexenone gave the enone-ester **61** that was transformed into compound **62** that upon intramolecular Diels–Alder reaction gave tetracyclic compound **63**. Regioselective functionalization of conjugated C=C bond furnished hydroxylactone **64**. Treatment of **64** with *m*-CPBA gave epoxide that upon reaction with *p*-toluenesulphonic acid furnished hydroxyl ether **65**. However, the stereochemistry at the newly generated centre was incorrect. Hence, compound **65** was converted into enolether **66**.

Reagents/conditions: i, Pd(TFA)₂, Ag₂CO₃, DMF/DMSO, 80°C, 3 h (89%); ii, BBr₃, CH₂Cl₂, -78 to 0°C, 2 h (98%); iii, NaH, MOMCl, THF, 0°C, 2 h (56%); iv, NaH, THF, **31**, 0 to 23°C; v, Na₂CO₃, MeI, MeOH, reflux, (57% two steps); vi, TBSOTf, Et₃N, CH₂Cl₂; vii, K₂CO₃, hydroquinone, toluene reflux, then aq. HCl (50%, both steps); viii, 6 N HCl, EtOH-CHCl₃, reflux, 3 h (83%); ix, PIFA, KHCO₃, MeOH, 0 to 23°C (83%); x, H₂, Pd-C, EtOH, 23°C, 10 h, (66%); xi, 1N NaOH, EtOH, reflux, then 1.0N aq. HCl; xii, ClCH₂I, KO^tBu, 18C₆, THF, 23°C, 3 h (42% both steps).

Scheme 4. Nicolaou's synthesis of pentacyclic core.

Reaction of **66** with dimethyldioxirane followed by BF₃ furnished the pentacyclic compound **68** having correct stereochemistry at C5 via stereospecific rearrangement of epoxide **67**.

Zakarian and Gu developed¹⁵ a strategy for the synthesis of tetracyclic network of maoecrystal V containing five-membered ring ether and lactone moiety that employed rhodium-catalysed CH functionalization,²⁶ oxidative dearomatization of appropriately substituted dihydrobenzofuran and intramolecular Diels–Alder reaction (scheme 9) as key features. Thus, sesamol **69** was converted into diazoester **70**. Rhodium-catalysed reaction of **70** gave compound **71** that upon alkylation and reduction of ester group furnished the alcohol **72**. Treatment of **72** with methyl magnesium bromide led to the cleavage of methylidene group to give the key precursor **73**. Oxidative dearomatization of **73** gave cyclohexadienone ketal **74** that was sufficiently stable to permit further transformation. The hydroxymethyl group in **74** was derivatized to give the

acrylate **75** that upon intramolecular Diels–Alder reaction furnished tetracyclic compound **76**.

Continuing with their studies, Chen and co-workers further reported the synthesis of pentacyclic compound **82** from the readily available precursor **77** (scheme 9).¹⁶ Thus, the dienone acetal **77** was elaborated into compound **78** in a few steps. Hydrolysis of acetal moiety in **78** followed by olefination with Tebbe's reagent and subsequent Simon–Smith readily furnished **79** that was converted into diketoester **80** after removal of benzyl groups, oxidation and reduction of spirocyclopropane ring. Oxidation of cyclohexanone ring followed by hydrolysis of ester group gave enone **81** that upon treatment with chloriodomethane in the presence of KO^tBu furnished pentacyclic compound **82** (scheme 10).

In continuation their studies, Thomson and co-workers recently reported synthesis of compound **88** having tricyclic fragment of maoecrystal V from epoxyacetal **83** (scheme 11).¹⁷ Reaction of epoxy acetal **83** with methylmethacrylate in the presence of

Reagents/conditions: i, acryloyl chloride, CH_2Cl_2 , diisopropyl ethyl amine, DMAP, 95%; ii, aq. HCl, THF, rt, (91%); iii, aq. NaIO_4 , CH_3CN , 0°C -rt (40% for **42**, 42% for **41**); iv, *o*-dichlorobenzene, 140°C (75%); v, Zn, NH_4Cl , aq. MeOH, rt (93%); vi, (a) Jones oxidation, (b) aq. THF, Δ (66%); vii, H_2 , Pd-C, EtOH (90%).

Scheme 5. Singh's route to tricyclic ketolactone.

$\text{Cp}_2(\text{Ti(III)Cl})$ gave the spirolactone **84** that upon α -hydroxylation with MoOPh followed by protection furnished compound **85**. Introduction of the double bond in cyclohexanone ring gave the enone **86**. Treatment of **86** with TBAF gave **87** that underwent intramolecular oxa-Michael reaction to afford the tricyclic compound **88** containing five-membered ether ring.

Recently, Chisholm and co-workers reported a strategy towards synthesis of pentacyclic core structure involving a hetero-Diels–Alder reaction as a key step (scheme 12).¹⁸ The authors conceptualized that hetero-Diels–Alder reaction in **97** would lead to tetracyclic compound **98** that may be elaborated into pentacyclic system of maoecrystal V. Thus, the tricyclic enone **90** was prepared from bicyclic keto-alcohol **89** in three steps. Michael addition of **91** on enone **90** furnished compound **92** that was converted into **94**. The enone **94** containing OPMB group was derivatized into compound **95** containing OBz group. Treatment of **95** with TIPSOTf furnished tricyclic dienol ether **96**. Removal of benzoyl group and oxidation gave the key precursor **97**. Unfortunately, compound **97** did not undergo

the desired intramolecular hetero-Diels–Alder reaction to give **98** (scheme 12).

3. Syntheses of maoecrystal V

3.1 Yang's synthesis

Continued efforts by Yang and co-workers led to first total synthesis of ($\pm$)-maoecrystal V that manifested an outstanding planning and brilliant execution (schemes 13 and 14).¹⁹ Design of appropriate precursor endowed with most of the structural features of maoecrystal V such as lactone moiety and five-membered ring ether, oxidative dearomatization and intramolecular cycloaddition are the key features of their design. Thus, coupling of aryl lead compound **99** with 6,6-dimethyl-2-carbomethoxycyclohex-4-enone **100** led to the precursor **101** that was converted into the diol **102** in stereoselective manner. The diol **102** was transformed into the diazo compound **103** that upon rhodium-mediated insertion of carbenoid across OH bond

Reagents/conditions: i, FeCl_3 (70%); ii, DIBAL-H; iii nitroethylene (44% for both steps); iv, KOH; v, Jones oxidation (86% for both steps); vi, HMDS, TMSI, *m*-CPBA (88%); vii, Pd-C, H_2 (71%); viii, H_5IO_6 , MeOH; ix, NaBH_4 (75% for both steps).

Scheme 6. Thomson's approach to tetracyclic lactone.

Reagents/conditions: i, HCl (56%); ii, TBSCl, Im (73%); iii, TMSA, BuLi (75%); iv, NaH, 40°C (82%); v, Pd/ CaCO_3 .Py, H_2 (96%); vi, O_3 , DMS (40%).

Scheme 7. Trauner's route to tetracyclic core.

Reagents/conditions: i, LDA, -78°C , THF (40%); ii, Toluene, sealed tube, 166°C , 1 h, then TBAF, THF (62%); iii, H_2O_2 , NaOH, MeOH, 0°C (95%); iv, MgI_2 , CH_2Cl_2 , 45°C ; v, Bu_3SnH -AIBN, toluene, reflux (50% two steps); vi, *m*-CPBA, CH_2Cl_2 , rt, 18 h (72%); vii, *p*-TsOH. H_2O , CH_2Cl_2 , rt, 1 h (90%); viii, DMDO, CH_2Cl_2 , 0°C , then ether, BF_3 (75%).

Scheme 8. Danishefsky's route to pentacyclic core.

furnished tricyclic compound **104**. Reaction of **104** with *p*-formaldehyde in the presence of KO^tBu followed by removal of protecting group gave the desired precursor **105** (scheme 13).

It is indeed highly remarkable to note that all the 19 carbons of maoecrystal V, bridged bicyclo[2.2.2]octane ring system, spiro-annulated cyclohexane ring, six-membered lactone, and the five-membered ring ether that is most difficult to construct, are all present in the substrate **105**, and unravelled upon dearomatization of phenolic ring and subsequent intramolecular Diels–Alder reaction. Thus, oxidation of **105** with $\text{Pb}(\text{OAc})_4$ led to the formation of α -acetoxycyclohexa-2,4-dienone **106** that underwent intramolecular Diels–Alder reaction upon heating to furnish a mixture of adducts from which the desired pentacyclic adduct **107** was isolated in moderate yield (scheme 14). This reaction further demonstrates that oxidative dearomatization of phenols and cycloaddition of the resulting cyclohexadienones is a powerful tool for creation of molecular complexity from aromatics.^{27–31} The adduct

107 was then transformed into maoecrystal V as presented in scheme 14.

Thus, introduction of allylic hydroxyl group gave the compound **108** that upon treatment with SmI_2 furnished product **109** in stereoselective fashion. However, the stereochemistry at C-16 was opposite to that required. Reduction of the double bond and oxidation of hydroxyl group with Dess–Martin periodinane (DMP) gave dione **110**. At this juncture, correction of stereochemical orientation of methyl group at C16 was necessary. This was easily done by epimerization. Thus, the compound **110** was refluxed in the presence of DBU that gave a 1:1 mixture of diastereomers (at C16) from which maoecrystal V **1** was isolated (scheme 14).

3.2 Danishefsky's synthesis

Sustained efforts made by Danishefsky's group also culminated in the total synthesis of maoecrystal that was reported recently.²⁰ Intermediate **65** was prepared

Reagents/conditions: i, $\text{Rh}_2(\text{OAc})_4$, 4A MS, CH_2Cl_2 (86%); ii, $\text{LiN}(\text{SiMe}_3)_2$, Et_2Zn , MeI, DMPU, THF (quant.); iii, LiAlH_4 , THF (63%); iv, MeMgBr , THF, benzene, 80°C (quant.); v, $\text{PhI}(\text{OCOCF}_3)_2$, NaHCO_3 , EtOH (95%); vi, DMAP, $i\text{-Pr}_2\text{NEt}$, $\text{CH}=\text{CHCOCl}$ (73%); vii, BHT, $o\text{-DCB}$, 140°C , 2 h, 160°C 12 h (98%).

Scheme 9. Zakarian's route to pentacyclic system.

Reagents/conditions: i, TFA, CH_2Cl_2 0°C , 1 h (90%); ii, Tebbe reagent, Toluene/Pyridine 0°C , 1 h (78%); iii, Et_2Zn , CH_2I_2 , Toluene, 40°C , 2 h (95%); iv, $\text{Pd}(\text{OH})_2$, H_2 , MeOH, 25°C , 2 h (87%); v, DMP, CH_2Cl_2 , 25°C , 5 h (86%); vi, PtO_2 , H_2 , AcOH, 40°C , 1 h (83%); vii, TMSCl, LHMDS, THF, -78°C , $\text{Pd}(\text{CO}_2\text{CF}_3)_2$, CH_3CN , 23°C , 8 h (52%); viii, NaOH, THF-EtOH, 70°C , 8 h (75%); ix, KOtBu , ICH_2Cl , 18-Crown-6, THF, 70°C , 8 h (23%).

Scheme 10. Chen's synthesis of pentacyclic core.

Scheme 11. Thomson's route to tricyclic fragment.

Scheme 12. Chisholm's route to pentacyclic core.

Reagents/conditions: i, Pyridine, **100**, CHCl_3 , 60°C (88%); ii, $(\text{Bu})_4\text{NBH}_4$ methanol (65%); iii, LiAlH_4 , THF, rt (88%); iv, 2-(diethoxyphosphoryl)-acetic acid, EDCl, DMAP, CH_2Cl_2 , rt (82%); v, TsN_3 , DBU, 0°C (81%); vi, $\text{Rh}_2(\text{OAc})_2$, benzene, Δ (60%); vii, KO^tBu , $(\text{HCHO})_n$ THF, 0°C (95%); viii, TFA, CH_2Cl_2 , rt (90%).

Scheme 13. Synthesis of embellished precursor **105**.

Reagents/conditions: i, $\text{Pb}(\text{OAc})_4$, AcOH, 0°C then toluene 145°C (36%); ii, NBS, $(\text{Ph}_2\text{CO}_2)_2\text{O}$, CCl_4 , reflux, 2 h (90%); iii, Bu_3SnH , TEMPO, benzene, reflux, 2 h, (75%); iv, Zn, AcOH, THF- H_2O , 70°C , 2 h, (85%); v, SmI_2 , THF, MeOH, rt (88%); vi, Lindlar catalyst, MeOH, THF, rt, 2 h (92%); vii, DMP, CH_2Cl_2 , rt, 1 h (88%); viii, DBU, toluene, 100°C , 1 h (48%).

Scheme 14. Synthesis of maoecrystal V by Yang and co-workers.¹⁹

as described previously and elaborated into maoecrystal (schemes 15 and 16). Transformation of **65** into maoecrystal required correction of stereogenic centre at C5 and manipulation of spiroannulated six-membered ring and introduction of a methyl group α -to the carbonyl group. Thus, the pentacyclic intermediate **65**

was converted into hydroxyl-acetate **111**. Protection of hydroxyl group as MOM ether followed by hydrolysis of acetate afforded compound **112** that upon epoxidation furnished **113**. Treatment of **113** with Dess-Martin periodinane (DMP) followed by chromatography on SiO_2 and acylation gave

Reagents/conditions: i, Ac_2O , Py, CH_2Cl_2 ; ii, NaBH_4 , CH_2Cl_2 /ethanol (85% two steps); iii, MOMCl, *i*-Pr₂EtN; iv, K_2CO_3 , MeOH (90% two steps); v, *m*-CPBA, rt (95%); vi, DMP, NaHCO_3 , CH_2Cl_2 , 0°C (85%); vii, Ac_2O , Py, CH_2Cl_2 (90%); viii, PhSH, Et₃N, then NaBH_4 , EtOH, CH_2Cl_2 (78%); ix, Raney Ni; x, MsCl, DMAP (65%, two steps); xi, K_2CO_3 , MeOH, rt (95%); xii, DMDO, then $\text{BF}_3\cdot\text{OEt}_2$ (82%).

Scheme 15. Synthesis of pentacyclic intermediate **118**.

Reagents/conditions: i, Lombardo reagent, CH_2Cl_2 , rt (85%); ii, CH_2I_2 , Zn/Ag, ether (88%); iii, PCC, CH_2Cl_2 , rt (76%); iv, H_2 , PtO₂, AcOH (40%); v, Lombardo reagent, CH_2Cl_2 , 0°C (80%); vi, *p*-TsOH. H_2O , benzene, 76°C (85%); vii, LDA, TMSCl, THF, -78°C (90%), then $\text{Pd}(\text{TFA})_2$, CH_3CN (80%); viii, TFDO, CH_2Cl_2 , -78°C to 0°C (90%); ix, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , rt (85%).

Scheme 16. Synthesis of maoecrystal V by Danishefsky and Peng.²⁰

acetoxo-enone **114**. 1,4-Addition of thiophenol followed by reduction of the carbonyl group gave compound **115** that was converted into enol ether **116**. Epoxidation of **116** to **117** followed by Lewis acid catalysed stereoselective rearrangement furnished the pentacyclic compound **118** having correct stereochemistry at C5.

The intermediate **118** was then elaborated into diketo-lactone **119** containing spirocyclopropane ring in three steps. Olefination of **118** using Lombardo reagent followed by Simon–Smith reaction and subsequent oxidation gave diketolactone **119**. Interestingly, methoxymethyl (MOM) ether was converted into methoxyethyl (MOE) due to CH₂ insertion during cyclopropanation step, which was cleaved during the oxidation step. Reduction of cyclopropane ring and olefination gave compound **120** that was converted into dienone **121**. Regioselective epoxidation of **120** gave a diastomeric mixture of two epoxides from which compound **122** was isolated. Lewis-catalysed rearrangement of epoxide ring furnished (±)-maoecrystal V (scheme 16).

4. Conclusion

We have presented synthetic efforts towards maoecrystal V. Various kinds of ingenious strategy and tactics were employed to construct framework of maoecrystal V. It appears that creation of spiro-annulated lactone and five-membered ether ring, quaternary centres and functionality poses significant problems. Groups led by Yang and Danishefsky successfully completed the synthesis of (±)-maoecrystal V in a highly unique fashion. While these achievements are remarkable feats, synthesis of natural optically pure (–)-maoecrystal remains a challenge.

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References

1. Newman D J and Cragg G M 2007 *Nat. Prod. Rep.* **70** 461
2. Genilloud O and Vicente F (eds) 2012 *Drug discovery from natural products*, Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 0WF, UK, 2012
3. (a) Wang J, Kodali S, Lee S H, Galgoci A, Painter R, Dorso K, Racine F, Motyl M, Hernandez L, Tinney E, Colletti S L, Herath K, Cummings R, Salazar O, Gonzalez I, Basilio A, Vicente F, Genilloud O, Pelaez F, Jayasuriya H, Young K, Cully D and Singh S B 2007 *Proc. Natl. Acad. Sci. USA* **104** 7612; (b) Jayasuriya H, Herath K B, Zhang C, Zink D L, Basilio A, Genilloud O, Diez M T, Vicente F, Gonzalez I, Salazar O, Pelaez F, Cummings R, Ha S, Wang J and Singh S B 2007 *Angew. Chem. Int. Ed.* **46** 4684
4. Wani M, Taylor H, Wall M, Coggon P and McPhail A 1971 *J. Am. Chem. Soc.* **93** 2325
5. Sun H D, Xu Y L and Jiang B 2001 *Diterpenoids from Isodon species*, Beijing, China: Science Press October
6. Li S-H, Wang J, Niu X-M, Shen Y-H, Zhang H-J, Sun H-D, Li M, Tian Q-E, Lu Y, Cao P and Zheng Q-T 2004 *Org. Lett.* **6** 4327
7. Gong J, Lin G, Li C C and Yang Z 2009 *Org. Lett.* **11** 4770
8. Krawczuk P J, Schone N and Baran P S 2009 *Org. Lett.* **11** 4774
9. Peng F, Yu M and Danishefsky S J 2009 *Tetrahedron Lett.* **50** 6586
10. Nicolaou K C, Dong L, Deng L, Talbot A C and Chen D Y-K 2010 *Chem. Commun.* **46** 70
11. Singh V, Bhalerao P and Mobin S M 2010 *Tetrahedron Lett.* **51** 3337
12. Lazarski K E, Hu D X, Stern C L and Thomson R J 2010 *Org. Lett.* **12** 3010
13. Baitinger I, Mayer P and Trauner D 2010 *Org. Lett.* **12** 5656
14. Peng F, Yu M and Danishefsky S J 2011 *Tetrahedron Lett.* **52** 2104
15. Gu Z and Zakarian A 2011 *Org. Lett.* **13** 1080
16. Dong L, Deng L, Lim Y H, Leung G Y, Chen C and Chen D Y-K 2011 *Chem. Eur. J.* **17** 5778
17. Lazarski K E, Akpinar B and Thomson R J 2013 *Tetrahedron Lett.* **54** 635
18. Carberry P, Viernes D R, Choi L B, Fegley M W and Chisholm J D 2013 *Tetrahedron Lett.* **54** 1734
19. Gong J, Lin G, Sun W, Li C C and Yang Z 2010 *J. Am. Chem. Soc.* **132** 16745
20. Peng F and Danishefsky S J 2012 *J. Am. Chem. Soc.* **51** 18860
21. Elliot G I, Konopelski J P and Olmstead M M 1999 *Org. Lett.* **1** 1867
22. (a) Zibral E, Wessely F and Sturn H 1962 *Monatsch. Chem.* **93** 15; (b) Zibral E, Wessely F and Lahrmann E 1961 *Monatsch. Chem.* **92** 654
23. Fox J M, Huang X, Chieffi A and Buchwald S 2000 *J. Am. Chem. Soc.* **122** 1360
24. Tanaka D and Myers A G 2004 *Org. Lett.* **6** 433
25. (a) Adler E, Bransen S and Miyake H 1971 *Acta Chem. Scand.* **25** 2055; (b) Singh V, Porinchu M, Vedantham P and Sahu P K 2005 *Organic Synthesis* **81** 171
26. (a) Pellissier H 2005 *Tetrahedron* **61** 6479; (b) Shimada N, Stewart C and Tius M A 2011 *Tetrahedron* **67** 5851

27. (a) Quideau S, Pouysegu L and Deffieux D 2008 *Synlett* 467; (b) Pouysegu L, Chassaing S, Dejugnac D, Lamidey A-M, Miqueu K, Sotiropoulos J-M and Quideau S 2008 *Angew. Chem. Int. Ed.* **47** 3552
28. (a) Luo S-Y, Jang Y-J, Liu J-Y, Chu C-S, Liao C-C and Hung S-C 2008 *Angew. Chem. Int. Ed.* **47** 8082; (b) Liao C-C and Peddinti R K 2002 *Acc. Chem. Res.* **35** 856
29. Magdziak D, Meek S J and Pettus T R R 2004 *Chem. Rev.* **104** 1383
30. Roche S P and Porco Jr J A 2011 *Angew. Chem. Int. Ed.* **50** 4068
31. (a) Singh V 1999 *Acc. Chem. Res.* **32** 324; (b) Singh V, Praveena G D, Karki K and Mobin S M 2007 *J. Org. Chem.* **72** 2058; (c) Singh V, Sahu P K, Sahu B C and Mobin S M 2009 *J. Org. Chem.* **74** 6092