Chapter 4

Enantioselective Total Synthesis of Epidithiodiketopiperazine Natural Product (–)-Acetylapoaranotin[†]

4.1 INTRODUCTION

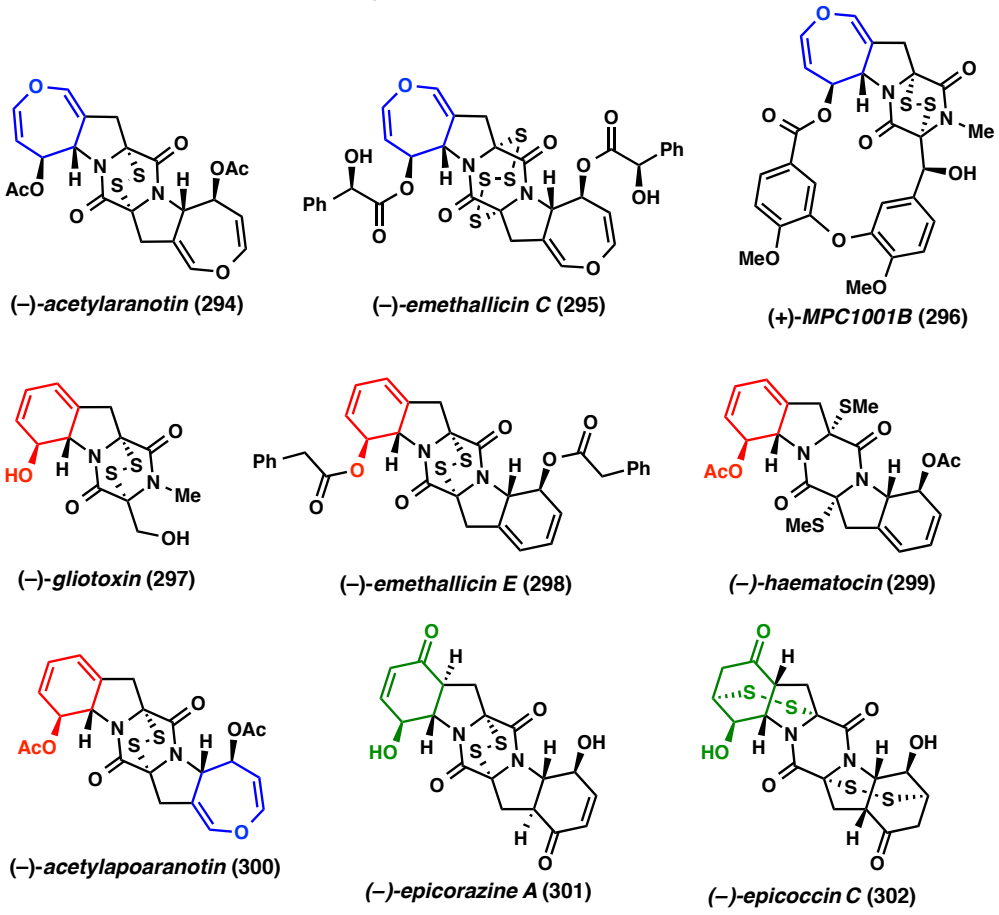
Polysulfide bridge-containing natural products, especially the epipolythiodiketopiperazine (ETP) family members, have become an important class of molecules at the interface between organic chemistry and chemical biology due to their activities in either redox-cycling to generate reactive oxygen species (ROS) or covalent modification of cysteine residues.[1] These complex molecules share a common polysulfide linkage, yet a wide range of biological activity, including antiproliferative and cytotoxic activities against various human cancer cell lines, have been identified within the ETP family members, indicating the importance of their diverse peripheral structural features (**294** to **302**, Figure 4.1).[2,3] Thus, the development of a modular synthetic strategy to

[†] The research discussed in this chapter was completed in collaboration with Clinton J. Regan (graduate student) and Dr. Paola Romanato (postdoctoral fellow) in the Reisman Laboratory.

access these related natural products could facilitate the corresponding structure-activity relationship (SAR) studies.

Among these compounds, our laboratory has accomplished the first asymmetric total synthesis of dihydrooxepine-containing natural product (–)-acetylaranotin (**294**),[4] which commenced our ongoing synthetic program to access other dihydrooxepine subfamily members such as (–)-emethallicin C (**295**) and (+)-MPC1001B (**296**). A related subfamily that has attracted our attention is the *cyclohexadienol*-containing natural products (motif highlighted in red) including C_2-symmetric (–)-emethallicin E (**298**) and (–)-haematocin (**299**), as well as the heterodimer natural product between those two subfamilies, namely (–)-acetylapoaranotin (**300**).

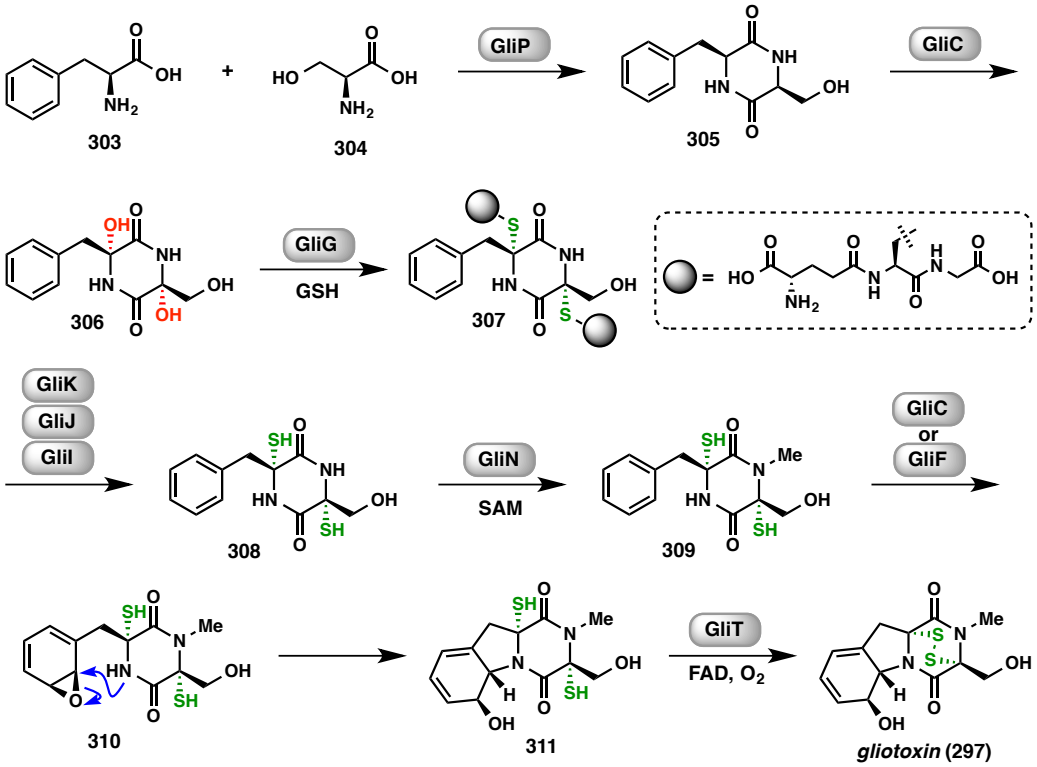
Figure 4.1. *Selected ETP natural products*



4.1.1 Biological Origins

Among the cyclohexadienol ETP subfamily, the biosynthesis of (–)-gliotoxin (**297**, Figure 4.1) has been intensely investigated.[5-8] Utilizing gene-mutagenesis and mass spectroscopy techniques, the entire biosynthetic pathway of **297** has been well mapped (Scheme 4.1).

Scheme 4.1. *A brief picture of (–)-gliotoxin biosynthesis*



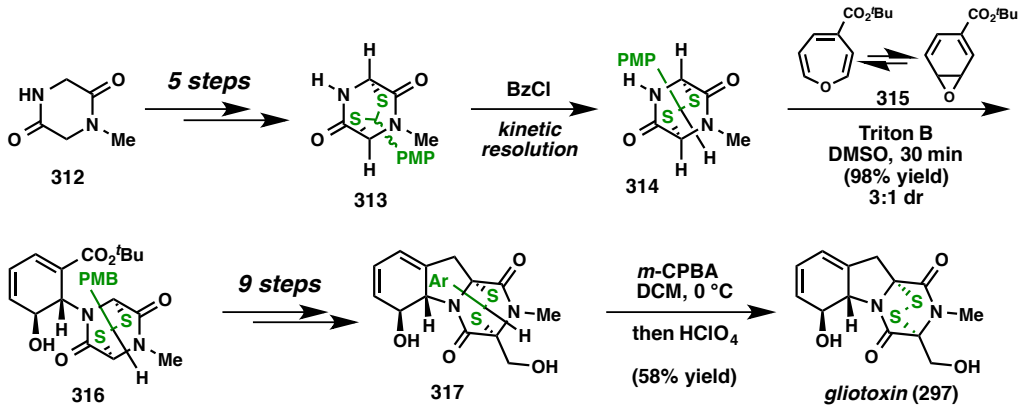
Starting with cyclization of L-phenylalanine (**303**) and L-serine (**304**) mediated by peptide synthetase GliP, the resulting DKP **305** is oxidized by a hydroxylase (GliC) to provide diol **306**. Subsequent elimination of hydroxyl groups in **306** followed by thiol addition of glutathiones (GSH) furnishes the key sulfur-transfer intermediate **307**, where the C-S bonds are cleaved by the enzyme sequence GliK/GliJ/GliI to produce free dithiol **308**. *N*-Methylation followed by a P450 enzyme (GliC or GliF)-mediated epoxidation

produces epoxide **310**, which undergoes intramolecular epoxide opening to furnish the core of gliotoxin. The final step includes oxidation of the free thiol groups to disulfide bridge via GliT enzyme and O_2. This biosynthetic pathway is likely related to other cyclohexadienol subfamily members (**297**-**300**).

4.1.2 Previous Synthetic Efforts

Due to the intriguing biological properties of these ETP natural products, a number of synthetic efforts toward them have been reported in the past few decades.[9] The simplest cyclohexadienol ETP family member, (–)-gliotoxin (**297**), was successfully synthesized by Kishi and coworkers in 1976 (Scheme 4.2).[10]

Scheme 4.2. *Total synthesis of gliotoxin by Kishi*

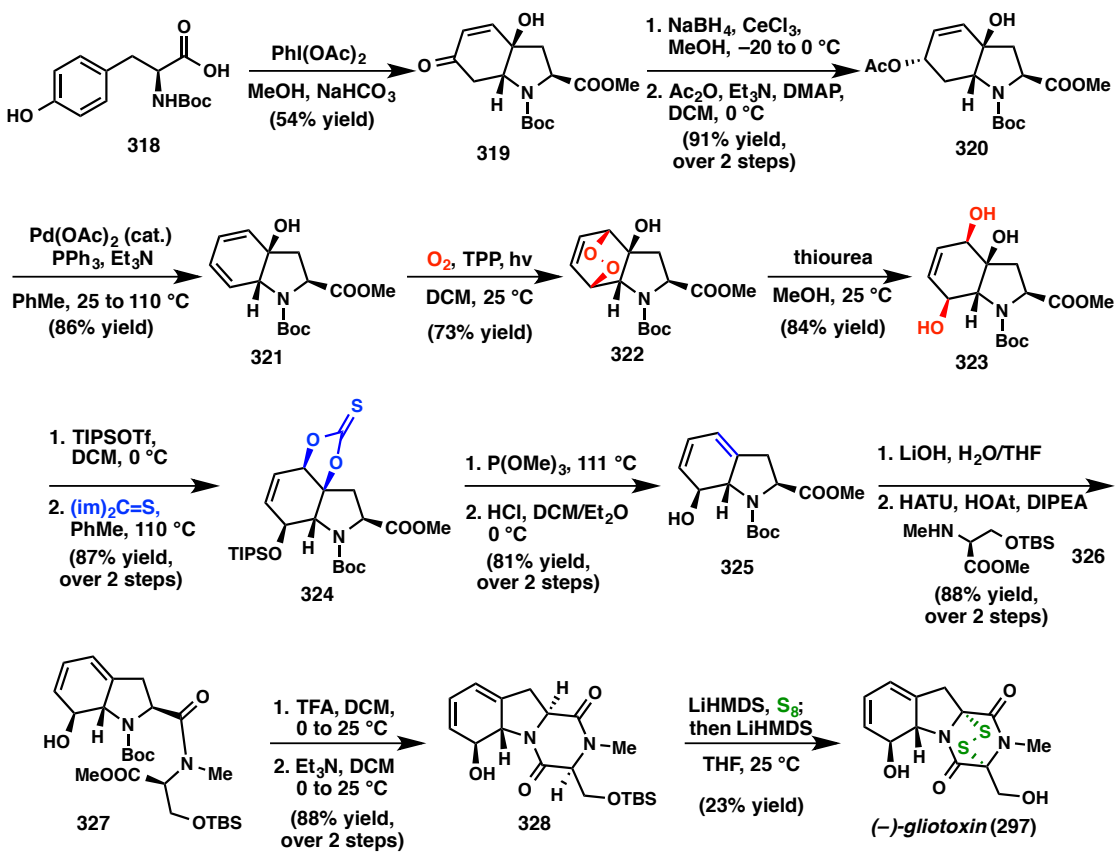


Beginning with glycine-derived diketopiperazine (DKP) **312**, dithioacetal **314** was prepared in six steps (including a kinetic resolution step). Deprotonation at the DKP nitrogen followed by nucleophilic addition to oxepine **315** provided cyclohexadienol **316** in 3 : 1 dr. Subsequent functional group manipulation in nine steps advanced **316** to diol **317**, which possesses the core of gliotoxin (**297**). Diol **317** was then subjected to

deprotection of the dithioacetal using *m*-CPBA and acidic workup to accomplish the synthesis of gliotoxin.

For a long period of time, the Kishi synthesis of gliotoxin utilizing the dithiol acetal-protecting strategy represented the state of the art for the preparation of ETP natural products. Since the early 2000s, a new wave of ETP synthesis has emerged featuring a late-stage sulfenylation strategy pioneered by Movassaghi,[11] Nicolaou,[12] and Reisman[4] groups.

Scheme 4.3. *Total synthesis of (–)-gliotoxin by Nicolaou*

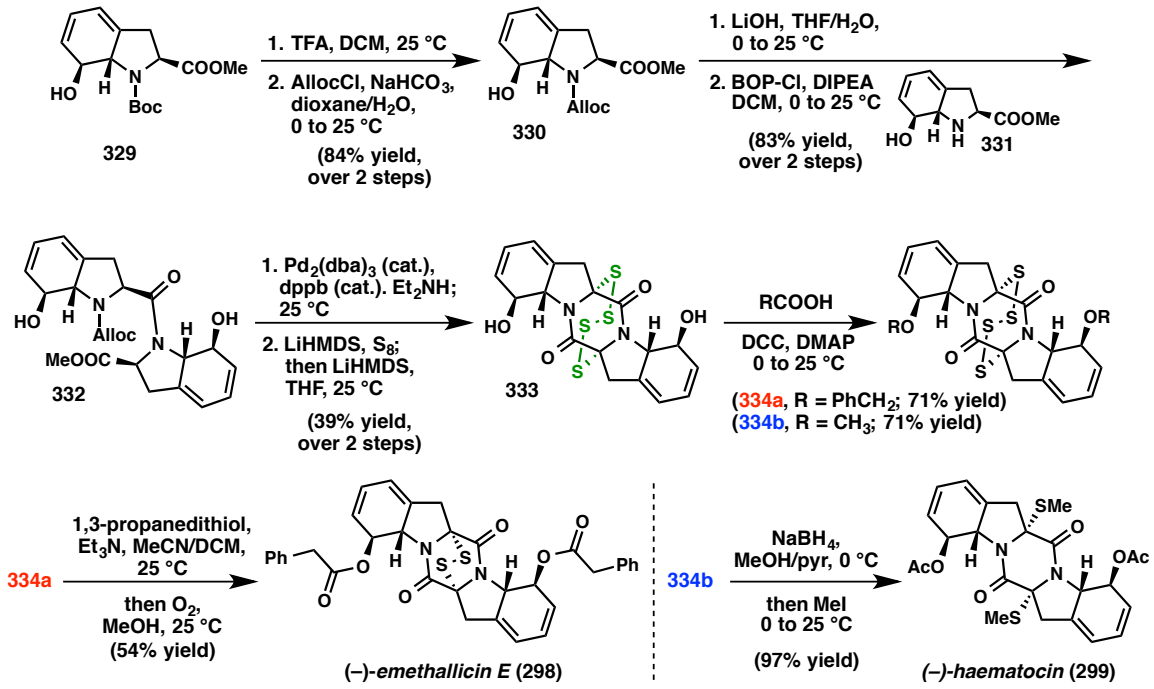


Based on the initial work by Sundberg and coworkers,[13] Nicolaou and coworkers began with enantiopure *N*-Boc-L-tyrosine **318** (Scheme 4.3), which was subjected to oxidative intramolecular dearomatization conditions followed by lactone opening with

methoxide and subsequent cyclization to yield hydroxyl enone[14] **319**.[2] Luche reduction and acetylation provided allylic acetate **320**, which was converted to diene **321** under palladium catalyzed elimination conditions. In order to install the correct oxidation states, diene **321** was subjected under photooxygenation conditions to form endoperoxide **322**, which was reduced with thiourea to afford triol **323**. Subsequent silylation, Corey-Winter olefination, and desilylation provided the cyclohexadienol core in **325**. DKP formation with L-serine derivative **326** and sulfenylation using LiHMDS and elemental sulfur accomplished the synthesis of gliotoxin (**297**), which represents a mild methodology to incorporate the sulfur bridge in DKP substrates.[15]

The cyclohexadienol intermediate **325** was used as the key intermediate to access C_2-symmetric ETP natural products (–)-emethallicin E (**298**) and (–)-haematocin (**299**),

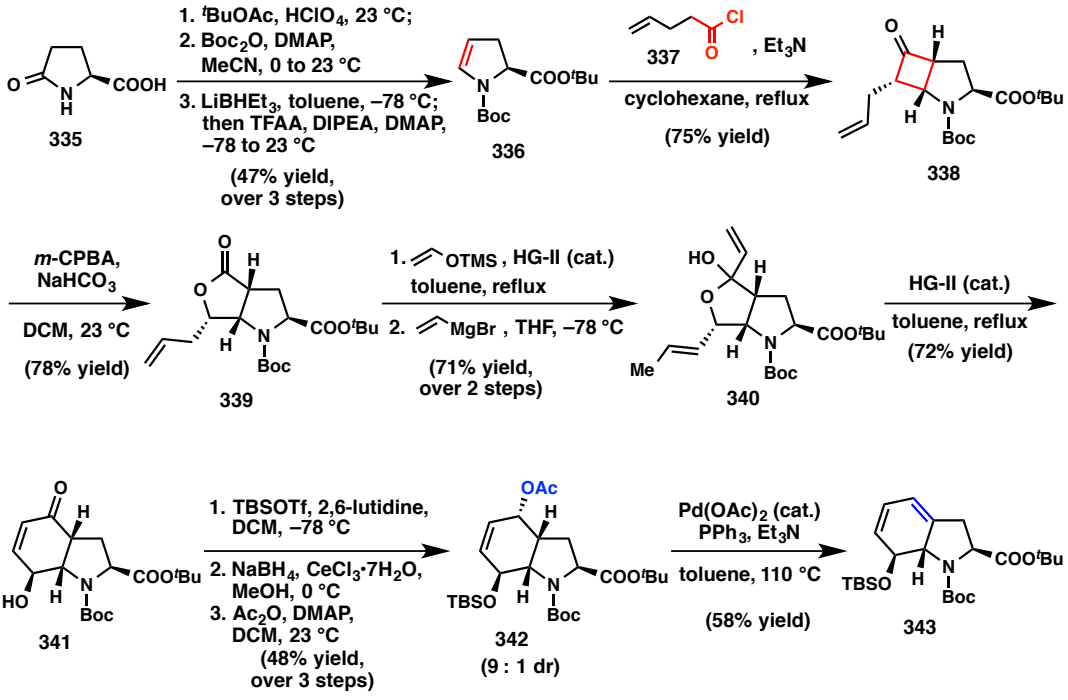
Scheme 4.4. *Total synthesis of (–)-emethallicin E and (–)-haematocin by Nicolaou*



illustrated by Nicolaou and coworkers.[2] The Boc protecting group in **329** was switched to allyl carbamate in **330** in two steps, which was hydrolyzed and coupled with secondary amine **331** to provide dipeptide **332**. Subsequent palladium-catalyzed deprotection of Alloc group triggered *in situ* DKP formation, which was followed by the sulfenylation step to form tetrasulfide **333**. Ester formation of diol **333** with phenylacetic acid or acetic acid afforded esters **334a** and **334b**, respectively. **334a** was then subjected to 1,3-propane dithiol-mediated reduction followed by aerobic oxidation to provide (–)-emethallicin E (**298**). On the other hand, **334b** was subjected to $NaBH_4$ reduction/methylation sequence to produce (–)-haematocin (**299**).

An alternative strategy to access the cyclohexadienol fragment was reported by Bräse and coworkers (Scheme 4.5).[16] L-Pyroglutamic acid (**335**) was converted to enamine **336** in a three-step sequence. The following key reaction involves a diastereoselective [2 + 2] ketene cycloaddition to provide bicyclic cyclobutanone **338**, which was subjected to the Baeyer-Villiger ring expansion to afford **339**. Ruthenium hydride catalyzed alkene isomerization and vinyl Grignard addition yielded lactol **340**, which was converted to hydroxyl enone **341** via a ring-closing metathesis. Enone **341** was then converted to allylic acetate **342** in three steps, which was subsequently treated under palladium-catalyzed elimination conditions to provide the cyclohexadienol building block **343**. However, Bräse and coworkers did not advance this key building block **343** to related cyclohexadienol ETP natural products in the report.

Scheme 4.5. *Preparation of cyclohexadienol fragment by Bräse*



4.2 SYNTHETIC EFFORTS TOWARD CYCLOHEXADIENOL ETP

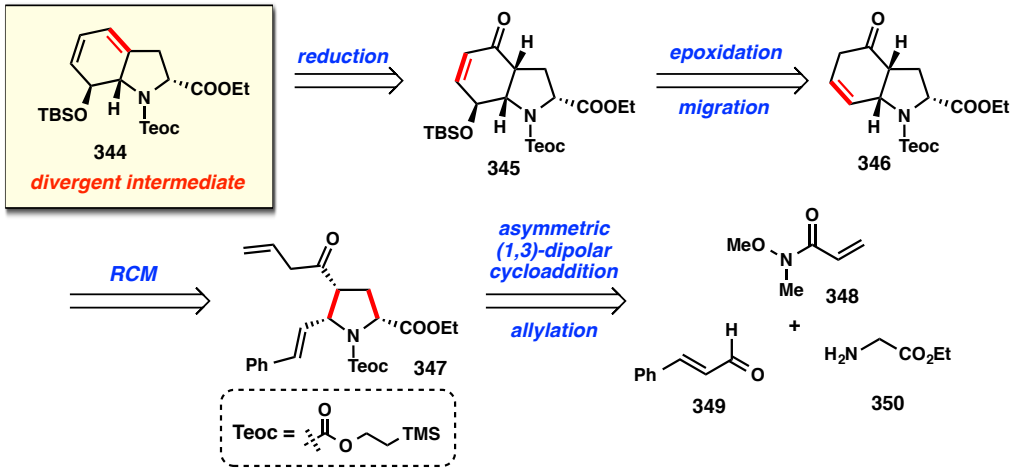
4.2.1 Retrosynthetic Analysis

Both strategies reported by Nicolaou and Bräse groups rely on starting materials from the chiral pool. As our ongoing project to access various ETP family members, especially the *cyclohexadienol* subfamily, a strategy involving a catalytic *asymmetric* stereocenters-assembling step is proposed to access the key cyclohexadienol fragment **344** (Scheme 4.6).

Retrosynthetically, this common cyclohexadienol building block **344** was envisioned to be prepared using an asymmetric (1,3)-dipolar cycloaddition to assemble the central pyrrolidine core, followed by chemo-selective allyl addition to a Weinreb amide to provide a ring-closing metathesis (RCM) substrate **347**. Subsequent

RCM/epoxidation/rearrangement would give access to enone **345**, which could then be converted to cyclohexadiene **344** through vinyl triflate formation and reduction.

Scheme 4.6. *Retrosynthesis analysis of cyclohexadienol building block **344***

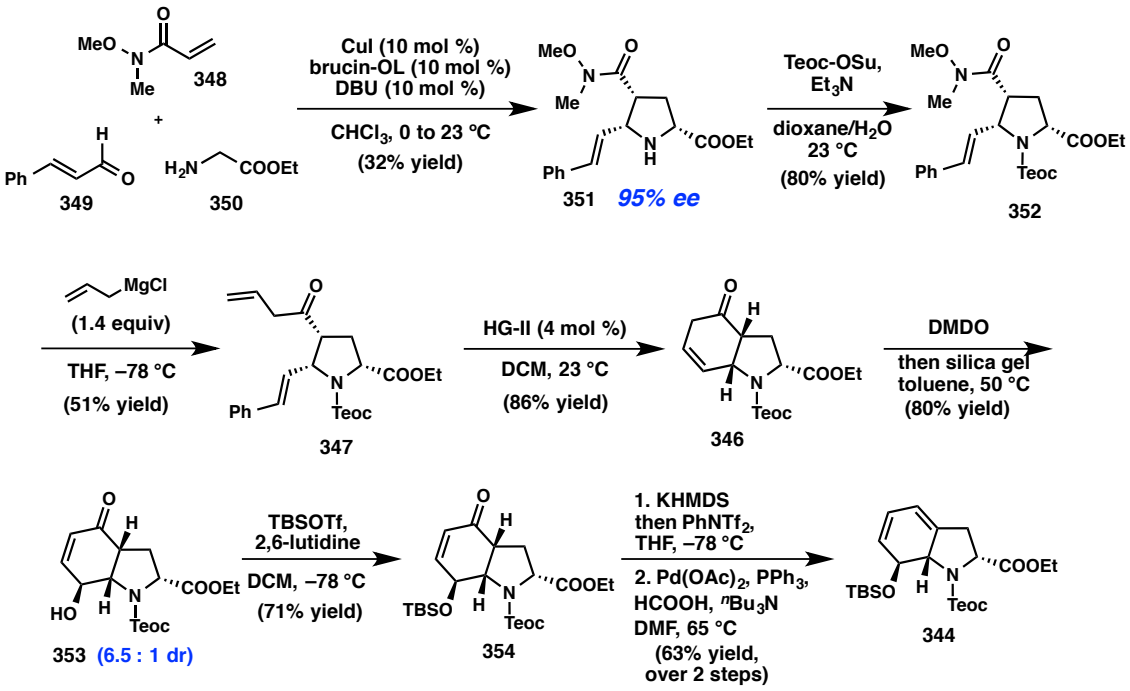


4.2.2 Preparation of Cyclohexadienol Fragment and Formal Synthesis of (–)-Emethallicin E and (–)-Haematocin

In the forward sense, copper/brucin-OL-catalyzed (1,3)-dipolar cycloaddition between Weinreb amide **348**, cinnamaldehyde **349**, and glycinate **350** provided pyrrolidine **351** in 32% yield and 95% ee (Scheme 4.7),[17] which was subsequently protected as its (trimethylsilyl)ethyl carbamate (Teoc) **352**. The following allyl Grignard addition proved to be challenging due to competitive addition to the ethyl ester. Nevertheless, with careful control of reagent stoichiometry, mono-addition product **347** could be isolated in 51% yield on a multi-gram scale.

Treatment of non-conjugated diene **347** with Hoveyda-Grubbs II catalyst yielded ring-closing product **346** in good yield. In order to install the allylic hydroxyl moiety, alkene **346** was oxidized with dimethyldioxirane (DMDO) and the resulting epoxide was

Scheme 4.7. *Asymmetric route accessing cyclohexadienol* ***344***

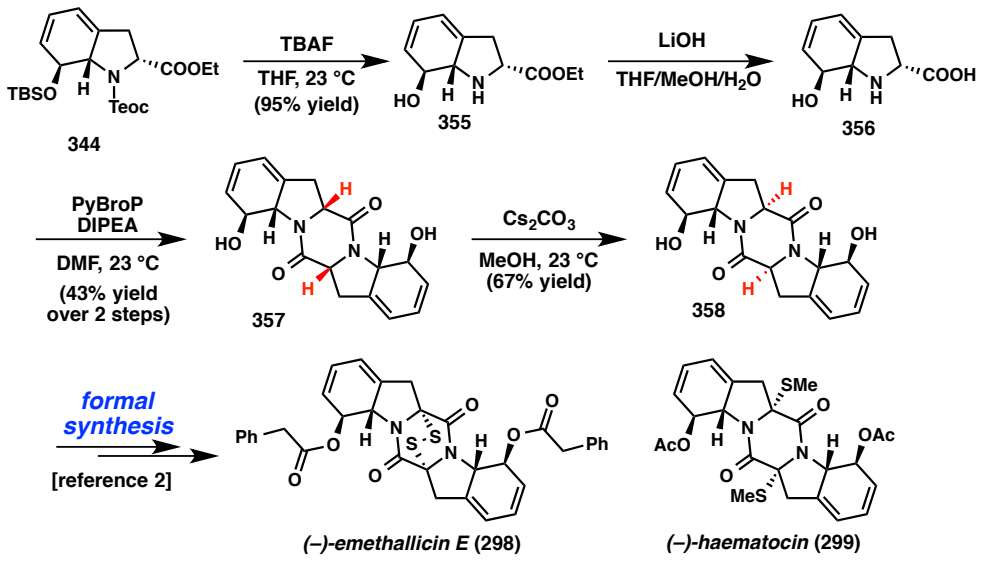


directly heated with silica gel in toluene to effect isomerization, providing the enone product as a 6.5 : 1 inseparable mixture of diastereomers. Protection of alcohol **353** as its TBS ether **354** allowed facile separation of the two diastereomers using silica gel chromatography. Subsequent formation of vinyl triflate followed by palladium-catalyzed reduction[18] provided the key divergent intermediate **344**.

In order to access C_2-symmetric emethallicin E (**298**) and haematocin (**299**), diene **344** was first globally deprotected with excess TBAF (Scheme 4.8), followed by hydrolysis, to afford amino acid **356**. Successful dimerization using peptide coupling reagent PyBroP furnished DKP **357**, which was then epimerized to form the thermodynamically more favored diastereomer **358** using cesium carbonate in MeOH. Dimeric intermediate **358** has been prepared by Nicolaou and coworkers to access both (–)-**298** and (–)-**299** in short sequences (Scheme 4.4)[2]. Thus, a formal total synthesis of

these natural products is completed. In comparison, our current synthetic route shortens their synthesis by three steps.

Scheme 4.8. *Formal synthesis of (–)-emethallicin E and (–)-haematocin*



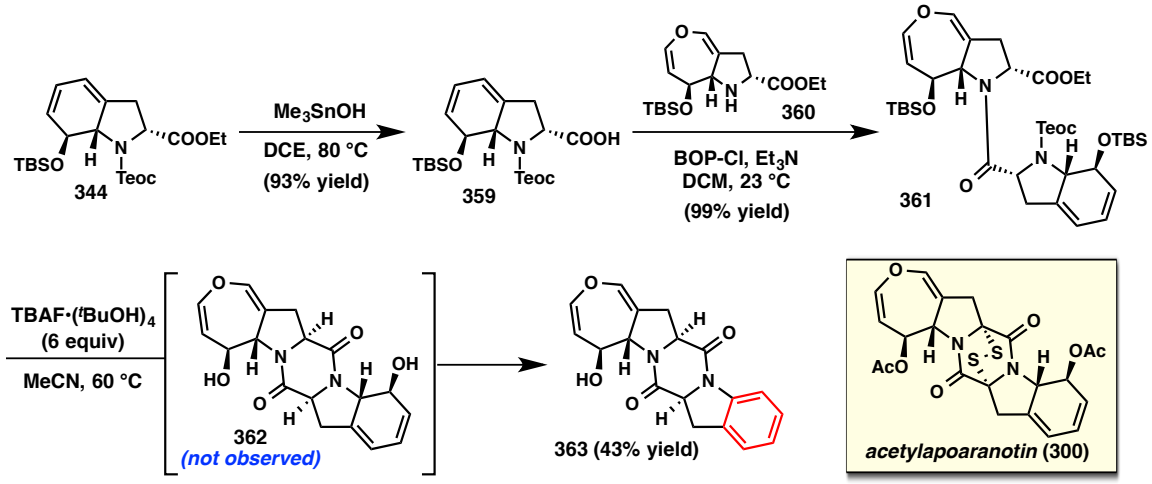
4.2.3 Attempts to Prepare (–)-Acetylapoaranotin

Having established an efficient route to prepare C_2-symmetric cyclohexadienol-containing ETP natural products, we next turned our attention to the hybrid natural product between the dihydrooxepine/cyclohexadiene subfamilies, (–)-acetylapoaranotin (**300**, Figure 4.1). It was recognized that the sequential peptide coupling strategy was preferred for the selective synthesis of heterodimeric diketopiperazines, such as **300**.

Starting from the key diene intermediate **344**, treatment with trimethyltinhydroxide afforded carboxylic acid **359**,[19] which was successfully coupled with amine **360** (prepared according to reference 4) in excellent yield. The resulting dipeptide **361** was subjected to the TBAF•(^{t}BuOH)$_4$ conditions reported in the total synthesis of acetylaranotin (**294**, Figure 4.1) by our group.[4] Unfortunately, undesired

aromatized product **363** was isolated. It is hypothesized that following the desired removal of the Teoc and TBS groups, cyclization and epimerization proceeded smoothly; however, the resulting allylic secondary alcohol on the cyclohexadienol fragment (**362**) was not stable under the reaction conditions and was further eliminated, giving rise to aromatized product **363**. Interestingly, this side product mapped well onto another ETP family member, deoxyapoaranotin, which shows direct cytotoxic effects toward HCT116 colon cancer cell lines.[20] A more expedient route toward deoxyapoaranotin could be accomplished starting from (*R*)-indoline carboxylic acid.

Scheme 4.9. *Attempts to prepare the DKP core in acetylapoaranotin*

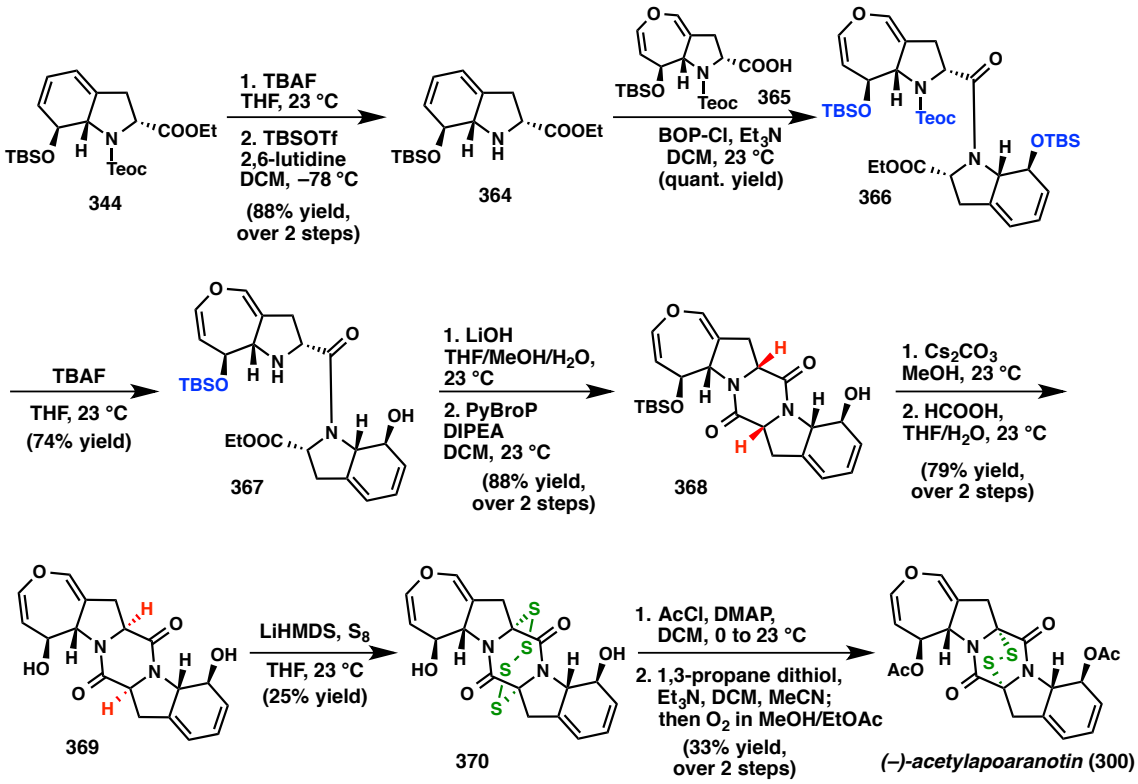


4.2.4 Total Synthesis of (–)-Acetylapoaranotin

Aware that the cyclohexadiene alcohol moiety readily undergoes both elimination and oxidation, a mild and *stepwise* DKP formation strategy was investigated.

Cyclohexadienol **344** was transformed to TBS-ether **364** by global desilylation and reprotection of the more reactive secondary alcohol group (Scheme 4.10). Secondary amine **364** was then coupled with carboxylic acid **365** (prepared according to reference 4)

Scheme 4.10. *Completion of (–)-acetylapoaranotin total synthesis*



to provide dipeptide **366**. Interestingly, it was found that the Teoc group as well as the TBS group on the cyclohexadienol fragment could be selectively removed using TBAF, while the TBS group on the dihydrooxepine fragment remained intact. The resulting ethyl ester was then hydrolyzed and subjected to peptide coupling reagent PyBroP to provide DKP **368** without any sign of aromatized product. DKP **368** was then epimerized using Cs_2CO_3 and removal of the last TBS group was effected under mildly acidic conditions. Notably, attempts to employ TBAF for desilylation gave exclusively aromatized side product. Diol **369** was subjected to LiHMDS/S_8 to afford tetrasulfide **370**, accompanied with a small amount of aromatized side product. Nevertheless, tetrasulfide **370** could be advanced to (–)-acetylapoaranotin (**300**) following the previously established two-step protocol.[4] Thus, (–)-**300** was successfully prepared for the first time in 22 steps starting

from commercially available starting materials. Ongoing efforts focus on optimization of the current synthetic route.

4.3 CONCLUDING REMARKS

In summary, we have developed an efficient asymmetric synthetic route allowing access to a series of natural products in the cyclohexadienol ETP subfamily including (–)-emethallicin E (**298**), (–)-haematocin (**299**), (–)-acetylapoaranotin (**300**). Through this endeavor, it was found that the labile nature of the allylic alcohol cyclohexadienol fragment required a mild and eventually stepwise DKP formation strategy to prepare the core of (–)-acetylapoaranotin (**300**). By employing this strategy, the first enantioselective total synthesis of (–)-**300** was accomplished in 22 steps (longest linear sequence).

Intermediates in this synthetic route could be intercepted to synthesize other related 6,5-bicyclic ETP subfamilies, for example, (–)-epicorazine A (**301**, Figure 4.1) and (–)-epiccocin C (**302**). Synthetic studies directed toward realizing this goal are ongoing in our laboratory.

4.4 EXPERIMENTAL SECTION

4.4.1 Materials and Methods

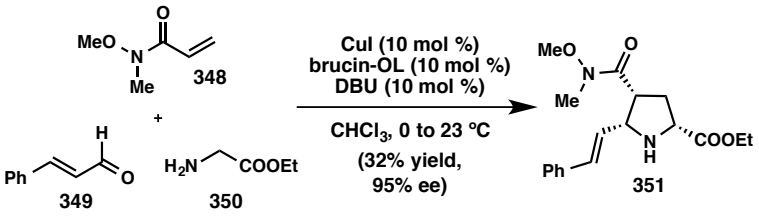
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and

reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[21] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Bruker 400 equipped with a cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), $CHDCl_2$ (^1H, $\delta = 5.32$), CD_2HOD (^1H, $\delta = 3.31$), MeCN-*d2* (^1H, $\delta = 1.94$), or DMSO-*d5* (^1H, $\delta = 2.50$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), CD_2Cl_2 (^{13}C, $\delta = 54.0$), CD_3OD (^{13}C, $\delta = 49.0$), MeCN-*d3* (^{13}C, $\delta = 118.3$), or DMSO-*d6* (^{13}C, $\delta = 40.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H

columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

4.4.2 Preparative Procedures and Spectroscopic Data

Preparation of pyrrolidine 351

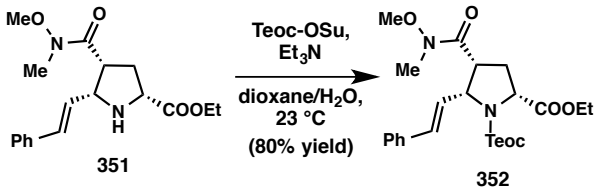


(Isolation of ethyl glycinate) The ethyl glycinate HCl salt (5.1 g, 36.5 mmol) was freebased by first being taken up in DCM (10 mL) then washed with 3.56M KOH (10 mL). The layers were separated and the aqueous phase was further extracted with DCM (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated down by rotary evaporation to yield 3.14 g of glycinate ethyl ester **350** (83% recovery).

(Formation of imime) The free amine **350** (3.14 g, 30.5 mmol, 1.0 equiv) was taken up in $CHCl_3$ (61 mL) with silica gel (9.1 g, 0.3 g/mmol) and cooled to 0 °C under air. Cinnamaldehyde **349** (3.8 mL, 30.5 mmol, 1.0 equiv) was added dropwise, and the solution was kept at 0 °C for 7 hours while capped. The silica gel was filtered off and rinsed with more $CHCl_3$. The resulting imine was used immediately.

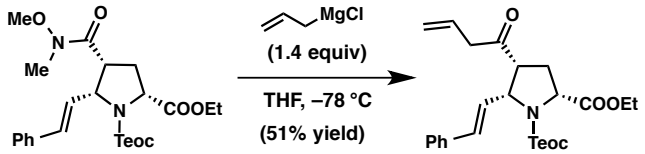
(Dipolar cycloaddition reaction) A round-bottom flask was charged with brucin-OL (1.31 g, 3.05 mmol, 10 mol %), CuI (580 mg, 3.05 mmol, 10 mol %) and $CHCl_3$ (61 mL) then cooled to 0 °C. After 5 minutes, DBU (0.46 mL, 3.05 mmol, 10 mol %) was added and the solution went from cream to deep jade-green over the next twenty minutes. Weinreb amide acrylamide **348** (3.88 g, 33.7 mmol, 1.1 equiv) was added followed by the filtered imine slowly over 10 minutes. The solution was kept at 0 °C for 5.5 hours before being warmed up to room temperature and stirred for another 23 hours. The crude reaction was concentrated down to roughly half the volume, and directly subjected to silica gel column chromatography using a gradient of 20 to 100% EtOAc in hexanes (with 1% Et_3N) to yield 3.21 g (32% yield, 9.7 mmol) of pyrrolidine **351** as a thick light brown oil. The enantiomeric excess of **351** was determined to be 95% by chiral HPLC analysis (OD, 1 mL/min, 15% IPA in hexanes, λ = 254 nm): t_R(major) = 24.2 min, t_R(minor) = 14.2 min. $[\alpha]_D^{25}$ = +152° (*c* = 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.10 (dd, *J* = 15.7, 8.3 Hz, 1H), 4.22 (qd, *J* = 7.1, 3.2 Hz, 2H), 4.12 (t, *J* = 7.9 Hz, 1H), 3.86 (t, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 3.59 (q, *J* = 7.7 Hz, 1H), 3.05 (s, 3H), 2.56 (s, 1H), 2.45 – 2.28 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$) δ 173.7, 173.4, 136.6, 131.9, 128.3, 127.5, 127.4, 126.4, 63.6, 61.3, 61.0, 59.8, 45.3, 33.2, 32.2, 14.1; FTIR (NaCl/thin film) 3340, 3298, 3057, 3024, 2979, 2937, 2902, 1955, 1882, 1735, 1654, 1599, 1493, 1448, 1388, 1321, 1255, 1197, 1108, 1073, 1056, 1028, 1008, 969, 901, 861, 834, 786, 754 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{24}N_2O_4$ $[M+H]^+$ 333.1809, found 333.1817.

Preparation of Teoc-pyrrolidine 352



Pyrrolidine **351** (1.77 g, 5.31 mmol, 1.0 equiv) was suspended in H_2O (14 mL) and 1,4-dioxane (14 mL). Triethylamine (1.48 mL, 10.62 mmol, 2.0 equiv) was added followed by Teoc-OSu (2.06 g, 7.96 mmol, 1.5 equiv). The resulting solution was allowed to stir for 20 hours at room temperature. The solution was acidified with 36 mL 1M HCl then extracted with DCM (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield a light orange oil. Flash chromatography (50% to 60% EtOAc in hexanes) afforded Teoc-pyrrolidine **352**, as a thick yellow oil (2.03 g, 4.26 mmol, 80% yield). $[\alpha]_D^{25}$ = +101° (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.70 (dd, *J* = 15.8, 1.1 Hz, 1H), 6.05 (dd, *J* = 15.8, 7.6 Hz, 1H), 4.92 (t, *J* = 7.8 Hz, 1H), 4.30 (dd, *J* = 10.3, 7.6 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.0 Hz, 2H), 4.18 – 4.12 (m, 2H), 3.75 (s, 3H), 3.61 (dt, *J* = 12.2, 7.4 Hz, 1H), 3.08 (s, 3H), 2.46 (q, *J* = 12.0 Hz, 1H), 2.33 (dt, *J* = 13.0, 7.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97 (dd, *J* = 8.8, 7.5 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a 1:1 mixture of rotamers) δ 173.8, 173.5, 171.3, 155.8, 155.0, 137.8, 132.8, 129.6, 128.6, 127.7, 127.3, 127.2, 64.3, 64.2, 62.3, 62.0, 61.8, 61.7, 61.2, 59.7, 59.4, 46.6, 45.9, 32.8, 31.6, 30.6, 18.4, 18.3, 14.6, -1.4, -1.5; FTIR (NaCl, thin film): 2953, 2900, 1747, 1700, 1668, 1404, 1345, 1282, 1250, 1186, 1112, 1038, 1012, 961, 860, 838, 756, 694 cm^{-1}; HRMS (MM) calc'd for $C_{22}H_{33}N_2O_6Si$ $[M–C_2H_4+H]^+$ 449.2102, found 449.2110 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of diene 347

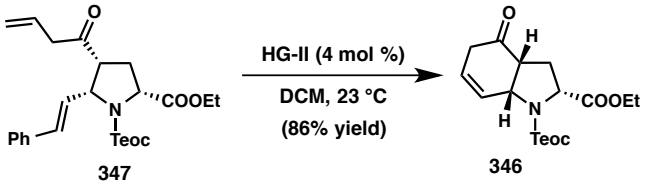


352 347

Weinreb amide **352** (2.37 g, 4.97 mmol, 1.0 equiv) was dissolved in dry THF (42 mL) under N_2 and the solution was brought to –78 °C. A solution of allyl Grignard (0.85M in THF, diluted two times with THF from commercially available reagent; 8.2 mL, 6.96 mmol, 1.4 equiv) was added slowly over the course of 4 hours using a syringe pump at –78 °C. When the addition was done, the reaction was allowed to stir for another 10 minutes before being quenched with 30 mL of AcOH/THF/H_2O (1:1:1) and warmed to room temperature. The reaction was then carefully basified with saturated $NaHCO_3$ solution until no more bubbles occurred. The aqueous layer was then extracted with EtOAc (3 x 150 mL). Combined organic layer was washed with brine (200 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow oil. Flash chromatography (5% to 30% EtOAc in hexanes) afforded diene **347**, as a yellow oil (1.15 g, 2.51 mmol, 51% yield). $[\alpha]_D^{25} = –8°$ (c = 0.495, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.39 – 7.29 (m, 4H), 7.29 – 7.21 (m, 1H), 6.77 (dd, J = 15.9, 0.9 Hz, 1H), 6.01 (ddd, J = 15.7, 8.1, 0.8 Hz, 1H), 5.95 – 5.77 (m, 1H), 5.16 – 5.10 (m, 1H), 5.12 – 5.07 (m, 1H), 4.97 (t, J = 8.0 Hz, 1H), 4.30 (dd, J = 9.8, 8.0 Hz, 1H), 4.20 (qt, J = 7.2, 1.2 Hz, 2H), 4.17 – 4.10 (m, 2H), 3.55 (dt, J = 11.6, 7.5 Hz, 1H), 3.26 (dt, J = 6.9, 1.3 Hz, 2H), 2.48 – 2.23 (m, 2H), 1.27 (td, J = 7.1, 0.7 Hz, 3H), 1.06 – 0.88 (m, 2H), 0.03 (d, J = 0.8 Hz, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a 1:1 mixture of rotamers) δ 205.5, 205.4, 173.6, 173.3, 155.6, 154.8, 137.5, 133.74, 133.68, 131.6, 129.7, 128.9,

128.8, 127.3, 126.6, 126.5, 119.1, 64.4, 64.3, 62.1, 62.0, 61.9, 61.7, 59.8, 59.5, 54.7, 54.1, 48.2, 30.5, 29.5, 18.4, 14.6, -1.47, -1.52; FTIR (NaCl, thin film): 3082, 3060, 3024, 2981, 2952, 2899, 1749, 1702, 1450, 1408, 1371, 1344, 1285, 1250, 1185, 1168, 1110, 1038, 962, 924, 860, 837, 751, 694 cm^{-1}; HRMS (MM) calc'd for $C_{23}H_{32}NO_5Si$ $[M–C_2H_4+H]^+$ 430.2044, found 430.2053 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

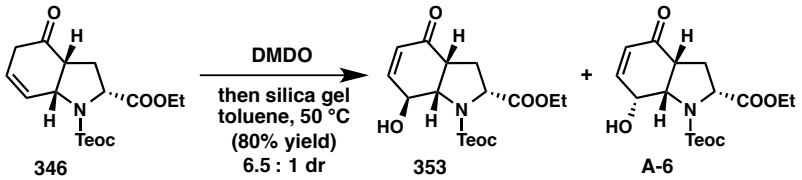
Preparation of ketone 346



To a 500 mL flame-dried flask was added diene **347** (1.15 g, 2.51 mmol, 1.0 equiv) and DCM (250 mL). Hoveyda-Grubbs II catalyst (63 mg, 0.10 mmol, 4 mol %) was added and the resulting light green solution was allowed to stir at room temperature for 4 hours. The reaction was then quenched with DMSO (380 μL, 50 equiv) and stirred for another 22 hours. It was filtered through a silica gel plug, eluting with EtOAc, and the filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 25% EtOAc in hexanes) afforded ketone **346**, as a light brown oil (761 mg, 2.15 mmol, 86% yield). $[\alpha]_D^{25} = –117°$ (c = 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 65 °C) δ 6.04 (dq, J = 10.2, 2.5 Hz, 1H), 5.80 (dtd, J = 10.2, 3.7, 1.6 Hz, 1H), 4.79 (dt, J = 7.6, 2.3 Hz, 1H), 4.32 (dd, J = 8.3, 7.1 Hz, 1H), 4.24 – 4.15 (m, 2H), 4.12 (qd, J = 7.1, 1.1 Hz, 2H), 3.05 (q, J = 8.0 Hz, 1H), 2.99 – 2.80 (m, 2H), 2.45 – 2.26 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 65 °C) δ 207.5, 173.3, 155.8, 128.1, 124.4, 64.7, 62.2, 61.2, 60.2, 51.0, 38.2, 32.8, 19.0, 14.8, -1.0; FTIR

(NaCl, thin film): 3042, 2953, 2899, 1749, 1703, 1454, 1412, 1350, 1249, 1186, 1112, 1033, 988, 964, 946, 860, 838, 769, 695 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_5Si$ [M–C_2H_4+H]$^+$ 326.1418, found 326.1419 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

Preparation of enone 353

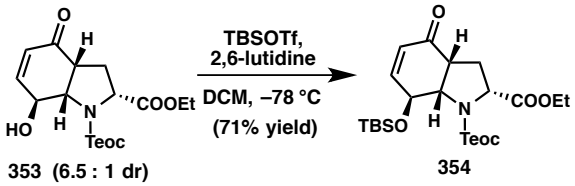


To ketone **346** (761 mg, 2.15 mmol, 1.0 equiv) in a 200 mL round-bottom flask was added freshly prepared DMDO acetone solution (0.0905 M, 48 mL, 4.30 mmol, 2.0 equiv) and the resulting solution was allowed to stir at room temperature for 90 minutes (the reaction was monitored by taking ^{1}H NMR spectra of aliquot of the reaction solution). The reaction was then concentrated down and put under high vacuum for 90 minutes to get rid of residue solvent. The crude material was then dissolved in toluene (215 mL) and mixed with silica gel (17.2 g). The resulting mixture was heated to 50 °C for 1 hour and cooled down to room temperature. It was filtered through a silica gel plug, eluting with EtOAc, and the filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 40% EtOAc in hexanes) afforded enone **353**, (6.5 : 1 mixture of diastereomers by ^{1}H NMR), as a thick colorless oil (630 mg, 1.71 mmol, 80% yield). The mixture of diastereomers was carried to the next reaction. Analytically pure products were isolated using preparative reverse phase HPLC (50% to 60% CH_3CN in H_2O over 10 minutes, t_R(**353**) = 8.0-8.7 min, t_R(**A-6**) = 9.5-10.0 min).

*Major diastereomer **353***. $[\alpha]_D^{25}$ = –23° (*c* = 1.925, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.4, 2.1 Hz, 1H), 6.00 (dd, *J* = 10.4, 2.5 Hz, 1H), 4.91 (s, 1H), 4.78 (dt, *J* = 7.2, 2.3 Hz, 1H), 4.38 (dd, *J* = 8.6, 7.3 Hz, 1H), 4.33 (dd, *J* = 9.8, 7.6 Hz, 1H), 4.25 – 4.12 (m, 4H), 3.04 (dt, *J* = 12.8, 8.2 Hz, 1H), 2.65 (dt, *J* = 12.7, 7.6 Hz, 1H), 1.95 (td, *J* = 12.8, 9.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 – 0.88 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 171.7, 156.8, 150.5, 126.9, 70.0, 65.2, 65.1, 61.6, 59.2, 45.6, 32.8, 17.7, 14.1, -1.6; FTIR (NaCl, thin film): 3413, 2953, 2899, 1744, 1676, 1457, 1420, 1374, 1350, 1304, 1250, 1215, 1188, 1166, 1118, 1069, 1032, 960, 861, 839, 770, 695 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_6Si$ $[M–C_2H_4+H]^+$ 342.1367, found 342.1378 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

*Minor diastereomer **A-6***. $[\alpha]_D^{25}$ = –58° (*c* = 0.405, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.08 (dd, *J* = 10.0, 5.9 Hz, 1H), 6.10 (d, *J* = 10.0 Hz, 1H), 4.70 – 4.56 (m, 1H), 4.39 (dd, *J* = 9.5, 7.9 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.27 – 4.15 (m, 5H), 3.08 (dt, *J* = 12.0, 8.3 Hz, 1H), 2.62 (dt, *J* = 12.2, 8.2 Hz, 1H), 2.13 (app q, *J* = 11.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.10 – 0.90 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, compound exists as a mixture of rotamers) δ 198.7, 175.2, 155.7, 148.0, 147.2, 132.3, 131.9, 64.9, 63.2, 62.7, 61.6, 60.8, 60.4, 47.1, 46.7, 34.5, 33.9, 18.3, 14.4, -1.5; FTIR (NaCl, thin film): 3445, 2953, 2900, 1698, 1404, 1377, 1348, 1303, 1251, 1203, 1177, 1114, 1065, 1030, 999, 975, 942, 899, 853, 838, 769, 696 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{24}NO_6Si$ $[M–C_2H_4+H]^+$ 342.1367, found 342.1376 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

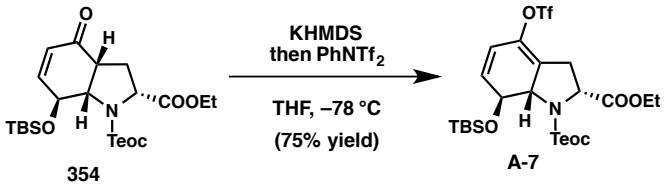
Preparation of TBS ether 354



To enone **353** (462 mg, 1.25 mmol, 1.0 equiv; as a 6.5 : 1 mixture of diastereomers) in a flame-dried 50 mL round-bottom flask was added dry DCM (12 mL), which was brought to –78 °C. 2,6-Lutidine (0.72 mL, 6.25 mmol, 5.0 equiv) was added, followed by slow addition of TBSOTf (0.57 mL, 2.50 mmol, 2.0 equiv). The resulting clear solution was allow to stir at –78 °C for 90 minutes. It was quenched with pH7 buffer (15 mL) and warmed to room temperature. The mixture was then separated and the aqueous layer was then extracted with EtOAc (3 x 20 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered and concentrated down to give a colorless oil (extra time under high vacuum could remove the residue 2,6-lutidine and help the subsequent purification step). Flash chromatography (1% to 18% EtOAc in hexanes) afforded TBS ether **354** as a single diastereomer, as a colorless oil (425 mg, 0.825 mmol, 71% yield). $[\alpha]_D^{25}$ = +49° (*c* = 0.650, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 6.79 (dd, *J* = 10.3, 2.8 Hz, 1H), 6.13 – 5.74 (m, 1H), 4.86 (br s, 1H), 4.43 – 4.37 (m, 2H), 4.22 (app q, *J* = 8.8 Hz, 1H), 4.18 – 4.04 (m, 3H), 2.96 (dt, *J* = 10.1, 7.5 Hz, 1H), 2.52 (dt, *J* = 12.9, 8.2 Hz, 1H), 2.11 (q, *J* = 10.5 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 8.5 Hz, 2H), 0.95 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 197.7, 173.6, 156.8, 151.9, 129.0, 69.4, 66.3, 64.8, 62.3, 61.3, 48.1, 33.4, 26.6, 19.0, 18.9, 14.9, -1.1, -4.0, -4.2; FTIR (NaCl, thin film): 2953, 2929, 2896, 2856, 1748, 1701, 1682, 1462, 1405, 1375, 1340, 1319, 1289, 1250, 1211, 1187, 1155, 1099, 1058, 985, 956, 939, 862, 829, 779 cm^{-1}; HRMS (MM) calc'd

for $C_{21}H_{38}NO_6Si_2$ $[M–C_2H_4+H]^+$ 456.2232, found 456.2231 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

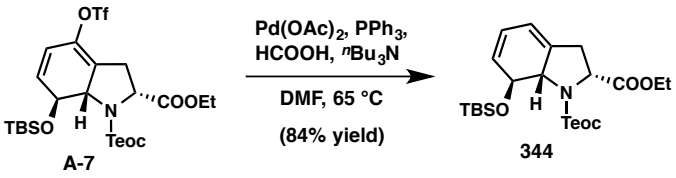
Preparation of vinyl triflate A-7



A flame-dried 50 mL round-bottom flask was charged with TBS ether **354** (200 mg, 0.41 mmol, 1.0 equiv), which was dissolved in dry THF (7.4 mL) and cooled to –78 °C. A solution of KHMDS (0.5M in toluene, 0.9 mL, 0.45 mmol, 1.1 equiv) was added slowly. The reaction solution turned dark red upon addition and was stirred for 5 minutes before the addition of a THF solution of $PhNTf_2$ (162 mg, 0.45 mmol, 1.1 equiv; prepared by dissolving 180 mg in 1 mL THF and used 0.9 mL). It was reacted for another 2 hours before quenching with 1% NaOH solution (10 mL) and warmed to room temperature. The mixture was then separated and the organic layer was washed with 1% NaOH solution (10 mL). The aqueous layer was then extracted with ether (3 x 20 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered and concentrated down to give a light yellow oil. Flash chromatography (1% to 8% EtOAc in hexanes) afforded vinyl triflate **A-7**, as a colorless oil (191 mg, 0.31 mmol, 75% yield; **A-7** was labile and it is recommended to carry to the next reaction as soon as possible). $[\alpha]_D^{25}$ = +14° (*c* = 0.69, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 5.96 (d, *J* = 10.2 Hz, 1H), 5.87 (dd, *J* = 10.2, 2.3 Hz, 1H), 5.06 – 4.90 (m, 3H), 4.28 (ddd, *J* = 10.9, 9.3, 7.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.09 (ddd, *J* = 10.8, 9.2, 7.1 Hz, 1H), 3.00 – 2.76 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.03 (ddd, *J* = 9.3, 7.0, 1.8 Hz, 2H), 0.93 (s,

9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 172.8, 157.1, 140.7, 138.6, 132.1, 124.6, 121.7, 121.5, 115.1, 75.6, 67.8, 65.2, 64.6, 62.7, 31.9, 26.7, 19.1, 18.8, 14.8, -1.1, -4.0, -4.4 (one of the quartet of -CF_3 carbons is masked under the solvent peak and the rest of the three peaks are underlined); FTIR (NaCl, thin film): 3426, 2954, 2930, 2898, 2857, 1750, 1722, 1709, 1423, 1403, 1361, 1334, 1295, 1251, 1213, 1142, 1104, 1037, 973, 943, 894, 839, 779, 769, 693, 619 cm^{-1}; HRMS (MM) calc'd for $C_{22}H_{37}F_3NO_8SSi_2$ $[M–C_2H_4+H]^+$ 588.1725, found 588.1744 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

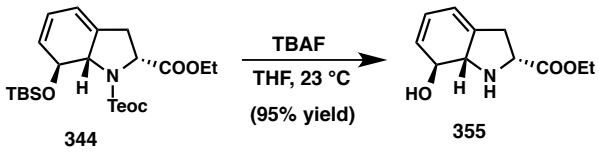
Preparation of diene 344



To a flame-dried 50 mL round-bottom flask was added vinyl triflate **A-7** (260 mg, 0.42 mmol, 1.0 equiv), $Pd(OAc)_2$ (19 mg, 0.084 mmol, 20 mol %), and PPh_3 (44 mg, 0.169 mmol, 40 mol %). The system was purged with N_2 and charged with dry DMF (8 mL), ^{n}Bu$_3$N (0.50 mL, 2.11 mmol, 5.0 equiv), and HCOOH (48 μL, 1.27 mmol, 3.0 equiv). The resulting yellow clear solution was then heated to 65 °C for 15 minutes, at which point the reaction turned black. It was then diluted with EtOAc (25 mL) and washed with 1M HCl (25 mL), H_2O (25 mL) and brine (25 mL). The aqueous layers were each extracted with ether (20 mL). Combined organic layer was then dried over Na_2SO_4, filtered and concentrated down to give a brown oil. Flash chromatography (1% to 10% EtOAc in hexanes) afforded diene **344**, as a light yellow oil (165 mg, 0.35 mmol, 84% yield). $[\alpha]_D^{25}$ = +55° (*c* = 1.43, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 5.88 –

5.81 (m, 1H), 5.81 – 5.73 (m, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 4.87 – 4.76 (m, 2H), 4.74 – 4.64 (m, 1H), 4.33 – 4.23 (m, 1H), 4.17 (qd, *J* = 7.1, 1.0 Hz, 2H), 4.07 (ddd, *J* = 10.8, 9.0, 7.3 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.63 (d, *J* = 15.9 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.02 (ddd, *J* = 8.8, 7.1, 1.1 Hz, 2H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 173.5, 157.6, 142.0, 135.3, 125.6, 119.1, 76.7, 66.7, 64.7, 64.3, 62.3, 35.1, 26.8, 19.2, 18.9, 15.0, -1.0, -3.8, -4.3; FTIR (NaCl, thin film): 3049, 2954, 2928, 2897, 2855, 1750, 1722, 1699, 1472, 1398, 1361, 1329, 1290, 1250, 1204, 1180, 1105, 1031, 958, 839, 776, 701, 670 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{38}NO_5Si_2$ $[M–C_2H_4+H]^+$ 440.2283, found 440.2298 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

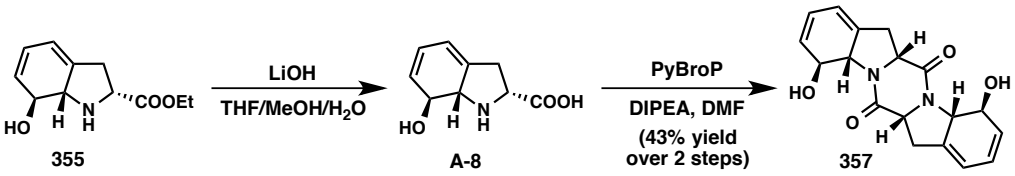
Preparation of dienol 355



Diene **344** (28.6 mg, 0.061 mmol, 1.0 equiv) was dissolved in dry THF (1.1 mL) in a 1-dram vial. TBAF (1M in THF, 0.18 mL, 0.18 mmol, 3 equiv) was added and the resulting light brown solution was allowed to stir at room temperature for 2 hours and 20 minutes before being quenched with saturated Na_2SO_4 solution (2 mL). The mixture was then further diluted with brine (1 mL) and extracted with EtOAc (12 x 5 mL). Each of the EtOAc extractions was filtered through a short silica gel plug. Combined organic layer was concentrated down to give a light brown oil. Flash chromatography (60% to 100% EtOAc in hexanes) afforded dienol **355**, as a light brown oil (12.9 mg, 0.06 mmol, 95% calculated yield, accompanied by 5% aromatized side product). $[\alpha]_D^{25}$ = +190° (*c* = 0.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 9.7, 4.8, 2.8 Hz, 1H), 5.71 (dt, *J* =

4.9, 2.5 Hz, 1H), 5.65 (d, *J* = 9.8 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 1H), 4.21 (qd, *J* = 7.1, 2.5 Hz, 2H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.82 (dd, *J* = 14.2, 2.8 Hz, 1H), 3.04 (br s, 2H), 2.90 (dd, *J* = 17.7, 8.3 Hz, 1H), 2.66 (dd, *J* = 17.6, 7.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 141.1, 130.3, 124.7, 115.9, 74.8, 66.4, 61.2, 59.3, 33.9, 14.2; FTIR (NaCl, thin film): 3337, 3043, 2980, 2928, 2853, 1738, 1553, 1446, 1377, 1329, 1200, 1082, 1061, 1033, 862, 750, 711 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125, found 210.1125.

Preparation of *syn*-diol 357

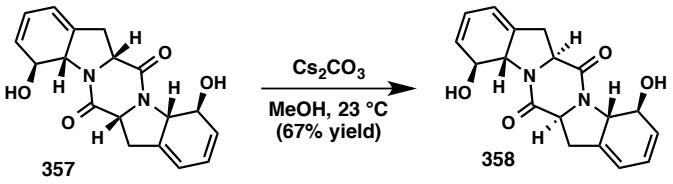


In a half-a-dram vial, dienol **355** (1.2 mg, 0.006 mmol, 1.0 equiv) was dissolved in THF (50 μL) and MeOH (50 μL). A solution of LiOH (1.4 mg, 0.060 mmol, 10 equiv) in water (50 μL) was added into the vial and the reaction was allowed to stir at room temperature for 10 minutes. It was then quenched with 1M HCl (57 μL) and all the solvents were removed under vacuum to provide a brown oil/solid crude material. It was subjected to the next reaction *directly*. Due to the high polarity of amino acid **A-8**, analytical pure sample could be obtained by preparative reverse phase HPLC (0% to 5% CH_3CN in H_2O over 10 minutes, t_R = 3.0-7.0 min). $[\alpha]_D^{25}$ = +254° (*c* = 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.91 (ddd, *J* = 9.7, 4.9, 2.7 Hz, 1H), 5.84 (dt, *J* = 5.0, 2.6 Hz, 1H), 5.68 (dd, *J* = 9.7, 1.8 Hz, 1H), 4.81 (d, *J* = 14.9 Hz, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 4.03 (dd, *J* = 9.1, 7.4 Hz, 1H), 3.05 (dd, *J* = 17.9, 9.0 Hz, 1H), 2.81 (dd, *J* = 17.7, 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 174.7, 138.1, 131.3, 125.7, 118.7, 72.3,

67.8, 62.9, 33.8; FTIR (NaCl, thin film): 3380, 3044, 2916, 2849, 1624, 1417, 1380, 1314, 1253, 1145, 1068, 987, 875, 833, 794, 762, 712, 624 cm^{-1}; HRMS (MM) calc'd for $C_9H_{12}NO_3$ $[M+H]^+$ 182.0812, found 182.0815.

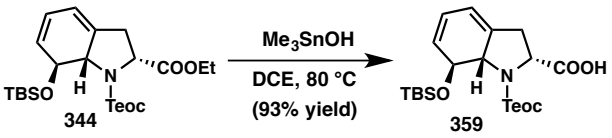
The crude material was first dissolved in small amount of MeOH (ca. 0.1 mL) and co-evaporated with benzene to further get rid of water. It was then dissolved in DMF (0.3 mL). Under N_2, DIPEA (6 μL, 0.034 mmol, 6 equiv), and PyBroP (10.7 mg, 0.023 mmol, 4 equiv) were added in sequence. The resulting light brown solution was allowed to stir at room temperature for 22 hours. It was then quenched with saturated $NaHCO_3$ (1 mL). The mixture was separated and the aqueous layer was then extracted with DCM (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light brown oil. Preparative TLC (80% EtOAc in hexanes) afforded *syn*-diol **357**, as a white solid (0.4 mg, 0.0012 mmol, 43% yield over 2 steps). $[\alpha]_D^{25}$ = +230° (*c* = 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 1.3 Hz, 1H), 5.93 (ddd, *J* = 9.5, 5.0, 2.8 Hz, 1H), 5.89 – 5.82 (m, 1H), 5.75 (ddt, *J* = 9.6, 2.0, 1.0 Hz, 1H), 4.75 – 4.65 (m, 1H), 4.48 (dd, *J* = 13.2, 3.0 Hz, 1H), 4.41 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.34 – 3.18 (m, 1H), 3.16 – 2.93 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 133.4, 129.5, 123.6, 118.7, 71.8, 68.9, 60.5, 29.3; FTIR (NaCl, thin film): 3281, 2922, 2853, 1651, 1423, 1381, 1351, 1336, 1295, 1273, 1255, 1230, 1192, 1147, 1083, 1061, 721, 671 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1339, found 327.1342.

Preparation of *anti*-diol 358



A 1-dram vial was charged with *syn*-diol **357** (1.2 mg, 0.0037 mmol, 1.0 equiv) and Cs_2CO_3 (48 mg, 0.147 mmol, 40 equiv). In the meantime, dry MeOH (0.75 mL) was fully degassed by bubbling N_2 through and was added to the vial under N_2. The resulting mixture gradually turned into a clear yellow solution and was stirred for 30 minutes. It was then quenched with saturated $NaHCO_3$ (3 mL) and the mixture was extracted with EtOAc (5 x 3 mL). Combined organic layer was washed with brine (15 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (20% to 100% EtOAc in hexanes) afforded *anti*-diol **358**, as a white solid (0.8 mg, 0.0024 mmol, 67% yield). $[\alpha]_D^{25} = -159°$ (c = 0.075, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.96 – 5.86 (m, 2H), 5.76 (dt, J = 9.5, 1.4 Hz, 1H), 4.78 – 4.63 (m, 3H), 2.99 (dd, J = 15.5, 7.2 Hz, 1H), 2.88 (t, J = 13.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 132.7, 130.0, 123.0, 119.0, 73.6, 68.1, 62.5, 32.2; FTIR (NaCl, thin film): 3305, 3039, 2924, 2853, 2713, 1626, 1553, 1447, 1381, 1354, 1330, 1290, 1265, 1237, 1201, 1139, 1087, 1057, 767, 710 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1339, found 327.1336.

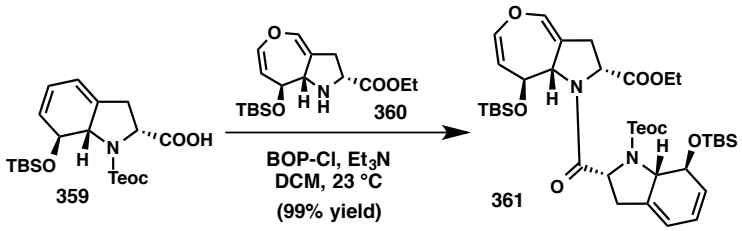
Preparation of carboxylic acid 359



Diene **344** (9.1 mg, 0.019 mmol, 1.0 equiv) was transferred to a 0.5-dram vial, to which was added Me_3SnOH (35.2 mg, 0.195 mmol, 10 equiv) and dry DCE (0.4 mL).

The vial was then sealed with a Teflon cap and heated to 80 °C for 22 hours. It was then cooled to room temperature and quenched with pH2.5 buffer (0.5 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light brown oil. Flash chromatography (1% to 6% MeOH in DCM) afforded carboxylic acid **359**, as a light brown oil (7.9 mg, 0.018 mmol, 93% yield). $[\alpha]_D^{25}$ = +44° (*c* = 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.77 (m, 2H), 5.69 (d, *J* = 9.5 Hz, 1H), 4.93 – 4.79 (m, 1H), 4.72 (d, *J* = 14.4 Hz, 1H), 4.58 (d, *J* = 14.4 Hz, 1H), 4.38 (d, *J* = 10.3 Hz, 1H), 4.09 (q, *J* = 9.5 Hz, 1H), 2.99 – 2.77 (m, 2H), 1.07 (dd, *J* = 9.6, 7.9 Hz, 2H), 0.90 (s, 9H), 0.04 (s, 3H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$, 45 °C) δ 175.1, 157.6, 139.4, 134.6, 124.3, 118.7, 75.4, 65.0, 64.6, 62.8, 32.8, 26.0, 18.2, 18.0, -1.5, -4.6, -5.1; FTIR (NaCl, thin film): 3121, 3051, 2954, 2928, 2897, 2856, 1747, 1699, 1471, 1418, 1360, 1335, 1250, 1178, 1107, 1042, 1020, 970, 957, 862, 838, 776, 700, 667, 627 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{34}NO_5Si_2$ [M–C_2H_4+H]$^+$ 412.1970, found 412.1977 (detected fragment has undergone elimination of ethylene from the Teoc protecting group).

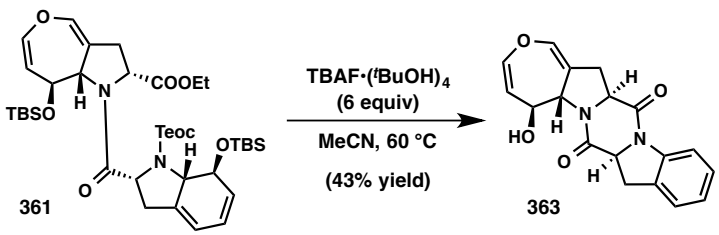
Preparation of dipeptide 361



To a 1-dram vial was transferred carboxylic acid **359** (7.9 mg, 0.018 mmol, 1.0 equiv) and amine **360** (6.7 mg, 0.020 mmol, 1.1 equiv), using DCM, and the mixture of starting materials was co-evaporated with benzene (1 mL). It was then dissolved in dry

DCM (0.35 mL), followed by the addition of Et_3N (25 μL, 0.18 mmol, 10 equiv) and BOP-Cl (22.9 mg, 0.09 mmol, 5 equiv). The mixture was allowed to stir at room temperature for 25 hours and quenched with saturated $NaHCO_3$ (1 mL). Then the mixture was extracted with EtOAc (5 x 1 mL). Combined organic layer was washed with brine (5 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a mixture of white solid and light brown oil. Flash chromatography (2% to 8% EtOAc in hexanes) afforded dipeptide **361**, as a colorless oil (13.4 mg, 0.018 mmol, 99% yield). $[\alpha]_D^{25}$ = +38° (*c* = 0.865, $CHCl_3$); ^{1}H NMR δ (400 MHz, CD_3CN) 6.48 (td, *J* = 2.5, 1.2 Hz, 1H), 6.23 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.87 – 5.80 (m, 1H), 5.72 (qd, *J* = 2.2, 1.3 Hz, 1H), 5.67 (br s, 1H), 5.57 (d, *J* = 9.6 Hz, 1H), 5.47 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.83 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.79 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.46 (dt, *J* = 7.9, 2.1 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.98 (dt, *J* = 16.4, 8.5 Hz, 1H), 2.87 (dddd, *J* = 15.8, 10.1, 2.6, 1.6 Hz, 1H), 2.68 (dq, *J* = 15.8, 1.6 Hz, 1H), 2.65 – 2.60 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.03 – 0.98 (m, 2H), 0.93 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.06 (s, 3H), 0.02 (s, 9H), -0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR δ (101 MHz, CD_3CN, 50 °C) 173.5, 173.3, 158.1, 145.7, 139.8, 137.3, 134.5, 126.2, 117.4, 116.9, 112.0, 75.8, 72.4, 67.7, 65.1, 64.2, 62.4, 61.7, 58.8, 35.4, 33.2, 26.8, 26.6, 19.1, 19.1, 19.0, 14.8, -1.2, -2.8, -4.1, -4.6, -5.1; FTIR (NaCl, thin film): 3049, 3014, 2954, 2929, 2895, 2856, 1747, 1717, 1694, 1652, 1472, 1463, 1428, 1393, 1348, 1329, 1315, 1250, 1213, 1179, 1139, 1094, 1039, 974, 949, 860, 837, 780, 756, 701, 667, 632 cm^{-1}; HRMS (MM) calc'd for $C_{38}H_{64}N_2O_8Si_3Na$ $[M+Na]^+$ 783.3863, found 783.3866.

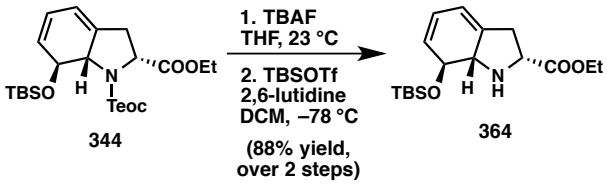
Preparation of DKP 363 (undesired reaction pathway)



A 5 mL Schlenk tube was added TBAF•(^{t}BuOH)$_4$ (4.8 mg, 0.009 mmol, 6 equiv), followed by addition of dipeptide **361** (1.1 mg, 0.0014 mmol, 1.0 equiv) as a CH_3CN solution (0.16 mL). The resulting solution was degassed using the freeze-pump-thaw technique. The vessel was sealed and the solution frozen by submersion in a bath of liquid N_2. The vessel was then placed under vacuum for ca. five minutes before once again being sealed and allowed to thaw under static vacuum by removal from the liquid N_2 bath. This procedure was repeated three times before the head-space was finally backfilled with N_2, the vessel sealed, and the solution heated to 70 °C with stirring. After 1 h and 30 min, the reaction mixture was cooled to room temperature, was diluted with saturated Na_2SO_4 solution, and extracted with EtOAc (5 x 0.5 mL). Each organic fraction was passed individually through a plug of SiO_2, which was then rinsed with excess EtOAc. The combined organic filtrates were then concentrated *in vacuo* to provide the crude product, which was purified by preparative TLC (50% EtOAc in hexanes) afforded alcohol **363**, as a white solid (0.2 mg, 0.0006 mmol, 43% yield). $[\alpha]_D^{25}$ = –331° (*c* = 0.355, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 6.53 (q, *J* = 2.0 Hz, 1H), 6.20 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.41 (d, *J* = 4.5 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.92 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.87 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.50 (td, *J* = 9.0, 1.7 Hz, 1H), 4.40 (ddt, *J* = 8.2, 4.3, 2.1 Hz, 1H), 3.61 (ddt, *J* = 16.6, 10.0, 1.2 Hz, 1H), 3.41 (dd, *J* = 16.5, 10.1 Hz, 1H), 3.06 (dt, *J* =

9.0, 1.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 163.6, 140.4, 138.5, 137.7, 129.7, 128.0, 125.4, 125.0, 116.2, 110.4, 110.3, 71.5, 64.4, 61.0, 58.8, 33.2, 30.7; FTIR (NaCl, thin film): 3338, 3013, 2928, 2859, 1668, 1602, 1486, 1464, 1418, 1328, 1287, 1248, 1192, 1129, 1077, 1047, 978, 916, 860, 821, 755, 665, 625 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{15}N_2O_3$ $[M–OH]^+$ 307.1077, found 307.1081 (detected fragment has undergone loss of hydroxyl anion).

Preparation of amine 364

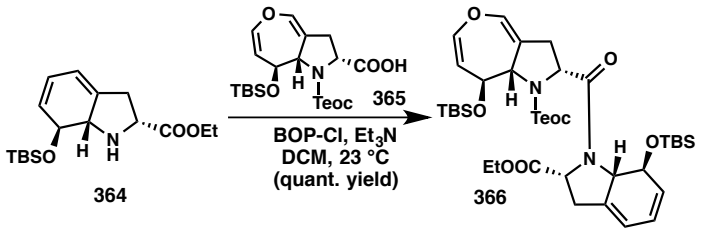


A 1-dram vial of diene **344** (24.7 mg, 0.053 mmol, 1.0 equiv) was dissolved in dry THF (0.85 mL), followed by addition of a THF solution of TBAF (1M in THF, 160 μL, 0.16 mmol, 3 equiv). The reaction solution was allowed to stir at room temperature for 2 hours and quenched with saturated Na_2SO_4 solution (5 mL). The solution was extracted using EtOAc (20 x 4 mL) and each EtOAc extraction was filtered through a short silica gel plug. Combined organic layer was concentrated down to give a brown oil, which was subjected to the next reaction immediately.

The crude material was dissolved in DCM (0.5 mL) and the solution was brought down to –78 °C. 2,6-Lutidine (31 μL, 0.265 mmol, 5 equiv) was added, followed by TBSOTf (24 μL, 0.106 mmol, 2 equiv). After stirring for 50 minutes, a second portion of TBSOTf (12 μL, 0.053 mmol, 1 equiv) was added, which was allowed to react for another 40 minutes. It was quenched with saturated NH_4Cl solution (2 mL) and extracted with EtOAc (3 x 3 mL). Combined organic layer was washed with saturated $NaHCO_3$

solution (10 mL) and brine (10 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a colorless oil. Flash chromatography (1% to 16% EtOAc in hexanes) afforded amine **364**, as a colorless oil (14.9 mg, 0.046 mmol, 88% yield). $[\alpha]_D^{25}$ = +181° (*c* = 0.745, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 9.6, 4.8, 2.1 Hz, 1H), 5.66 (dt, *J* = 5.0, 2.5 Hz, 1H), 5.55 (d, *J* = 9.6 Hz, 1H), 4.61 (d, *J* = 14.0 Hz, 1H), 4.20 (qd, *J* = 7.2, 1.8 Hz, 2H), 3.90 – 3.63 (m, 2H), 2.85 (dd, *J* = 17.7, 8.2 Hz, 1H), 2.68 (dd, *J* = 17.5, 6.8 Hz, 1H), 1.28 (td, *J* = 7.2, 1.9 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 141.4, 131.4, 124.3, 115.4, 76.2, 65.9, 60.9, 59.2, 33.4, 25.9, 18.1, 14.2, -4.38, -4.40; FTIR (NaCl, thin film): 3366, 3045, 2955, 2929, 2896, 2856, 1739, 1472, 1464, 1384, 1330, 1253, 1198, 1156, 1097, 1035, 1006, 983, 921, 892, 859, 837, 777, 705 cm^{-1}; HRMS (MM) calc'd for $C_{17}H_{30}NO_3Si$ $[M+H]^+$ 324.1989, found 324.1980.

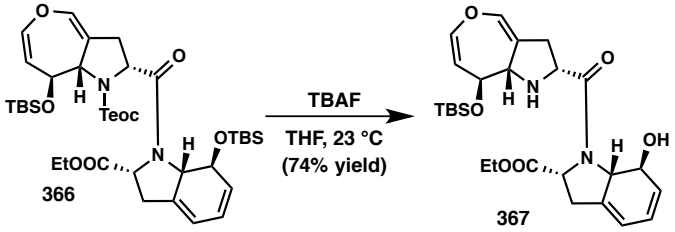
Preparation of bisTBS-dipeptide 366



To a 1-dram vial was transferred amine **364** (14.5 mg, 0.045 mmol, 1.0 equiv) and carboxylic acid **365** (21.5 mg, 0.047 mmol, 1.05 equiv), using DCM, and the mixture of starting materials was co-evaporated with benzene (1 mL). It was then dissolved in dry DCM (0.9 mL), followed by the addition of Et_3N (63 μL, 0.45 mmol, 10 equiv) and BOP-Cl (57 mg, 0.224 mmol, 5 equiv). The mixture was allowed to stir at room temperature for 25 hours and quenched with saturated $NaHCO_3$ (2 mL). The mixture was extracted with EtOAc (5 x 2 mL). Combined organic layer was washed with brine (10

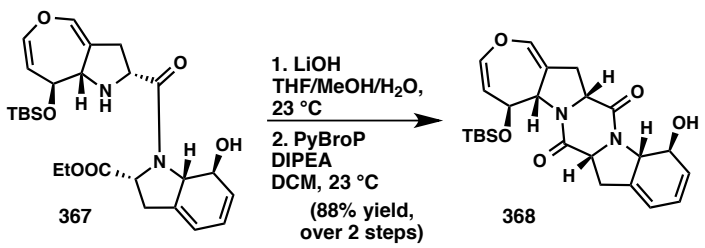
mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a mixture of white solid and light brown oil. Flash chromatography (1% to 8% EtOAc in hexanes) afforded dipeptide **366**, as a colorless oil (35 mg, 0.046 mmol, quantitative yield). $[\alpha]_D^{25}$ = +42° (*c* = 0.865, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 6.50 – 6.39 (m, 1H), 6.21 (dt, *J* = 8.2, 1.1 Hz, 1H), 5.91 (ddd, *J* = 9.6, 4.5, 1.8 Hz, 1H), 5.88 – 5.81 (m, 2H), 5.78 (d, *J* = 9.7 Hz, 1H), 5.55 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.16 (t, *J* = 5.2 Hz, 1H), 4.90 (d, *J* = 14.6 Hz, 1H), 4.68 (d, *J* = 8.3 Hz, 1H), 4.50 (s, 2H), 4.29 – 4.13 (m, 3H), 4.05 (q, *J* = 10.5, 9.7 Hz, 1H), 2.86 (ddd, *J* = 15.0, 8.6, 2.6 Hz, 2H), 2.79 – 2.74 (m, 2H), 2.61 (d, *J* = 14.9 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.07 – 1.01 (m, 1H), 0.97 (s, 9H), 0.87 (s, 9H), 0.12 (s, 6H), 0.04 (s, 3H), 0.04 (s, 9H), -0.09 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN, 60 °C) δ 174.8, 172.9, 142.8, 139.5, 135.7, 135.5, 126.3, 119.5, 111.9, 76.4, 72.0, 65.9, 65.5, 65.1, 62.9, 62.6, 56.9, 35.8, 34.3, 27.2, 26.9, 26.6, 19.3, 19.2, 18.9, 14.9, -1.1, -2.7, -3.8, -4.3, -4.4; FTIR (NaCl, thin film): 3052, 2954, 2928, 2897, 2856, 1745, 1715, 1686, 1655, 1473, 1463, 1431, 1359, 1331, 1304, 1290, 1251, 1208, 1188, 1176, 1143, 1102, 1063, 1029, 929, 837, 779, 701, 666 cm^{-1}; HRMS (MM) calc'd for $C_{26}H_{33}N_2O_6Si$ [M–$C_6H_{16}OSi$–$C_6H_{15}OSi$]$^+$ 497.2101, found 497.2110 (detected fragment has undergone elimination of *tert*-butyldimethylsilanol, as well as loss of *tert*-butyldimethylsilanolate anion).

Preparation of dipeptide 367



A 2-dram vial of bisTBS dieptide **366** (11.3 mg, 0.015 mmol, 1.0 equiv) was dissolved in dry THF (1.4 mL), followed by addition of a THF solution of TBAF (1M in THF, 90 μL, 0.09 mmol, 6 equiv). The reaction solution was allowed to stir at room temperature for 2 hours and quenched with saturated Na_2SO_4 solution (3 mL). The solution was extracted with EtOAc (4 x 3 mL) and each EtOAc extraction was filtered through a short silica gel plug. Combined organic layer was washed with brine (15 mL) and concentrated down to give a brown oil. Flash chromatography (10% to 60% EtOAc in hexanes) afforded dipeptide **367**, as a colorless oil (5.5 mg, 0.011 mmol, 74% yield). $[\alpha]_D^{25}$ = +37° (*c* = 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 – 6.28 (m, 2H), 6.09 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.84 – 5.75 (m, 2H), 5.75 – 5.67 (m, 1H), 4.96 (d, *J* = 8.6 Hz, 1H), 4.84 (dq, *J* = 13.0, 1.6 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.66 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.41 (dt, *J* = 7.3, 2.1 Hz, 1H), 4.31 – 4.13 (m, 2H), 3.94 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.85 – 3.80 (m, 1H), 2.99 (ddt, *J* = 14.9, 8.1, 1.8 Hz, 1H), 2.88 (dddd, *J* = 13.6, 9.2, 3.0, 1.7 Hz, 1H), 2.84 – 2.70 (m, 1H), 2.48 (ddt, *J* = 14.9, 5.5, 1.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 170.6, 138.4, 135.0, 132.8, 130.9, 122.1, 118.8, 115.4, 110.9, 73.8, 71.4, 68.4, 65.3, 62.2, 61.0, 58.7, 34.64, 34.57, 25.9, 18.0, 14.1, -4.48, -4.52; FTIR (NaCl, thin film): 3345, 2955, 2927, 2885, 2855, 1740, 1685, 1639, 1437, 1370, 1327, 1297, 1253, 1206, 1181, 1087, 1065, 1025, 878, 838, 778 cm^{-1}; HRMS (MM) calc'd for $C_{26}H_{39}N_2O_6Si$ $[M+H]^+$ 503.2572, found 503.2585.

Preparation of TBS-DKP 368

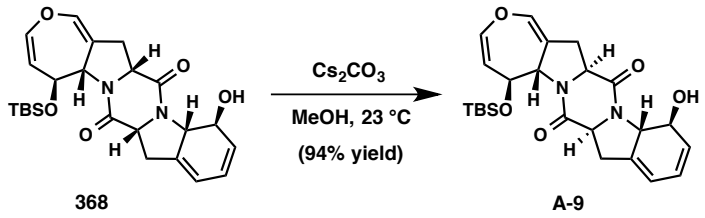


In a 1-dram vial, bisTBS-dipeptide **367** (5.5 mg, 0.011 mmol, 1.0 equiv) was dissolved in THF (180 μL) and MeOH (180 μL). A solution of LiOH (1.3 mg, 0.055 mmol, 5 equiv) in water (180 μL) was added into the vial and the reaction was allowed to stir at room temperature for 30 minutes. It was then quenched with pH7 buffer (3 mL)/brine (0.2 mL) and extracted with EtOAc (10 x 2 mL). The combined organic layer was concentrated under vacuum to provide a light yellow oil crude material. It was subjected to the next reaction directly.

The crude material was first dissolved in small amount of DCM (ca. 0.1 mL) and co-evaporated with benzene (1 mL). It was then dissolved in DCM (2.2 mL). Under N_2, DIPEA (5.7 μL, 0.033 mmol, 3 equiv) and PyBroP (10.2 mg, 0.022 mmol, 2 equiv) were added in sequence. The resulting light yellow solution was allowed to stir at room temperature for 18 hours. It was then quenched with saturated $NaHCO_3$ (4 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (5 x 4 mL). Combined organic layer was washed with brine (25 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a light yellow solid. Flash chromatography (10% to 90% EtOAc in hexanes) afforded TBS-DKP **368**, as a white solid (4.4 mg, 0.010 mmol, 88% yield over 2 steps). $[\alpha]_D^{25}$ = +38° (*c* = 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.48 (s, 1H), 6.22 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.91 (ddd, *J* = 9.8, 5.0, 2.8 Hz, 1H), 5.83 (dq, *J* = 5.3, 2.8 Hz, 1H), 5.74 (d, *J* = 9.7 Hz, 1H), 4.81 – 4.63 (m, 3H),

4.47 (dd, *J* = 13.3, 3.0 Hz, 1H), 4.39 (dd, *J* = 11.8, 8.3 Hz, 1H), 4.35 (dd, *J* = 11.7, 7.1 Hz, 1H), 4.02 (dt, *J* = 8.2, 1.7 Hz, 1H), 3.30 – 3.19 (m, 1H), 3.08 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.90 (ddt, *J* = 16.0, 7.5, 0.9 Hz, 1H), 2.81 (ddt, *J* = 16.0, 11.0, 2.5 Hz, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 169.0, 140.9, 138.0, 133.9, 129.2, 123.5, 118.2, 117.8, 109.4, 71.6, 71.3, 68.7, 64.2, 61.9, 61.5, 29.8, 27.9, 25.9, 18.4, -4.5, -4.9; FTIR (NaCl, thin film): 3260, 2949, 2926, 2892, 2855, 1693, 1646, 1471, 1460, 1428, 1388, 1355, 1329, 1289, 1249, 1232, 1155, 1133, 1101, 1066, 981, 940, 898, 837, 775, 721, 670, 630 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ [M–$C_6H_{15}OSi$]$^+$ 325.1183, found 325.1191 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

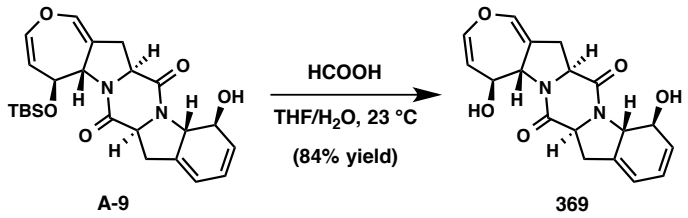
Preparation of *anti*-DKP A-9



A flame-dried 15 mL round-bottom flask was charged with TBS-DKP **368** (5.8 mg, 0.013 mmol, 1.0 equiv) and Cs_2CO_3 (166 mg, 0.508 mmol, 40 equiv). In the meantime, dry MeOH (2.6 mL) was fully degassed by bubbling N_2 through and was added to the flask under N_2. The resulting mixture gradually turned into a clear yellow solution and was stirred for 50 minutes. It was then quenched with saturated $NaHCO_3$ (20 mL) and the mixture was extracted with EtOAc (5 x 10 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded *anti*-DKP **A-9**, as a white solid (5.4 mg, 0.012 mmol, 94% yield). $[\alpha]_D^{25}$ = –305°

(c = 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (td, J = 2.5, 1.0 Hz, 1H), 6.15 (dd, J = 8.2, 2.2 Hz, 1H), 6.00 (s, 1H), 5.93 – 5.83 (m, 2H), 5.81 – 5.71 (m, 1H), 5.06 (dd, J = 7.8, 2.1 Hz, 1H), 4.91 – 4.64 (m, 3H), 4.52 (ddd, J = 11.1, 6.9, 2.0 Hz, 1H), 4.35 (ddd, J = 11.1, 7.0, 1.9 Hz, 1H), 4.22 (dt, J = 7.9, 2.0 Hz, 1H), 3.05 – 2.78 (m, 4H), 0.90 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 163.3, 138.7, 137.3, 133.3, 130.1, 123.0, 118.8, 112.1, 110.1, 73.5, 69.8, 68.3, 62.7, 62.7, 57.8, 34.6, 32.9, 25.7, 18.0, -4.6, -4.8; FTIR (NaCl, thin film): 3304, 2947, 2928, 2884, 2855, 1671, 1634, 1423, 1342, 1290, 1248, 1230, 1197, 1128, 1103, 1051, 1033, 1003, 904, 883, 870, 838, 809, 777, 750, 717 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ $[M–C_6H_{15}OSi]^+$ 325.1183, found 325.1194 (detected fragment has undergone loss of *tert*-butyldimethylsilanolate anion).

Preparation of diol 369

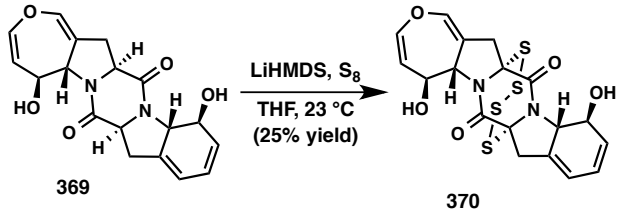


A-9 369

A 15 mL round-bottom flask was charged with *anti*-DKP **A-9** (5.4 mg, 0.012 mmol, 1.0 equiv). It was then dissolved in a mixed solvent including THF (1.44 mL), H_2O (0.24 mL), and HCOOH (0.72 mL). The resulting light yellow clear solution was allowed to stir at room temperature for 8 hours before being carefully quenched with saturated $NaHCO_3$ (15 mL); and the mixture was extracted with EtOAc (5 x 10 mL). Combined organic layer was washed with brine (30 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (10% to 95% EtOAc in hexanes) afforded diol **369**, as a white solid (3.4 mg, 0.010 mmol, 84%

yield). $[\alpha]_D^{25}$ = –456° (*c* = 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (td, *J* = 2.5, 1.1 Hz, 1H), 6.19 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.93 (s, 1H), 5.92 – 5.84 (m, 2H), 5.79 – 5.72 (m, 1H), 5.20 (d, *J* = 4.6 Hz, 1H), 4.90 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.87 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.81 – 4.73 (m, 1H), 4.73 – 4.63 (m, 2H), 4.45 (ddd, *J* = 10.2, 7.5, 2.2 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.05 – 2.96 (m, 2H), 2.92 (ddt, *J* = 15.2, 10.7, 2.2 Hz, 1H), 2.81 (dddt, *J* = 17.8, 12.1, 2.5, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.7, 138.4, 137.8, 132.6, 130.2, 123.0, 119.1, 110.4, 109.6, 73.5, 71.3, 68.2, 64.2, 62.3, 58.0, 33.5, 32.6; FTIR (NaCl, thin film): 3253, 3048, 2923, 2851, 2787, 1667, 1622, 1441, 1386, 1350, 1284, 1267, 1250, 1236, 1206, 1187, 1132, 1084, 1047, 1002, 852, 823, 750, 736, 708, 629 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{17}N_2O_4$ $[M–OH]^+$ 325.1183, found 325.1194 (detected fragment has undergone loss of hydroxyl anion).

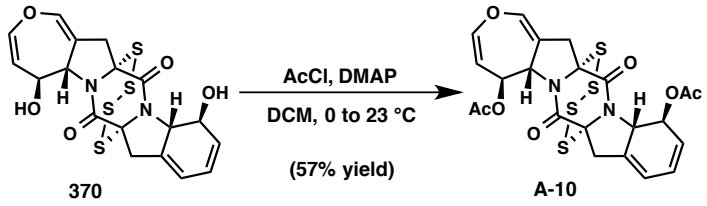
Preparation of tetrasulfide 370



To a suspension of S_8 (9 mg, 0.035 mmol, 5 equiv) in THF (3 mL) at 0 °C under argon was added LiHMDS (1 M in THF, 420 μL, 0.42 mol, 60 equiv) dropwise over 2 min. This solution was stirred for an additional 1 min, and DKP **369** (2.4 mg, 0.007 mmol, 1.0 equiv) dissolved in THF (1 mL) was added dropwise at room temperature over 2 min and rinsed with 0.3 mL THF. The reaction mixture was allowed to stir for 50 minutes and quenched with saturated $NaHCO_3$ (5 mL), and then the mixture was extracted with EtOAc (4 x 5 mL). Combined organic layer was washed with brine (20 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow

solid. Preparative TLC (60% EtOAc in hexanes) afforded tetrasulfide **370**, as a yellow solid (0.8 mg, 0.0017 mmol, 25% yield). $[\alpha]_D^{25}$ = –375° (*c* = 0.045, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 2.3 Hz, 1H), 6.21 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.98 – 5.91 (m, 1H), 5.92 – 5.86 (m, 1H), 5.79 (d, *J* = 9.8 Hz, 1H), 5.33 (s, 1H), 5.08 – 4.98 (m, 2H), 4.93 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.78 (d, *J* = 13.3 Hz, 1H), 4.60 (d, *J* = 4.5 Hz, 1H), 4.46 (td, *J* = 4.9, 2.3 Hz, 1H), 3.30 – 3.19 (m, 2H), 3.03 (dd, *J* = 16.1, 3.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.4, 138.9, 138.0, 131.0, 129.5, 122.9, 121.2, 110.4, 106.4, 78.1, 74.5, 72.7, 71.5, 70.1, 65.3, 41.5, 40.4; FTIR (NaCl, thin film): 3407, 2924, 2852, 1644, 1379, 1289, 1262, 1234, 1188, 1132, 1082, 1053, 971, 902, 861, 819, 744, 722, 622 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{16}N_2O_5S_4Cl$ $[M+Cl]^-$ 502.9636, found 502.9633.

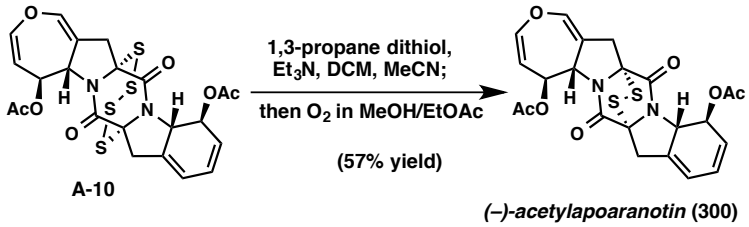
Preparation of diacetate A-10



To a stirred solution of diol **370** (0.9 mg, 1.9 μmol, 1.0 equiv) and DMAP (5.9 mg, 48 μmol, 25 equiv) in DCM (0.2 mL) at 0 °C was added acetyl chloride (2.0 μL, 29 μmol). After 10 min, the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After an additional 30 min, the reaction mixture was quenched with saturated $NaHCO_3$ (0.5 mL) and extracted five times with a mixture of hexanes and EtOAc (1 : 1). Each organic fraction was passed individually through a plug of SiO_2, which was subsequently rinsed with excess hexanes/EtOAc. The combined filtrates were concentrated *in vacuo* to provide the crude product, which was purified by preparative TLC (60% EtOAc in hexanes) to afford diacetate **A-10**, as a yellow solid (0.6

mg, 1.1 μmol, 57% yield). $[\alpha]_D^{25} = -327°$ (c = 0.03, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (t, J = 2.5 Hz, 1H), 6.26 (dd, J = 8.2, 2.3 Hz, 1H), 6.00 – 5.91 (m, 2H), 5.83 (d, J = 14.2 Hz, 1H), 5.68 – 5.59 (m, 1H), 5.37 (d, J = 14.4 Hz, 1H), 5.29 (d, J = 8.2 Hz, 1H), 5.22 (dt, J = 8.4, 2.1 Hz, 1H), 4.70 (dd, J = 8.2, 1.9 Hz, 1H), 3.31 – 3.21 (m, 2H), 3.04 (dd, J = 16.5, 6.4 Hz, 2H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.4, 166.6, 165.8, 139.6, 138.6, 131.9, 128.8, 124.9, 120.9, 108.1, 106.0, 79.4, 75.4, 74.2, 71.1, 64.2, 60.7, 41.8, 41.2, 21.5, 21.4; FTIR (NaCl, thin film): 2923, 2854, 1734, 1685, 1369, 1293, 1236, 1187, 1135, 1046, 753, 710 cm^{-1}; HRMS (LC-MM) calc'd for $C_{20}H_{17}N_2O_5S_4$ $[M–C_2H_3O_2]^+$ 493.0026, found 493.0015 (detected fragment has undergone loss of acetate anion).

Preparation of (–)-acetylapoaranotin (300)



A solution of tetrasulfide **A-10** (0.6 mg, 1.1 μmol) in DCM (0.12 mL) was diluted with MeCN (3.6 mL), then treated with a solution of Et_3N in MeCN (0.05 μL, 0.36 μmol in 10 μL of MeCN), followed by 1,3-propanedithiol (11 μL, 0.11 mmol). The resulting mixture was allowed to stand for 20 min, and was then washed with hexanes (5 x 4 mL, the final hexanes wash was back-extracted once with MeCN to ensure material recovery), and concentrated *in vacuo*. The resulting residue was dissolved in DCM/PhMe and loaded onto a short plug of SiO_2. Residual propanedithiol and other nonpolar impurities were eluted with 4 : 1 hexanes–EtOAc before the presumed dithiol intermediate was

eluted with 50 to 100% EtOAc in hexanes. Collected the fractions and concentrated *in vacuo*. The resulting material was taken up in EtOAc (12 mL) and MeOH (12 mL). The resulting solution was sparged with O_2 for 1 hour and allowed to stir for another 4 hours. The solution was then concentrated *in vacuo*, and purified by preparative TLC (60% EtOAc in hexanes) to provide (–)-acetylapoaranotin (**300**) as a yellow solid (0.3 mg, 0.6 μmol, 57% yield). $[\alpha]_D^{25} = -281°$ (c = 0.015, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 2.4 Hz, 1H), 6.30 (dd, J = 8.3, 2.1 Hz, 1H), 6.04 (d, J = 12.7 Hz, 1H), 6.00-5.95 (m, 2H), 5.69 (d, J = 8.6 Hz, 1H), 5.55 (d, J = 8.2 Hz, 1H), 5.14-5.06 (m, 1H), 5.00 (d, J = 13.1 Hz, 1H), 4.60 (dd, J = 8.2, 1.7 Hz, 1H), 4.01 (d, J = 18.3 Hz, 1H), 3.80 (d, J = 18.1 Hz, 1H), 2.99 (d, J = 18.2 Hz, 1H), 2.87 (d, J = 17.9 Hz, 1H), 2.14 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.9, 163.1, 162.2, 141.1, 139.2, 132.2, 127.8, 124.5, 119.9, 113.4, 105.3, 100.0, 78.2, 75.9, 73.9, 69.8, 64.5, 62.8, 36.1, 34.5, 21.3, 20.9; FTIR (NaCl, thin film): 2919, 2850, 1737, 1706, 1552, 1435, 1367, 1302, 1279, 1233, 1143, 1041, 962, 752, 720, 655 cm^{-1}; HRMS (ESI) calc'd for $C_{22}H_{20}N_2O_7S_2Na$ $[M+Na]^+$ 511.0610, found 511.0621.

Table 4.1. *Comparison of ^1H NMR data for natural vs. synthetic (–)-acetylapoaranotin (**300**)*

Yang et al. Report,[20] Natural (–)-acetylapoaranotin ^1H NMR, 500 MHz, $CDCl_3$	This Work, Synthetic (–)-acetylapoaranotin ^1H NMR, 400 MHz, $CDCl_3$
δ 6.61 (br ddd, *J* = 2.5, 2.0, 2.0 Hz, 1H)	δ 6.60 (d, *J* = 2.4 Hz, 1H)
6.31 (dd, *J* = 8.5, 2.0 Hz, 1H)	6.30 (dd, *J* = 8.3, 2.1 Hz, 1H)
6.05 (br dm, *J* = 13.2 Hz, 1H)	6.04 (d, *J* = 12.7 Hz, 1H)
5.99 (m, 1H)	6.00-5.95 (m, 2H)
5.96 (m, 1H)	
5.70 (ddd, *J* =8.5, 2.0, 2.0 Hz, 1H)	5.69 (d, *J* = 8.6 Hz, 1H)
5.56 (br dm, *J* = 13.2 Hz, 1H)	5.55 (d, *J* = 8.2 Hz, 1H)
5.10 (br dddd, *J* = 8.5, 2.0, 2.0, 1.5, 1H)	5.14-5.06 (m, 1H)
5.00 (br dm, *J* = 13.2 Hz, 1H)	5.00 (d, *J* = 13.1 Hz, 1H)
4.61 (dd, *J* = 8.5, 2.0 Hz, 1H)	4.60 (dd, *J* = 8.2, 1.7 Hz, 1H)
4.02 (br ddd, *J* = 18.0, 2.5, 1.5 Hz, 1H)	4.01 (d, *J* = 18.3 Hz, 1H)
3.81 (dm, *J* = 18.5 Hz, 1H)	3.80 (d, *J* = 18.1 Hz, 1H)
2.99 (ddd, *J* = 18.0, 2.0, 2.0 Hz, 1H)	2.99 (d, *J* = 18.2 Hz, 1H)
2.88(br dd, *J* = 18.5, 1.5)	2.87 (d, *J* = 17.9 Hz, 1H)
2.15 (s, 3H)	2.14 (s, 3H)
2.03 (s, 3H)	2.03 (s, 3H)

Table 4.2. *Comparison of ^{13}C NMR data for natural vs. synthetic (–)-acetylapoaranotin (**300**)*

Yang et al. Report,[20] Natural (–)-acetylapoaranotin ^{13}C NMR, 126 MHz, $CDCl_3$	This Work, Synthetic (–)-acetylapoaranotin ^{13}C NMR, 101 MHz, $CDCl_3$	Chemical Shift Difference, $\Delta\delta$
δ 170.5	δ 170.5	0.0
170.0	169.9	0.1
163.1	163.1	0.0
162.2	162.2	0.0
141.2	141.1	0.1
139.2	139.2	0.0
132.2	132.2	0.0
127.8	127.8	0.0
124.5	124.5	0.0
119.9	119.9	0.0
113.4	113.4	0.0
105.3	105.3	0.0
78.2	78.2	0.0
75.9	75.9	0.0
73.9	73.9	0.0
69.8	69.8	0.0
64.5	64.5	0.0
62.9	62.8	0.1
36.1	36.1	0.0
34.5	34.5	0.0
21.3	21.3	0.0
21.0	20.9	0.1

4.5 NOTES AND REFERENCES

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