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Total Syntheses of (+)-Peniciketals A-B and (−)-Diocollettines A Exploiting a Photoisomerization/Cyclization Union Protocol

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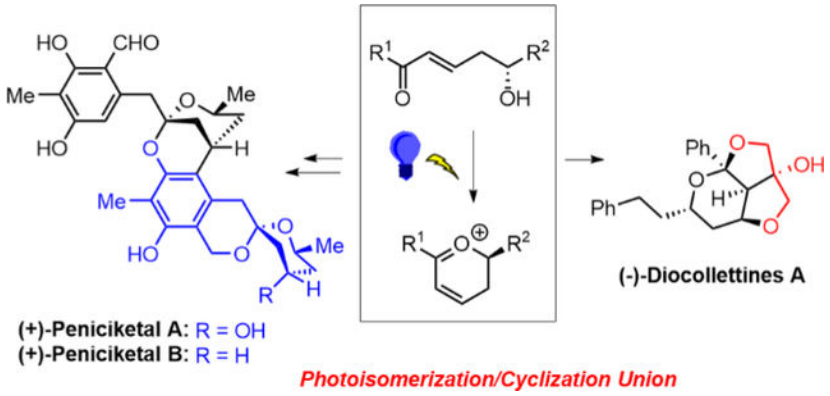
Abstract

A late-stage photoisomerization/cyclization union tactic, in conjunction with Type I Anion Relay Chemistry (ARC) permits enantioselective total syntheses and then biological evaluation of (+)-peniciketals A and B. The photochemical protocol was further showcased by an efficient three-step construction of the architecturally complex polycyclic skeleton found in (−)-diocollettines A. The mechanism and diastereoselectivity of the photochemical protocol have also been explored by both experiment and DFT calculations.

Graphical Abstract



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ASSOCIATED CONTENT

Supporting Information.

The Supporting Information: (PDF)

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1. INTRODUCTION

The peniciketals A-C (**1-3**; Scheme 1), reported by Pan and Zhu in 2014,[1] constitute an architecturally intriguing family of benzo-fuzed spiroketals that were found to possess significant anticancer activity. The unprecedented structure of the peniciketals, assigned by X-ray diffraction and NMR spectra, contains a benzannulated spiroketal and a benzo-fused 2,8-dioxabicyclo[3.3.1]nonane skeleton. Both peniciketals A and B (**1-2**) possess the benzo-fused [6,6]- spiro-ring while A bears a C(3)-OH. Peniciketal C (**3**) instead possesses a benzo-fused [5,6]-spiro-ring and also bears a C(3)-OH.

Peniciketal A (**1**) was further demonstrated by Pan and Zhu to display selective cytotoxicity against both leukemia cells (IC_{50} = 3.2 μM against HL-60 cell line) and human non-small lung cancer cells (IC_{50} = 22.33 μM against A549 cell line), but less toxic when treated with normal cells.[2–4] As we report here, with synthetic samples, the cytotoxicity and selectivity of peniciketal A-B is valid, with synthetic peniciketal B more potent than A against lung cancer cell lines. Given the unique structures of the peniciketals, in conjunction with their potential as antitumor drug lead candidates, we were attracted to launch synthetic studies toward members of the peniciketal family and eventually to potential analogs for structure-activity relationship studies.

Our group has had a long-standing interest in the development of novel photochemical protocols for construction of fused polycyclic natural products, for example the paniculides,[5] hibiscone C,[6] echinosporin,[7] and recently the danshenspiroketallactones.[8] The potential to partner with Anion Relay Chemistry (ARC),[9] also developed in our laboratory, would extend considerably this construction paradigm. To this end, we reported the first enantioselective syntheses of (+)-peniciketals A-B earlier this year.[10] In this synthesis, Type I ARC was employed to synthesize the benzo-fused spiro-ring[11] and a new photoisomerization/cyclization union strategy was developed for the rapid access to the complex benzo-fuzed bicyclo[3.3.1]nonane structure. The reaction mechanism was proposed as outlined in Scheme 2: *trans*-enone **A** was irradiated under UV-A light (335nm) to undergo isomerization to *cis*-isomer **B**, which under the acid condition undergoes cyclization to form diene **C**. Protonation of **C** then generates carboxonium **D**. At this stage, a stereoselective [3+3] cyclization between diene **D** and nucleophiles **4** delivers the complex benzo-fused bicyclo[3.3.1] nonane skeleton **E**.

We further envision the photochemical protocol would hold potential for the rapid construction of oxygen-containing 6/5/5 tricyclic ring skeletons, recently disclosed in nature to include diocollettines A (**5**),[12] streptoglycerides A-D (**6-9**)[13] and two bafilomycin derivatives (**10-11**)[14] (Scheme 3a). Diocollettines A, isolated in 2016 from the rhizomes *Dioscorea collettii*, also displayed moderate anticancer activity with an IC_{50} value of 20.15 μM against human lung cancer NCL-H460 cell line.[12] To date, two total syntheses of diocollettines A have been reported.[15,16] Inspired by the second synthesis from the Kuwahara group,[16] we reasoned the proposed photoisomerization/cyclization protocol would be an efficient method to construct such polycyclic ring skeletons in a straightforward fashion under very mild conditions (*vide infra*). That is, as proposed in Scheme 3b, we envision that under irradiation with UV-A light and acidic conditions, the *in-situ* generated

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oxonium **C**, when treated with 1,3-dihydroxyacetone (**12**), would undergo a tandem *oxa*-Michael addition/aldol/acetalization reaction sequence to furnish the 6/5/5 tricyclic ring skeleton **F** in a one-flask manner. As such, this photochemical protocol would also serve as an efficient method to construct such polycyclic natural products.

Herein we report a full account on the development of the above photoisomerization/cyclization union tactic, first with a model system, and then showcased with the total syntheses of peniciketals A-B (**1**-**2**) and an efficient 3-step synthesis of diocollettines A (**5**). Computational studies of the mechanism and diastereoselectivity of this photochemical protocol, as well as biological evaluation of peniciketals A and B, are also reported.

2. RESULTS AND DISCUSSION

Synthetic Analysis and Model Experiments.

From the retrosynthetic perspective, we envisioned the disconnection of peniciketals at the featured bicyclo[3.3.1] nonane core presented the possibility of the late-stage photochemical union to unite the northern and southern hemispheres (**13** and **14** respectively). The [6,6]-spiroketal **14** would be assembled by a Type I ARC tactic from commercially available linchpin **15** and two different electrophiles **16** and (+)-**17**.[17]

We initiated the synthesis with model reactions to validate the photoisomerization/cyclization union tactic with enone (+)-**18** and commercial resorcinol **19** (Scheme 5a). Under UV-A light and acidic conditions the desired adduct (+)-**20** was isolated in 45% yield with >20:1 *dr* (entry 1). Following an investigation of acid catalysts and solvents, we determined that under the optimal condition (20 mol% camphor sulfonic acid (CSA) and 0.2 M THF solution), adduct (+)-**20** could be obtained in 80% yield (entry 3). Key intermediate diene (+)-**21** was isolated and characterized as a single isomer. Control experiments were conducted to support the proposed mechanism (Scheme 5b). First, (+)-**21** was resubjected to acidic condition in the dark with **19** to afford (+)-**20** in 61% yield. We also conducted the reaction in dark and found neither isomerization nor cyclization occurred without UV-A irradiation.

Computational Studies of the Model System.

As illustrated (Scheme 5b), attack of resorcinol **19** from either the top or bottom face of the oxocarbenium generated from (+)-**21** would produce two possible diastereomers, but (+)-**20** was the only diastereomer observed experimentally. We applied DFT calculations to explore the stereoselectivity of this reaction. At the outset, we proposed that the initial Michael addition of **19** to the oxocarbenium determines the stereochemical outcome of the overall transformation. We therefore calculated the geometries and energies of the two stereoselective Michael addition transition states with the ωB97X-D/def2svp/CPCM(THF) method (Figure 1).[18] Attacking from the *si* face of the oxocarbenium (**TS1a**) proceeds via a pseudo chair conformation of the dihydropyran ring, where the C1-Me is in the gauche conformation with C2-H, leading to formation of the CC bond. Alternatively, attacking from the *re* face of the oxocarbenium (**TS1b**) would assume a pseudo boat conformation of the dihydropyran ring, where C1-Me is located more towards an eclipsed conformation

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with C2-H (a dihedral angle of 32°). The latter results in disfavored steric interactions. The preference for a higher energy pseudo boat conformation for **TS1b** is to avoid the undesired 1,3-diaxial interaction of the axial-Me group with **19** when attacking from the *re* face, via a pseudo chair conformation **TS1b-ax**; this conformation increases the barrier height to 17.6 kcal/mol. Therefore **TS1a** (12.9 kcal/mol) is preferred over **TS1b** (14.9 kcal/mol). **TS1a** leads to Michael addition adduct **INT1a** (4.4 kcal/mol) which is thermodynamically uphill (Figure 2), but proton transfer generates a stable oxocarbenium intermediate **INT2a** (−10.0kcal/mol). Cyclization followed by another proton transfer generates the product (+)-**20**, which has a free energy of −25.1 kcal/mol relative to the neutral starting material (+)-**21** and **19**. No cyclization transition state was located. The other pathway starting from **TS1b** could generate the diastereomer **20a** that is not observed by experiments and is disfavored in both kinetic and thermodynamic perspectives.

Total Syntheses and Biological Evaluation of Peniciketals A and B.

We began the synthesis of peniciketals A and B (**1** and **2**) with the common northern hemisphere **13** (Scheme 6a). The initial devised route was to disconnect **13** via a Weinreb-Nahm ketone synthesis to ester **22** and Weinreb amide **23**. To this end, TBS protection of the naturally abundant andcommercially available atraric acid **24** delivered **22** in 90% yield. The Weinreb amide (−)-**23** was then prepared in 84% yield via amidation of *α,β*-unsaturated ester (−)-**26**, which in turn could be constructed from (*S*)-3-hydroxy-butanoate (+)-**25** in a 4-step sequence.[19] At this stage, we found with freshly prepared lithium 2,2,6,6-tetramethylpiperidide (LTMP), the deprotonation of **22** went completely to generate the *ortho*-ester *meta*-OTBS benzylic anion **27**, which was stable at −78 °C.[20] In the same pot, slow addition of a pre-cooled solution of (−)-**23** into anion **27** solution delivered the desired 1,2-addition product (−)-**28**, albeit in only 35% yield. The presumed reason for the low yield was competition with 1,4-addition.[20] Although a variety of conditions were explored, we were not able to increase the yield of (−)-**28**. Removal of the THP group then completed the synthesis of the northern hemisphere (+)-**13**. Although having arrived successfully at (+)-**13**, the 7-step route (7.4% overall yield) did not appear suitable for a large-scale synthetic venture.

We therefore devised an alternate scalable synthetic route to (+)-**13**. We envisioned that the northern hemisphere (+)-**13** could be disconnected into ester **22**, acyl chloride **29** and chiral alcohol (+)-**30**, via a 2-step cross-coupling/olefin metathesis sequence (Scheme 6b). At this stage, the *in-situ* formed anion **27** was stable for transmetallation with $ZnCl_2$ at −78 °C. The following addition of acyl chloride **29** and palladium catalyst then permitted the Negishi cross-coupling[21] reaction to afford the desired adduct **31** in 80% yield on gram-scale. The following cross-metathesis to complete the synthesis of (+)-**13** was then achieved in 84% yield in the presence of Hoveyda-Grubbs II promoter.[22] The second route permitted construction of the highly functionalized enone (+)-**13** in only 3 steps in 60% yield and 675 mg (+)-**13** was prepared.

We next explored construction of the southern hemisphere (**14**) of peniciketal A (Scheme 7). The synthesis of the requisite benzyl bromide **16** for Type I ARC proposed in Scheme 4 started with commercially available compound **32**, which was then converted

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to resorcinol **33** in 5 steps.[23] Benzyl bromide **16** was then constructed from **33** via a 3-step sequence of TBS protection, DIBAL-H reduction and removal of TBS groups. The Type I ARC union was then initiated by nucleophilic attack of the deprotonated linchpin **15** to epoxide (+)-**17** to generate alkoxide **36**. Upon the addition of HMPA, [1,4]-Brook rearrangement[24] then translocated the silyl group from the carbon to the oxygen to generate the resulting carbanion **37**. Capture with the second electrophile **16** in turn completed the three-component union to afford adduct **38**. Without further purification, the crude adduct **38** was directly treated with $Hg(ClO_4)_2$ and $CaCO_3$ to remove both the TMS and dithiane groups and as such furnished (+)-**39** in an overall 64% yield in 2 steps on a 2-gram scale. We then attempted to achieve the global removal of all four TBS groups in one step. Unfortunately, with various fluorine reagents tested, including TBAF, HF, and their buffers, only decomposition of (+)-**39** was observed. We next turned to acidic conditions including PTSA and CSA. Again, a significant decomposition of (+)-**39** was observed under these conditions. Pleasingly we finally found with 5 mol% $NaAuCl_4$ in MeOH, the two aliphatic TBS groups were selectively removed followed by a high diastereoselective spiroketalization to afford (−)-**41** as a single diastereomer! Completion of the synthesis of the southern hemisphere (−)-**14** was then achieved by TBS removal with TBAF; 360 mg (−)-**14** was prepared.

Having constructed both the northern and western fragments (+)-**13** and (−)-**14** respectively, we turned to the late-stage photoisomerization/cyclization union protocol (Scheme 8). Under irradiation, the photoisomerization of (+)-**13** followed by [3+3]-cyclization with (−)-**14** successfully generated the desired coupling adduct (−)-**43** in 72% yield (*dr* = 13:1). Direct reduction of the ester in (−)-**43** to aldehyde to complete the synthesis of peniciketal A (**1**) proved unsuccessful. Therefore, we detoured with TBS protection and DIBAL-H reduction to generate alcohol analog (−)-**46**. As it turned out, TBS protection of (−)-**43** was necessary, otherwise the naked phenol group would decompose in the further oxidation step. Finally, oxidation of (−)-**46** with Dess-Martin periodinane (DMP) and TBS removal delivered over 100 mg synthetic (+)-peniciketal A (**1**). The NMR spectra (^1H and ^{13}C) and single-crystal X-ray including anomalous dispersion of synthetic (+)-**1** were identical to the literature values reported by Pan and Zhu.[1]

With the total synthesis of (+)-peniciketal A (**1**) accomplished, we next turned to the total synthesis of peniciketal B (**2**). To this end, Barton-McCombie deoxygenation[26] of (−)-**43** was first explored (Scheme 9). However, only a trace amount of product (−)-**47** was observed. We therefore started the synthesis with Barton-McCombie deoxygenation of (−)-**41**. Pleasingly, the deoxygenation of (−)-**41** successfully yielded (−)-**48** without any epimerization. After TBS removal, 90 mg of the requisite southern hemisphere (−)-**49** for peniciketal B (**2**) was obtained. Again, the late-stage photochemical union of northern hemisphere (+)-**13** and southern hemisphere (−)-**49** furnished the coupling adduct (−)-**47** in 73% yield (*dr* = 12:1). Completion of total synthesis of peniciketal B (**2**) was finally achieved with the same 4-step reduction/oxidation elaboration of (−)-**47**; 22 mg synthetic (+)-peniciketal B (**2**) was obtained with an overall 24% yield in 8 steps from (−)-**41**. The spectral properties of the synthetic (+)-**2** proved identical to literature values.

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With both synthetic (+)-peniciketals A (**1**) and B (**2**) in hand, we next turn to study their cytotoxicity against lung cancer cells (Table 1). Peniciketals A (**1**) displayed moderate cytotoxicity against two human lung cancer cell lines A549 cells and H1975 with IC_{50} values of 16.4 and 14.3 μM, respectively, which are similar to the literature values,[2] Interestingly, it turned out peniciketal B (**2**) displayed more cytotoxic against both lung cancer cell lines (IC_{50} = 6.8 μM against A549 and 7.3 μM against H1975). The selectivity of peniciketals was also validated. Lower toxicity to human normal cells IMR90 was observed for both synthetic peniciketals A (**1**) and B (**2**).

Total Synthesis of Diocollettines A.

To validate the potential application of this photochemical protocol in the construction of 6/5/5 tricyclic ring skeletons, we next turned to the total synthesis of diocollettines A (**5**, Scheme 10). Beginning with aldehyde **52**, the reported asymmetric allylation was performed to deliver the desired homoallylic alcohol (−)-**53**,[15] which in turn underwent olefin cross-metathesis with **54** to produce the requisite enone (−)-**55** in 82% yield. Irradiation of enone (−)-**55** generated oxonium **56** *in situ* and then the oxo-Michael/adol/acetalization reaction cascade with **12** successfully furnished (−)-diocollettines A (**5**) in a single step as a single diastereomer on a 48 mg scale. The spectral properties of synthetic (−)-**5** proved identical to the literature values.[12] This result suggests that this photochemical protocol can serve as an efficient method to construct this structural array of 6/5/5 tricyclic natural products.

3. CONCLUSIONS

In summary, highly convergent total syntheses of (+)-peniciketal A (**1**) and B (**2**), along with an efficient 3-step total synthesis of (−)-diocollettines A (**5**) have been achieved. The longest linear sequence for the synthesis of (+)-peniciketal A (**1**) is 17 steps from commercially available acid **32**. The key transformation in these syntheses is the development and application of photoisomerization/cyclization union protocol to construct both benzo-fused bicyclo[3.3.1]nonane structure and 6/5/5 tricyclic ring skeleton. DFT calculations revealed the origin of the high stereoselectivity of the photochemical protocol.

4. Experimental Section

General Information.

All substrates whose syntheses were not described were either obtained from commercial suppliers or prepared using the referenced literature procedures. Photochemical experiments were performed in a RayonetTM Srinivasan-Griffin Photoreactor (The Southern new England Ultraviolet Company) using Hitachi FL9BL-B bulbs (part # 6201 – 7532). ^{1}H and ^{13}C NMR spectra were collected at 500 MHz on a Bruker Avance III 500 MHz spectrometer. For ^{1}H-NMR, reported chemical shifts are relative to acetone-d_6 (δ 2.05) and chloroform (δ 7.26). For ^{13}C-NMR, reported chemical shifts are relative to acetone-d_6 (δ 29.82) and chloroform (δ 77.16). Infrared spectra were measured on a Jasco FT/IR 480 plus spectrometer. Circular dichroism spectra, High-resolution mass spectrometry (HRMS) and single-crystal X-ray structure were determined at the University of Pennsylvania.

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Synthesis and Characterization of Compounds.

Compound (+)-18.—To a solution of 1-phenylbut-3-en-2-one (438 mg, 3 mmol, 1 eq.) in DCM (20 mL) was added (+)-**30** (1.29 g, 15 mmol, 5 eq.) in 10 ml DCM under N_2 atmosphere and HG-II (38 mg, 0.06 mmol, 0.02 eq.) in DCM (10 mL). The resulting mixture was refluxed for 2 days before being quenched by exposure to air. The mixture was then concentrated. Purification via chromatography (EtOAc/hexanes =1/2 to 1/1) provided (+)-**18** (526 mg, 2.58 mmol, 86% yield) as a colorless oil $[\alpha]_D^{20}$ +13.2 (*c* 1.0, acetone); **IR** (film, cm^{-1}) 3417 (br), 2965, 2925, 1664, 1628, 1454, 1336, 1259, 1118, 982, 846, 703; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.32–7.29 (m, 2H), 7.25–7.21 (m, 3H), 7.01 (dt, *J* = 15.8, 7.3 Hz, 1H), 6.19 (dt, *J* = 15.9, 1.4 Hz, 1H), 3.91–3.87 (m, 3H), 3.76 (d, *J* = 4.8 Hz, 1H), 2.34 (dd, *J* = 9.8, 3.8 Hz, 2H), 1.13 (d, *J* = 6.2 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 197.0, 145.5, 136.0, 131.9, 130.2, 129.0, 127.1, 66.6, 47.2, 42.7, 23.5; **HRMS** (EI) *m/z* 204.1143 [$(M)^+$; calcd for $C_{13}H_{16}O_2$: 204.1150].

Compound (+)-20.—To a solution of (+)-**18** (40.8 mg, 0.2 mmol, 1 equiv.) and **19** (25 mg, 0.2 mmol, 1 equiv.) in 1 mL THF was added CSA (9.3 mg, 0.04 mmol, 0.2 equiv.) under N_2 and irradiated under UV-A light (355 nm) for 24 hours. The reaction was then quenched with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated and purified by chromatography (EtOAc/hexanes =1/20 to 1/3) to afford the desired product (+)-**20** (49 mg, 0.16 mmol, 80% yield, dr > 20:1): $[\alpha]_D^{20}$ +102.3 (*c* 1.4, $CHCl_3$); **IR** (film, cm^{-1}) 3369 (br), 2926, 1608, 1447, 1334, 1273, 1167, 1084, 978, 744, 702; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.96 (s, 1H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 3.71–3.65 (m, 1H), 3.14 (d, *J* = 13.5 Hz, 1H), 3.01 (d, *J* = 13.5 Hz, 1H), 3.00 (m, 1H), 2.12 (s, 3H), 1.88 (dd, *J* = 12.5, 2.6 Hz, 1H), 1.59–1.53 (m 2H), 1.49 (dd, *J* = 12.5, 2.6 Hz, 1H), 1.07 (d, *J* = 6.2 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 155.4, 154.9, 137.1, 131.6, 128.4, 127.1, 125.5, 117.8, 110.5, 107.7, 99.5, 65.6, 47.5, 40.6, 32.7, 30.7, 21.6, 8.6; **HRMS** (EI) *m/z* 310.1558 [$(M)^+$; calcd for $C_{20}H_{22}O_3$: 310.1569].

*Compound (+)-**21*** was isolated as a colorless oil as a byproduct in the preparation of (+)-**20** (7 mg, 0.04 mmol, 19% yield, a mixture of E/Z isomers): $[\alpha]_D^{20}$ +65.5 (*c* 1.1, acetone); **IR** (film, cm^{-1}) 3050, 2975, 2925, 2891, 1604, 1489, 1448, 1387, 1326, 1184, 1116, 1057, 957, 825, 749; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.15 (dd, *J* = 9.8, 2.3 Hz, 1H), 5.99 (ddd, *J* = 9.4, 6.2, 2.7 Hz, 1H), 5.39 (s, 1H), 4.13 (dqd, *J* = 9.8, 6.2, 3.5 Hz, 1H), 2.33 (ddd, *J* = 17.8, 6.2, 3.4 Hz, 1H), 2.17 (ddt, *J* = 17.7, 10.3, 2.6 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 152.0, 137.9, 129.5, 129.0, 127.1, 126.4, 126.2, 108.5, 72.3, 32.5, 21.5; **HRMS** (EI) *m/z* 186.1040 [$(M)^+$; calcd for $C_{13}H_{14}O$: 186.1045].

Compound 22.—To a solution of the atraric acid **24** (1.96 g, 10 mmol, 1 eq.) in DCM (40 mL) was added 2,6-lutidine (3.42 g, 32 mmol, 3.2 eq.) and TBSOTf (6.34 g, 24 mmol, 2.4 eq.) under N_2 atmosphere at 0 °C. The reaction was stirred overnight and then quenched with a sat. $NaHCO_3$ solution, followed by extraction with DCM. The combined organic layers were dried, concentrated and purified via chromatography (EtOAc/hexanes =1/40) to

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provide the product **22** (3.82 g, 9.0 mmol, 90% yield) as a pale-yellow oil: **IR** (film, cm^{-1}) 2929, 2858, 1731, 1601, 1570, 1473, 1409, 1330, 1282, 1152, 1123, 827, 780, 676; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.32 (s, 1H), 3.83 (s, 3H), 2.24 (s, 3H), 2.03 (s, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.19 (s, 6H), 0.08 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 169.0, 156.1, 152.3, 135.0, 119.6, 118.6, 114.9, 51.7, 26.0, 25.9, 20.4, 18.6, 18.4, 11.3, −3.8, −4.0; **HRMS** (EI) *m/z* 367.1758 [(M-*t*Bu)$^+$; calcd for $C_{18}H_{31}O_4Si_2$: 367.1761].

Compound (−)-23.—To a solution of acrylate (−)-**26** (2.8 g, 12.3 mmol, 1 eq., prepared in 27% yield over 4 steps following the same literature procedure)[19] and dried *N,O*-dimethylhydroxylamine hydrochloride (2.4 g, 24.6 mmol, 2 eq.) in THF (30 mL) was slowly added *i*-PrMgCl (27 mL, 2 M in THF, 54 mmol, 4.4 eq.) at 0 °C under N_2 atmosphere. The reaction was stirred at 0 °C for 30 minutes and then quenched with a sat. NH_4Cl solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/3 to 1/1) to provide the diastereomers (−)-**23** (2.65 g, 10.3 mmol, 84% yield, dr = 1:1) as a colorless oil:$[\alpha]_D^{20}$ −9.8 (*c* 1.3, $CHCl_3$); **IR** (film, cm^{-1}) 3498, 2939, 1668, 1633, 1417, 1380, 1125, 1074, 1027, 993, 873, 812, 690; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.00–6.87 (m, 1H), 6.46–6.40 (m, 1H), 4.70–4.68 (m, 0.5H), 4.63–4.61 (m, 0.5H), 3.93–3.81 (m, 2H), 3.66 (s, 1.5H), 3.66 (s, 1.5H), 3.47–3.43 (m, 1H), 3.20 (s, 3H), 2.55–2.49 (m, 0.5H), 2.45–2.30 (m, 1.5H), 1.79–1.75 (m, 1H), 1.68–1.66 (m, 1H), 1.51–1.49 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 1.5H), 1.11 (d, *J* = 6.3 Hz, 1.5H),; **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.8, 166.7, 144.1, 143.7, 121.0, 120.8, 98.4, 95.9, 72.4, 70.3, 62.8, 62.4, 61.8, 40.6, 39.6, 32.4, 31.1, 31.0, 25.6, 25.5, 21.7, 19.9, 19.6, 91.1; **HRMS** (EI) *m/z* 257.1644 [(M)$^+$; calcd for $C_{13}H_{23}NO_4$: 257.1627].

Compound (−)-28.—To a solution of diisopropylamine (2.2 g, 22 mmol, 2.2 eq.) in THF (20 mL) was added *n*BuLi (8.8 mL, 2.5 M in hexanes, 22 mmol, 2.2 eq.) at −78 °C. The resulting mixture was warmed to 0 °C and stirred for 30 minutes before it was cooled to −78 °C. A solution of ester **22** (6.36 g, 15 mmol, 1.5 eq.) in THF (20 mL) was added slowly and the red solution was stirred at −78 °C for 30 minutes before a solution cooled to −78 °C of amide (−)-**23** (2.57 g, 10 mmol, 1 eq.) in THF (20 mL) was added via cannula. The mixture was stirred for 1h at −78 °C and was then quenched with sat. NH_4Cl solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/10 to 1/5) to provide the diastereomers (−)-**28** (2.17 g, 3.5 mmol, 35% yield, dr = 1:1) as a colorless oil:$[\alpha]_D^{20}$ −2.4 (*c* 1.0, $CHCl_3$); **IR** (film, cm^{-1}); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95–6.90 (m, 1H), 6.30 (s, 1H), 6.17–6.12 (m, 1H), 4.69–4.59 (m, 1H), 3.91–3.81 (m, 4H), 3.76 (s, 3H), 3.47–3.45 (m, 1H), 2.49–2.27 (m, 2H), 2.04 (s, 3H), 1.80–1.65 (m, 2H), 1.53–1.48 (m, 4H), 1.21 (d, *J* = 6.3 Hz, 1.5H), 1.10 (d, *J* = 6.3 Hz, 1.5H), 1.01 (s, 9H), 0.98 (s, 9H), 0.17 (s, 6H), 0.05 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 196.7 (196.73), 196.7 (196.65), 168.6, 156.5 (156.54), 156.5 (156.50), 153.0 (153.04), 153.0 (153.01), 144.3, 143.8, 132.3, 132.2, 131.3, 131.2, 120.4 (120.40), 120.4 (120.36), 119.5, 119.4, 115.5, 115.4, 98.3, 96.2, 72.2, 70.4, 62.9, 62.6, 51.8 (51.84), 51.8 (51.82), 46.0, 45.8, 40.6, 39.5, 31.2, 31.0, 25.9, 25.8, 25.6, 25.5, 21.7, 20.0, 19.7, 19.3, 18.5, 18.4, 11.3, −3.9, −4.1; **HRMS** (EI) *m/z* 620.3552 [(M)$^+$; calcd for $C_{33}H_{56}O_7Si_2$: 620.3565].

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Compound (+)-13.

Method 1: To a solution of THP ether (−)-**28** (953 mg, 1.54 mmol, 1 eq.) in DCM (8 mL) and methanol (8 mL) was added PPTS (38 mg, 0.154 mmol, 0.1 eq.). The resulting mixture was stirred at rt for 2 days and monitored by TLC before being quenched with sat. $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/2 to 1/1) to provide the northern hemisphere (+)-**13** (768 mg, 1.43 mmol, 93% yield) as a colorless oil:$[\alpha]_D^{20}$ +5.7 (*c* 1.1, $CHCl_3$); **IR** (film, cm^{-1}) 3436 (br), 2936, 2860, 1714, 1595, 1411, 1261, 1151, 973, 833, 779; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 15.5, 7.6 Hz, 1H), 6.32 (s, 1H), 6.17 (d, *J* = 15.5 Hz, 1H), 3.85–3.3.91 (m, 1H), 3.82 (s, 2H), 3.77 (s, 3H), 2.34–2.30 (m, 2H), 2.05 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H), 0.18 (s, 6H), 0.06 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 196.8, 168.8, 156.6, 153.1, 143.7, 132.2, 131.6, 120.5, 119.3, 115.5, 66.9, 51.9, 46.0, 42.3, 25.9 (25.94), 25.9 (25.86), 23.3, 18.5, 18.4, 11.3, −3.9, −4.0; **HRMS** (EI) *m/z* 521.2744 $[(M\text{-}CH_3)^+$; calcd for $C_{27}H_{45}O_6Si_2$: 521.2755].

Method 2: To a solution of **31** (720 mg, 1.5 mmol, 1 eq.) in DCM (10 mL) was added a solution of homoallylic alcohol (+)-**30** (645 mg, 7.5 mmol, 5 eq.) in 5 ml DCM under N_2 atmosphere and a solution of HG-II (19 mg, 0.03 mmol, 0.02 eq.) in DCM (5 mL). The reaction was refluxed for 2 days before being quenched by exposure to air. The mixture was then concentrated and purified via chromatography (EtOAc/hexanes =1/2 to 1/1) to provide the northern hemisphere (+)-**13** (675 mg, 1.26 mmol, 84% yield) as a colorless oil: $[\alpha]_D^{20}$ +5.7 (*c* 1.0, $CHCl_3$); **IR** (film, cm^{-1}) 3436 (br), 2936, 2860, 1714, 1595, 1411, 1261, 1151, 973, 833, 779; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 15.5, 7.6 Hz, 1H), 6.32 (s, 1H), 6.17 (d, *J* = 15.5 Hz, 1H), 3.95–3.91 (m, 1H), 3.82 (s, 2H), 3.77 (s, 3H), 2.34–2.30 (m, 2H), 2.05 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H), 0.18 (s, 6H), 0.06 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 196.8, 168.8, 156.6, 153.1, 143.7, 132.2, 131.6, 120.5, 119.3, 115.5, 66.9, 51.9, 46.0, 42.3, 25.9 (25.94), 25.9 (25.86), 23.3, 18.5, 18.4, 11.3, −3.9, −4.0; **HRMS** (EI) *m/z* 521.2744 $[(M\text{-}CH_3)^+$; calcd for $C_{27}H_{45}O_6Si_2$: 521.2755].

Compound 31.—To a solution of TMP (425 mg, 3 mmol, 1.2 eq.) in THF (5 mL) was added *n*-BuLi (1.2 mL, 2.5 M in hexanes, 3 mmol, 1.2 eq.) at −78 °C. The resulting mixture was warmed to rt and stirred for 30 minutes before cooled to −78 °C. A solution of **22** (1.06 g, 2.5 mmol, 1 eq.) in THF (5 mL) was added and the red solution was stirred at −78 °C for 2 hours before $ZnCl_2$ (6 mL, 0.5 M in THF, 3 mmol, 1.2 eq.) was added. The mixture was stirred for 30 minutes at −78 °C and was then warmed up to rt and stirred for 30 minutes. A solution of $Pd(PPh_3)_4$ (145 mg, 0.125 mmol, 0.05 eq.) in 5 mL THF was prepared under N_2 and was added into the reaction mixture at rt. Acryloyl chloride **29** (495 mg, 5.5 mmol, 2.2 eq.) was then added and the resulting reaction mixture was stirred at rt overnight before quenched by water. The resulting mixture was extracted with EtOAc. The organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/20) to provide the enone **31** (960 mg, 2.0 mmol, 80% yield) as a colorless oil: $[\alpha]_D^{20}$**IR** (film, cm^{-1}) 2939, 2856, 1717, 1597, 1564, 1468, 1409, 1153, 1123, 966, 833, 780, 677; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.5, 10.4 Hz, 1H), 6.30 (s, 1H), 6.25 (d, *J* = 16.9

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Hz, 1H), 5.76 (d, *J* = 11.0 Hz, 1H), 3.87 (s, 2H), 3.76 (s, 3H), 2.05 (s, 3H), 1.01 (s, 9H), 0.98 (s, 9H), 0.18 (s, 6H), 0.05 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 197.2, 168.6, 156.6, 153.1, 135.6, 132.0, 128.5, 120.5, 119.3, 115.5, 51.8, 45.6, 25.9, 25.8, 18.5, 18.4, 11.3, −3.9, −4.1; **HRMS** (EI) *m/z* 463.2338 [$(M\text{-}CH_3)^+$; calcd for $C_{24}H_{39}O_5Si_2$: 463.2336].

Compound 34.—To a solution of **33** (4.1 g, 15 mmol, 1 eq.) in DCM (60 mL) was added 2,6-lutidine (5.14 g, 48 mmol, 3.2 eq.) under N_2 atmosphere at 0 °C. The reaction was stirred at 0 °C for 10 minutes and then TBSOTf (9.5 g, 36 mmol, 2.4 eq.) was added. The resulting mixture was stirred at rt overnight and then was quenched with a sat. $NaHCO_3$ solution, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated and purified via chromatography (EtOAc/hexanes =1/40) to provide the product **34** (6.63 g, 13.2 mmol, 88% yield) as a colorless oil: **IR** (film, cm^{-1}) 2929, 2893, 2858, 1718, 1596, 1473, 1408, 1333, 1256, 1192, 1158, 1066, 966, 835, 781; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.51 (s, 1H), 4.55 (s, 2H), 3.88 (s, 3H), 2.06 (s, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.22 (s, 6H), 0.08 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 168.0, 156.4, 153.0, 134.9, 122.3, 119.0, 114.9, 52.2, 31.6, 25.9, 25.8, 18.5, 18.4, 11.5, −3.8, −4.0; **HRMS** (EI) *m/z* 502.1568 [$(M)^+$; calcd for $C_{22}H_{39}BrO_4Si_2$: 502.1570].

Compound 35.—To a solution of **34** (6.63 g, 13.2 mmol, 1 eq.) in toluene (60 mL) was added DIBAL-H (33 mL, 1 M in toluene, 33 mmol, 2.5 eq.) under N_2 atmosphere at −78 °C. The reaction was then warmed up to 0 °C and stirred for 3 hours. The resulting mixture was quenced with sat. NH_4Cl solution, washed with 0.5 N HCl, and extracted with EtOAc. The organic layers were dried over $MgSO_4$, concentrated and purified via chromatography (EtOAc/hexanes =1/20) to provide the product **35** (5.21 g, 11 mmol, 86% yield) as a white solid: **m.p.** 84–85 °C; **IR** (film, cm^{-1}) 3342 (br), 2929, 2891, 2857, 1572, 1470, 1412, 1324, 1259, 1134, 1075, 996, 839, 780; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 4.75 (s, 2H), 4.62 (s, 2H), 2.07 (s, 3H), 1.79 (br, 1H), 1.05 (s, 9H), 1.01 (s, 9H), 0.22 (s, 6H), 0.19 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 154.6, 153.4, 135.5, 123.6, 121.7, 115.2, 57.0, 32.2, 26.2, 25.9, 18.8, 18.4, 12.0, −3.3, −4.0; **HRMS** (EI) *m/z* 474.1614 [$(M)^+$; calcd for $C_{21}H_{39}BrO_3Si_2$: 474.1621].

Compound 16.—To a solution of the alcohol **35** (4.74 g, 10 mmol, 1 eq.) in DCM (50 mL) was added 2,6-lutidine (2.14 g, 20 mmol, 2.0 eq.) under N_2 atmosphere at 0 °C. The reaction was stirred at 0 °C for 10 minutes and then TBSOTf (3.96 g, 15 mmol, 1.5 eq.) was added. The resulting mixture was stirred at 0 °C for 1 hours and then was quenched with a sat. $NaHCO_3$ solution. The resulting mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/100 to 1/40) to provide the benzyl bromide **16** (5.3 g, 9 mmol, 90% yield) as a colorless oil: **IR** (film, cm^{-1}) 2929, 2890, 2858, 1572, 1473, 1411, 1324, 1257, 1133, 1064, 1005, 958, 839, 779; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 4.79 (s, 2H), 4.72 (s, 2H), 2.05 (s, 3H), 1.05 (s, 9H), 1.01 (s, 9H), 0.88 (s, 9H), 0.21 (s, 6H), 0.12 (s, 6H), 0.06 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 154.1, 152.3, 136.2, 123.8, 121.0, 115.6, 57.3, 32.7, 26.2, 26.1, 25.9, 18.7, 18.4, 18.3, 12.0, −3.5, −4.0, −5.2; **HRMS** (EI) *m/z* 588.2487 [$(M)^+$; calcd for $C_{27}H_{53}BrO_3Si_3$: 588.2486].

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Compound (+)-39.—To a flamed dried flask was added a solution of dithiane linchpin **15** (1.06 g, 5.5 mmol, 1.1 eq.) in Et_2O/THF (10 mL/5 mL) under N_2 atmosphere. The reaction flask was cooled down to −78 °C and *n*-BuLi (2.64 mL, 2.5 M in hexane, 6.6 mmol, 1.32 eq.) was added. The resulting mixture was warmed up to 0 °C for 20 minutes and cooled down to −40 °C. A solution of epoxide (+)-**17** (1.08 g, 5 mmol, 1 eq.) in Et_2O (10 mL) was added. The resulting solution was stirred at −40 °C for 2 hours and then cooled to −50 °C. A premixed solution of **16** (4.4 g, 7.5 mmol, 1.5 eq.) and HMPA (1.8 g, 10 mmol, 2 eq.) in Et_2O (10 mL) was added. The reaction mixture was gradually warmed up to rt and stirred overnight before being quenched with a sat. $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. The adduct **38** was inseparable from the excessive **16**, and was directly used in the next step. To a solution of **38** in THF (40 mL) and H_2O (10 mL) was added $Hg(ClO_4)_2$ (4.0 g, 10 mmol, 2 eq.) and $CaCO_3$ (2.0 g, 20 mmol, 4 eq.). The suspension was stirred vigorously at rt for 30 minutes, then filtrated through Celite. The filtrate was washed with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/20) to provide the advanced intermediate (+)-**39** (2.4 g, 3.2 mmol, 64% yield for 2 steps) as a colorless oil:$[\alpha]_D^{20}$ +11.5 (*c* 1.1, $CHCl_3$); **IR** (film, cm^{-1}) 3519 (br), 2935, 2892, 2859, 1707, 1571, 1469, 1414, 1321, 1255, 1124, 1076, 901, 834, 778; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 4.66–4.61 (m, 2H), 4.15 (m, 1H), 4.08–4.01 (m, 1H), 3.86–3.79 (m, 2H), 3.58–3.57 (m, 1H), 2.62–2.51 (m, 2H), 2.04 (s, 3H), 1.61–1.55 (m, 1H), 1.48–1.44 (m, 1H), 1.15 (d, J = 6.0 Hz, 3H), 1.04 (s, 9H), 0.99 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.18 (s, 6H), 0.09 (s, 6H), 0.07 (s, 6H), 0.00 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 209.3, 154.1, 152.3, 133.0, 123.7, 119.2, 115.5, 68.4, 66.9, 58.2, 49.1, 48.2, 45.7, 26.2, 26.1, 26.0, 25.9, 24.1, 18.7, 18.4, 18.1, 11.9, −3.5, −4.0 (−3.96), −4.0 (−3.99), −4.0 (−4.00), −4.7, −5.1 (−5.10), −5.1 (−5.12); **HRMS** (ESI) *m/z* 777.4765 [$(M+Na)^+$; calcd for $C_{39}H_{78}O_6NaSi_4$: 777.4773].

Compound (−)-41.—To a solution of (+)-**39** (2.04 g, 2.7 mmol, 1 eq.) in MeOH (16 mL) was added $NaAuCl_4$ (dihydrate, 54 mg, 0.13 mmol, 0.05 eq.). The reaction suspension was stirred at rt for 3 hours before quenched with sat. $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/10 to 1/5) to provide the desired product (−)-**41** (809 mg, 1.6 mmol, 59% yield) as a colorless oil: $[\alpha]_D^{20}$ −81.8 (*c* 1.0, $CHCl_3$); **IR** (film, cm^{-1}) 3533 (br), 2933, 2860, 1586, 1471, 1429, 1374, 1316, 1255, 1124, 1053, 984, 903, 836, 779; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.21 (s, 1H), 4.68 (d, *J* = 14.3 Hz, 1H), 4.53 (d, *J* = 14.3 Hz, 1H), 4.22–4.19 (m, 1H), 4.12 (m, 1H), 4.04 (d, *J* = 8.4 Hz, 1H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.64 (d, *J* = 16.5 Hz, 1H), 2.02 (s, 3H), 2.01–1.98 (m, 1H), 1.85–1.76 (m, 2H), 1.49–1.44 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 153.5, 149.9, 128.6, 117.7, 117.3, 112.5, 97.7, 65.3, 61.6, 59.2, 39.6 (39.60), 39.6 (39.59), 38.5, 26.2, 25.9, 21.5, 18.9, 18.4, 11.4, −3.0, −4.0, −4.1; **HRMS** (EI) *m/z* 508.3025 [$(M)^+$; calcd for $C_{27}H_{48}O_5Si_2$: 508.3040].

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Compound (−)-14.—To a solution of (−)-**41** (711 mg, 1.4 mmol, 1 eq.) in 1 mL THF was added TBAF (3.5 mL, 1.0 M in THF, 3.5 mmol, 2.5 eq.) under N_2 atmosphere at 0 °C. The reaction mixture was then stirred at 0 °C for 1 hour and then quenched with a sat. NH_4Cl solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes = 2/1) to provide the southern hemisphere (−)-**14** (360 mg, 1.29 mmol, 92% yield) a white foam.: $[\alpha]_D^{20}$ −92.1 (*c* 1.4, acetone); **IR** (film, cm^{-1}) 3374 (br), 2935, 1602, 1443, 1344, 1235, 1157, 1093, 992, 837; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.92 (s, 1H), 7.26 (s, 1H), 6.17 (s, 1H), 4.74 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J* = 14.3 Hz, 1H), 4.21–4.18 (m, 1H), 4.06–3.94 (m, 1H), 3.82 (d, *J* = 9.3 Hz, 1H), 2.74 (d, *J* = 16.5 Hz, 1H), 2.52 (d, *J* = 16.5 Hz, 1H), 2.09 (s, 3H), 1.92–1.89 (m, 1H), 1.80–1.68 (m, 2H), 1.45–1.37 (m, 1H), 1.09 (d, *J* = 6.2 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 155.3, 151.8, 129.9, 112.9, 109.2, 107.4, 98.0, 65.4, 61.9, 59.2, 40.4 (40.43), 40.4 (40.42), 39.0, 21.7, 8.5; **HRMS** (EI) *m/z* 280.1315 [$(M)^+$; calcd for $C_{15}H_{20}O_5$: 280.1311].

Compound (−)-43.—To a solution of northern hemisphere (+)-**13** (620 mg, 1.15 mmol, 1.5 equiv.) and southern hemisphere (−)-**14** (216 mg, 0.77 mmol, 1 equiv.) in 7.5 mL THF was added CSA (36 mg, 0.16 mmol, 0.2 equiv.). The reaction mixture was evacuated and refilled with N_2 (3 times) and then irradiated (355 nm) for 48 hours. The mixture was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/4 to 1/2) to afford the desired product (−)-**43** (442 mg, 0.55 mmol, 72% yield, *dr* =13:1) as a white foam, in conjunction with the recovery of the southern hemisphere (−)-**14** (39 mg, 0.14 mmol, 18%): $[\alpha]_D^{20}$ −7.5 (*c* 1.1, $CHCl_3$); **IR** (film, cm^{-1}) 3459 (br), 2935, 2861, 1722, 1599, 1566, 1410, 1261, 1152, 1122, 1056, 997, 834, 755; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.25 (s, 1H), 6.76 (s, 1H), 4.76 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J* = 14.3 Hz, 1H), 4.22–4.19 (m, 1H), 4.01 (m, 1H), 3.82–3.73 (m, 1H), 3.79 (s, 3H), 3.70–3.65 (m, 1H), 3.19 (d, *J* = 13.9 Hz, 1H), 3.14 (d, *J* = 13.9 Hz, 1H), 3.08 (m, 1H), 2.72 (d, *J* = 16.5 Hz, 1H), 2.49 (d, *J* = 16.5 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 1.93–1.89 (m, 1H), 1.85–1.80 (m, 2H), 1.72–1.70 (m, 1H), 1.50–1.48 (m, 3H), 1.42–1.40 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.03 (s. 9H), 1.02 (s, 9H), 0.25 (s, 3H), 0.23 (s, 3H), 0.10 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 169.2, 156.2, 153.4, 152.8, 150.2, 134.2, 126.5, 122.7, 120.0, 117.5, 115.9, 113.9, 108.5, 99.8, 98.2, 66.3, 65.5, 62.0, 59.0, 52.1, 44.4, 40.9, 40.5, 38.4, 35.9, 32.9, 26.5, 26.4, 26.3, 22.0, 21.9, 19.2, 19.0, 12.0, 9.0, −3.3, −3.7, −3.9; **HRMS** (ESI) *m/z* 799.4261 [$(M+H)^+$; calcd for $C_{43}H_{67}O_{10}Si_2$: 799.4273].

Compound (+)-45.—To a solution of (−)-**43** (415 mg, 0.52 mmol, 1 eq.) in DCM (8 mL) was added 2,6-lutidine (780 mg, 7.28 mmol, 14 eq.) under N_2 atmosphere at −78 °C. The reaction was stirred at −78 °C for 10 minutes and then TBSOTf (1.37 g, 5.2 mmol, 10 eq.) was added. The resulting mixture was stirred at rt for 5 hours before being quenched by a sat. $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/20) to provide the product (+)-**45** (456 mg, 0.44 mmol, 85% yield) as a colorless oil: $[\alpha]_D^{20}$ +7.3 (*c* 1.4, $CHCl_3$); **IR** (film, cm^{-1}) 2932, 2859, 1726, 1597, 1466,

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1259, 1123, 1057, 1002, 835, 776; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.60 (d, *J* = 14.6 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34–4.28 (m, 1H), 4.15 (m, 1H), 3.80 (s, 3H), 3.73 (m, 1H), 3.21 (d, *J* = 13.9 Hz, 1H), 3.12 (d, *J* = 13.9 Hz, 1H), 2.97 (m, 1H), 2.62 (d, *J* = 16.6 Hz, 1H), 2.42 (d, *J* = 16.6 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 1.90–1.87 (m, 1H), 1.77–1.75 (m, 1H), 1.60–1.53 (m, 3H), 1.46–1.42 (m, 3H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.02 (s. 9H), 1.01 (s, 9H), 0.99 (s, 9H), 0.90 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 169.0, 155.6, 152.9, 151.8, 148.2, 133.1, 126.4, 121.1, 119.9, 117.4, 117.2, 116.6, 112.6, 99.1, 96.2, 65.8, 64.9, 61.2, 59.0, 51.9, 43.8, 40.4 (40.44), 40.4 (40.43), 37.3, 36.1, 31.8, 26.2, 26.0, 25.9, 25.7, 21.7, 21.6, 18.9, 18.6, 18.4, 18.2, 11.6, 10.8, −2.7, −3.0, −3.7 (−3.67), −3.7 (−3.70), −3.9, −4.1, −4.5, −4.7; **HRMS** (ESI) *m/z* 1027.6008 [$(M+H)^+$; calcd for $C_{55}H_{95}O_{10}Si_4$: 1027.6002].

Compound (−)-46.—To a solution of (+)-**45** (456 mg, 0.44 mmol, 1 eq.) in DCM (10 mL) was added DIBAL-H (1.32 mL, 1 M in toluene, 1.32 mmol, 3 eq.) under N_2 atmosphere at −78 °C. The reaction was stirred at −78 °C for 3 hours before being quenched by sat. Rochelle's salt solution (stirring for 1 hour). The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/10) to provide the product (−)-**46** (385 mg, 0.38 mmol, 88% yield) as a white foam: $[\alpha]_D^{20}$ −8.4 (*c* 1.1, $CHCl_3$); **IR** (film, cm^{-1}) 3464 (br), 2934, 2856, 1596, 1466, 1416, 1256, 1124, 1057, 1002, 834, 777; **^{1}H NMR** (500 MHz, acetone-d_6) δ 6.71 (s, 1H), 4.68 (s, 2H), 4.60 (d, *J* = 14.5 Hz, 1H), 4.51 (d, *J* = 14.5 Hz, 1H), 4.32–4.29 (m, 1H), 4.26 (m, 1H), 3.68 (m, 1H), 3.61 (m, 1H), 3.32 (d, *J* = 14.2 Hz, 1H), 3.21 (d, *J* = 14.2 Hz, 1H), 3.15 (m, 1H), 2.69 (d, *J* = 16.8 Hz, 1H), 2.46 (d, *J* = 16.7 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.02–1.99 (m, 1H), 1.90–1.87 (m, 1H), 1.75–1.69 (m, 2H), 1.63–1.60 (m, 1H), 1.54–1.43 (m, 3H), 1.08–1.03 (m, 24H), 1.03 (s, 9H), 0.93 (s, 9H), 0.22 (m, 18H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 154.2, 153.8, 149.0, 135.3, 127.9, 126.9, 119.1, 118.4, 117.8 (117.80), 117.8 (117.78), 112.8, 100.0, 96.9, 66.8, 65.9, 61.8, 59.3, 57.0, 44.1, 41.6, 41.1, 38.3, 36.6, 33.6, 26.9, 26.7, 26.6, 26.4, 26.3, 22.0, 21.7, 19.6 (19.61), 19.6 (19.57), 19.1, 18.8, 12.5, 11.4, −2.4, −2.8, −3.0, −3.7, −4.3, −4.4; **HRMS** (ESI) *m/z* 1021.5856 [$(M+Na)^+$; calcd for $C_{54}H_{94}O_9NaSi_4$: 1021.5873].

Compound (+)-1.—To a solution of the alcohol (−)-**46** (340 mg, 0.34 mmol, 1 eq.) in DCM (12 mL) was added DMP (283 mg, 0.68 mmol, 2 eq.) and $NaHCO_3$ (283 mg, 3.4 mmol, 10 eq.). The reaction was stirred at rt for one hour. The resulting mixture was filtered through Celite and concentrated. The crude product was a mixture of the fully-protected aldehyde and ortho-OH aldehyde and was directly used in the next step. To the crude mixture was added TBAF solution (2 mL, 1 M in THF) under N_2 atmosphere at rt. The reaction was stirred at rt for 36 hours before being quenched by sat NH_4Cl solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =2/1) to provide the (+)-**1** (112 mg, 0.21 mmol, 62% yield for 2 steps) as a white foam: **m.p.** 185–187 °C decompose; $[\alpha]_D^{20}$ +1.8 (*c* 1.0, acetone, value obtained from the crystalized sample); **IR** (film, cm^{-1}) 3370 (br), 2971, 2931, 2873, 1705, 1616, 1445, 1355, 1304, 1254, 1166, 1122,

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1097, 1049, 970, 929, 877, 852, 788, 740; **^{1}H NMR** (500 MHz, acetone-d_6) δ 12.96 (s, 1H), 10.26 (s, 1H), 9.36 (br, 1H), 7.27 (br, 1H), 6.55 (s, 1H), 4.74 (d, J = 14.6 Hz, 1H), 4.54 (d, J = 14.6 Hz, 1H), 4.23–4.17 (m, 1H), 4.01 (m, 1H), 3.77 (d, J = 9.3 Hz, 1H), 3.66–3.59 (m, 1H), 3.41 (d, J = 14.0 Hz, 1H), 3.28 (d, J = 14.0 Hz, 1H), 3.13 (m, 1H), 2.72 (d, J = 16.8 Hz, 1H), 2.50 (d, J = 16.8 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.98 (dd, J = 12.6, 2.3 Hz, 1H), 1.92 (bd, J = 14.3 Hz, 1H), 1.84 (dd, J = 14.3, 3.5 Hz, 1H), 1.71 (bd, J = 13.0 Hz, 1H), 1.63 (dd, J = 12.5, 2.6 Hz, 1H), 1.58–1.52 (m, 2H), 1.43 (td, J = 13.3, 2.4 Hz, 1H), 1.09 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.1 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 196.6, 164.7, 162.9, 153.2, 150.2, 140.4, 126.5, 115.7, 114.4, 114.1, 113.2, 110.5, 108.6, 98.7, 98.2, 66.5, 65.4, 61.9, 58.9, 42.7, 40.8, 40.4, 38.3, 35.9, 33.7, 26.4, 21.8, 21.6, 8.9, 7.4; (ESI) *m/z* 563.2261 [(M+Na)$^+$; calcd for $C_{30}H_{36}O_9Na$: 563.2268].

The synthetic (+)-**1** was further recrystallized from MeOH as a colorless crystal. 60 mg of synthetic peniciketal A was dissolved in 6 mL hot methanol. The solution was cooled down to 0 °C slowly and kept in the refrigerator at 0 °C overnight. 29 mg colorless crystals were collected as (+)-**1** tri-methanol crystal ($C_{30}H_{36}O_9$•3CH3OH).

Compound (−)-48.—To a solution of (−)-**41** (240 mg, 0.47 mmol, 1 eq.) in 24 mL DCM was added pentafluorophenyl chlorothionoformate (371 mg, 1.4 mmol, 3 eq.) and pyridine (186 mg, 2.35 mmol, 5 eq.) under N_2 atmosphere at rt. The reaction mixture was then stirred at rt overnight and then quenched with a sat. NH_4Cl solution, washed with 0.5% HCl solution, sat. $NaHCO_3$ and water. The resulting mixture was dried over $MgSO_4$ and concentrated. The crude yellow product was then dissolved in 7 mL and refluxed under N_2 atmosphere. A mixture of Bu_3SnH (440 mg, 1.5 mmol, 3 eq.) and AIBN (37 mg, 0.23 mmol, 0.5 eq.) dissolved in 3 mL toluene was then added to the hot solution. After being heated for 15 min, the color faded and there action was quenched by 0.1 mL water. The solvent was then removed, and the crude was purified via chromatography (EtOAc/hexanes = 1/20) to provide (−)-**48** (185 mg, 0.38 mmol, 80% yield) as a colorless oil: $[\alpha]_D^{20}$ −59.3 (*c* 1.0, $CHCl_3$); **IR** (film, cm^{-1}) 2935, 2861, 1582, 1472, 1372, 1254, 1125, 1001, 904, 835, 779; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.21 (s, 1H), 4.64 (d, J = 14.5 Hz, 1H), 4.49 (d, J = 14.3 Hz, 1H), 3.87–3.84 (m, 1H), 2.77 (d, J = 16.5 Hz, 1H), 2.62 (d, J = 16.6 Hz, 1H), 2.02 (s, 3H), 1.96–1.94 (m, 1H), 1.75–1.65 (m, 1H), 1.65–1.52 (m, 3H), 1.25–1.19 (m, 1H), 1.10 (d, J = 6.3 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.18 (s, 3H), 0.17 (s, 9H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 153.3, 150.0, 129.7, 118.2, 117.4, 112.6, 95.8, 66.9, 59.1, 39.0, 34.3, 32.6, 26.2, 26.0, 21.9, 19.3, 18.9, 18.4, 11.4, −2.9, −4.0, −4.1; **HRMS** (EI) *m/z* 492.3102 [(M)$^+$; calcd for $C_{27}H_{48}O_4Si_2$: 492.3091].

Compound (−)-49.—To a solution of (−)-**48** (185 mg, 0.38 mmol, 1 eq.) in 1 mL THF was added TBAF (1 mL, 1.0 M in THF, 1.0 mmol, 2.6 eq.) under N_2 atmosphere at rt. The reaction mixture was then stirred at rt for 1 hour before being quenched with a sat. NH_4Cl solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography column chromatography (EtOAc/hexanes = 1/3) to provide the southern hemisphere (−)-**49** (90 mg, 0.34 mmol, 89% yield) as a white foam.: $[\alpha]_D^{20}$ −68.3 (*c* 1.0, acetone); **IR** (film, cm^{-1}) 3373 (br), 2938, 1602, 1446, 1343, 1229, 1185, 1092, 996, 822; **^{1}H NMR** (500 MHz, acetone-d_6)

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δ 7.86 (br, 1H), 7.18 (br, 1H), 6.16 (s, 1H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.3 Hz, 1H), 3.85–3.79 (m, 1H), 2.66 (d, *J* = 16.6 Hz, 1H), 2.49 (d, *J* = 16.4 Hz, 1H), 2.08 (s, 3H), 1.94–1.89 (m, 1H), 1.70–1.67 (m, 1H), 1.61–1.59 (m, 2H), 1.53–1.46 (m, 1H), 1.17–1.12 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-d_6) δ 155.0, 151.8, 130.7, 113.5, 108.9, 107.4, 96.0, 67.2, 58.8, 39.3, 35.0, 33.2, 22.0, 19.9, 8.4; **HRMS** (EI) *m/z* 264.1355 [(M)$^+$; calcd for $C_{15}H_{20}O_4$: 264.1362].

Compound (−)-47.—To a solution of northern hemisphere (+)-**13** (209 mg, 0.39 mmol, 1.5 equiv.) and southern hemisphere (−)-**49** (69 mg, 0.26 mmol, 1 equiv.) in 2 mL THF was added CSA (12 mg, 0.04 mmol, 0.2 equiv.). The reaction mixture was then irradiated (355 nm) for 48 hours before being quenched with sat. $NaHCO_3$. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/8 to 1/3) to afford the desired product (−)-**47** (148 mg, 0.19 mmol, 73% yield, *dr* =12:1) as a white foam, in conjunction with the recovery of the southern hemisphere (−)-**49** (15 mg, 0.057 mmol, 22%): $[\alpha]_D^{20}$ −1.1 (*c* 1.3, $CHCl_3$); **IR** (film, cm^{-1}) 3435 (br), 2937, 2861, 1722, 1599, 1410, 1262, 1123, 1057, 1000, 835, 756, 674; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 4.72 (d, *J* = 14.6 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 4.49 (br, 1H), 3.88–3.85 (m, 1H), 3.81 (s, 3H), 3.78–3.73 (m, 1H), 3.22 (d, *J* = 14.0 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 3.00 (m, 1H), 2.63 (d, *J* = 16.4 Hz, 1H), 2.48 (d, *J* = 16.7 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 3H), 2.00–1.92 (m, 1H), 1.80–1.75 (m, 2H), 1.64–1.52 (m, 4H), 1.47–1.45 (m, 2H), 1.23–1.21 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.01 (s. 9H), 0.99 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 169.0, 155.6, 152.3, 151.9, 148.3, 133.0, 126.7, 121.1, 119.9, 117.0, 115.8, 112.8, 106.4, 99.3, 95.7, 66.8, 65.8, 57.8, 51.9, 43.7, 37.4, 35.6, 34.7, 32.6, 31.8, 26.0, 25.9, 25.7, 21.9, 21.5, 19.4, 18.6, 18.4, 11.6, 8.1, −3.7 (−3.66), −3.7 (−3.69), −3.9, −4.1; **HRMS** (ESI) *m/z* 783.4327 [(M+H)$^+$; calcd for $C_{43}H_{67}O_9Si_2$: 783.4324].

Compound (+)-50.—To a solution of (−)-**47** (117 mg, 0.15 mmol, 1 eq.) in DCM (4 mL) was added 2,6-lutidine (225 mg, 2.1 mmol, 14 eq.) under N_2 atmosphere at 0 °C. The reaction was stirred at 0 ^{o}C for 10 minutes and then TBSOTf (317 mg, 1.2 mmol, 8 eq.) was added. The resulting mixture was stirred at rt for 5 hours before being quenched with a sat. $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/20) to provide the product (+)-**50** (122 mg, 0.14 mmol, 91% yield) as a white foam: $[\alpha]_D^{20}$ +11.6 (*c* 1.3, $CHCl_3$); **IR** (film, cm^{-1}) 2936, 2861, 1724, 1595, 1465, 1260, 1129, 1058, 1001, 969, 836, 758, 674; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.63 (d, *J* = 14.3 Hz, 1H), 4.47 (d, *J* = 14.0 Hz, 1H), 3.90–3.83 (m, 1H), 3.81 (s, 3H), 3.80–3.73 (m, 1H), 3.23 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.8 Hz, 1H), 2.99 (m, 1H), 2.64 (d, *J* = 16.7 Hz, 1H), 2.45 (d, *J* = 16.6 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.00–1.92 (m, 1H), 1.78–1.72 (m, 2H), 1.64–1.55 (m, 4H), 1.47–1.43 (m, 2H), 1.23–1.21 (m, 1H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.02 (s. 9H), 1.01 (s, 9H), 0.99 (s, 9H), 0.18 (s, 9H), 0.15 (s, 3H), 0.07 (s, 6H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 169.0, 155.6, 153.0, 151.8, 148.2, 133.1, 126.2, 121.1, 119.9, 117.3, 117.1, 116.7, 112.6, 99.2, 95.8, 66.8, 65.8, 58.7, 51.9, 43.8, 37.3, 35.8, 34.7,

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32.5, 31.7, 26.2, 26.0, 25.9, 25.7, 21.9, 21.6, 19.4, 18.8, 18.6, 18.4, 11.6, 10.7, −2.7, −3.0, −3.7 (−3.67), −3.7 (−3.71), −3.9, −4.2; **HRMS** (ESI) *m/z* 919.4999 [(M+Na)$^+$; calcd for $C_{49}H_{80}O_9NaSi_3$: 919.5008].

Compound (−)-51.—To a solution of (+)-**50** (106 mg, 0.12 mmol, 1 eq.) in DCM (1 mL) was added DIBAL-H (0.36 mL, 1 M in toluene, 0.36 mmol, 3 eq.) under N_2 atmosphere at −78 °C. The reaction was stirred at −78 °C for 3 hours before being quenched by the addition of sat. Rochelle's salt solution. The resulting mixture was stirred for 1 hour at rt. The crude mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/10) to provide the product (−)-**51** (80 mg, 0.09 mmol, 78% yield) as a white foam: $[\alpha]_D^{20}$ −9.9 (*c* 1.4, CH_2Cl_2); **IR** (film, cm^{-1}) 3464 (br), 2935, 2857, 1596, 1466, 1415, 1257, 1128, 1058, 1002, 835, 781; **^{1}H NMR** (500 MHz, acetone-*d*$_6$) δ 6.72 (s, 1H), 4.69 (d, *J* = 5.0 Hz, 2H), 4.61 (d, *J* = 14.4 Hz, 1H), 4.50 (d, *J* = 14.3 Hz, 1H), 3.85–3.82 (m, 1H), 3.71–3.66 (m, 1H), 3.61 (t, *J* = 5.2 Hz, 1H), 3.33 (d, *J* = 14.2 Hz, 1H), 3.21 (d, *J* = 14.3 Hz, 1H), 3.18 (m, 1H), 2.69 (d, *J* = 16.8 Hz, 1H), 2.50 (d, *J* = 16.8 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.02–2.01 (m, 1H), 1.98–1.89 (m, 1H), 1.72–1.69 (m, 2H), 1.62–1.51 (m, 5H), 1.20–1.16 (m, 1H), 1.07–1.06 (m, 24H), 1.04 (s, 9H), 0.23 (m, 18H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-*d*$_6$) δ 154.2, 153.8, 149.0, 135.3, 127.8, 126.9, 119.1, 118.2, 117.8 (117.78), 117.8 (117.77), 112.8, 100.0, 96.4, 67.4, 66.8, 59.3, 56.9, 44.0, 38.2, 36.4, 35.4, 33.5, 33.3, 26.8, 26.6, 26.5, 26.4, 22.3, 21.7, 20.1, 19.6, 19.5, 19.0, 12.5, 11.4, −2.5, −2.8, −3.0, −3.7; **HRMS** (ESI) *m/z* 891.5059 [(M+Na)$^+$; calcd for $C_{48}H_{80}O_8NaSi_3$: 891.5059].

Compound (+)-2.—To a solution of the alcohol (−)-**51** (60 mg, 0.069 mmol, 1 eq.) in DCM (1 mL) was added PCC (30 mg, 0.14 mmol, 2 eq.), $NaHCO_3$ (30 mg, 0.35 mmol, 5 eq.) and 30 mg 4Å molecular sieves. The reaction was stirred at rt for 1.5 hours and then filtered through Celite. The crude product was concentrated and directly used in the next step. To a solution of crude product in THF (0.8 mL) was added TBAF (0.13 mL, 1 M in THF) under N_2 atmosphere at rt. The crude mixture was stirred at rt for 1 hour before being quenched by sat NH_4Cl solution. The mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/2) to provide (+)-**2** (22 mg, 0.042 mmol, 61% yield for 2 steps) as a white foam: $[\alpha]_D^{20}$ +12.9 (*c* 1.1, acetone); **IR** (film, cm^{-1}) 3264, 2933, 2905, 1704, 1620, 1446, 1373, 1355, 1304, 1253, 1163, 1122, 1089, 1053, 998, 974, 926, 873, 755; **^{1}H NMR** (500 MHz, acetone-*d*$_6$) δ 12.96 (s, 1H), 10.26 (s, 1H), 9.36 (br, 1H), 7.19 (br, 1H), 6.54 (s, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.47 (d, *J* = 14.6 Hz, 1H), 3.82 (m, 1H), 3.64 (m, 1H), 3.40 (d, *J* = 14.0 Hz, 1H), 3.28 (d, *J* = 14.0 Hz, 1H), 3.14 (m, 1H), 2.65 (d, *J* = 16.7 Hz, 1H), 2.47 (d, *J* = 16.7 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.98 (dd, *J* = 12.5, 2.5 Hz, 1H), 1.93 (m, 1H), 1.71–1.69 (m, 1H), 1.64–1.53 (m, 6H), 1.22–1.13 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H); **^{13}C {^{1}H} NMR** (125 MHz, acetone-*d*$_6$) δ 196.6, 164.7, 162.8, 153.0, 150.2, 140.4, 127.3, 115.6, 114.8, 114.4, 113.2, 110.5, 108.4, 98.6, 96.3, 67.3, 66.5, 58.5, 42.7, 38.3, 36.1, 35.4, 33.8, 33.3, 30.7, 26.4, 22.2, 21.6, 20.1, 8.9, 7.5; **HRMS** (ESI) *m/z* 525.2477 [(M+H)$^+$; calcd for $C_{30}H_{37}O_8$: 525.2488].

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Compound (−)-55.—To a solution of (−)-**53** (352 mg, 2 mmol, 1 eq.)[15] in DCM (12 mL) was added a solution of enone **54** (1.32 g, 10 mmol, 5 eq.) in 6 ml DCM under N_2 atmosphere and a solution of HG-II (25 mg, 0.04 mmol, 0.02 eq.) in DCM (6 mL). The resulting mixture was heated to reflux for 2 days before being quenched by exposure to air. The mixture was then concentrated and purified via chromatography (EtOAc/hexanes =1/2 to 1/1) to provide (−)-**55** (457 mg, 1.63 mmol, 82% yield) as a colorless oil:$[\alpha]_D^{20}$ −8.3 (*c* 1.0, $CHCl_3$); **IR** (film, cm^{-1}) 3437 (br), 3028, 2927, 1663, 1617, 1446, 1229, 984, 749, 695; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.60–7.55 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.22–7.19 (m, 3H), 7.06 (dt, *J* = 14.7, 7.2 Hz, 1H), 6.97 (d, *J* = 15.5 Hz, 1H), 3.88–3.83 (m, 1H), 2.86–2.69 (m, 2H), 2.57–2.46 (m, 2H), 1.88–1.83 (m, 2H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 190.5, 145.3, 141.7, 137.8, 133.0, 128.7 (128.73), 128.7 (128.67), 128.7 (128.65), 128.6, 128.5, 126.2, 70.1, 41.1, 39.0, 32.1; **HRMS** (ESI) *m/z* 281.1537 [$(M+H)^+$; calcd for $C_{19}H_{21}O_2$: 281.1542].

Compound (−)-5.—To a solution of (−)-**55** (56 mg, 0.2 mmol, 1 equiv.) and **12** (36 mg, 0.4 mmol, 2 equiv.) in 2 mL THF/DMF (3:1) solution was added CSA (9.3 mg, 0.16 mmol, 0.2 equiv.). (−)-**55** is not dissolvable in THF so a mixture solvent of THF/DMF is necessary. The reaction mixture was evacuated and refilled with N_2 (3 times) and then irradiated (355 nm) for 48 hours. The mixture was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified via chromatography (EtOAc/hexanes =1/1) to afford the desired product (−)-**5** (48 mg, 0.14 mmol, 68% yield, *dr* >20:1) as a white solid: $[\alpha]_D^{20}$ −113.0 (*c* 0.83, MeOH); **IR** (film, cm^{-1}) 3427, 2927, 2865, 1493, 1452, 1307, 1241, 1061, 913, 816, 756; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.54 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.2, Hz, 1H), 5.45 (s, 1H), 4.29 (m, 1H), 4.01 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 8.7 Hz, 1H), 3.77 (d, *J* = 9.2 Hz, 1H), 3.51 (d, *J* = 8.7 Hz, 1H), 2.66–2..61 (m, 3H), 1.80 (d, *J* = 14.3 Hz, 1H), 1.78–1.58 (m, 3H); **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 144.6, 141.9, 128.4, 128.2, 127.8, 127.6, 125.8, 125.7, 107.5, 87.8, 78.3, 76.7, 75.1, 63.7, 52.6, 36.8, 32.1, 30.8; **HRMS** (ESI) *m/z* 353.1753 [$(M+H)^+$; calcd for $C_{22}H_{25}O_4$: 353.1753].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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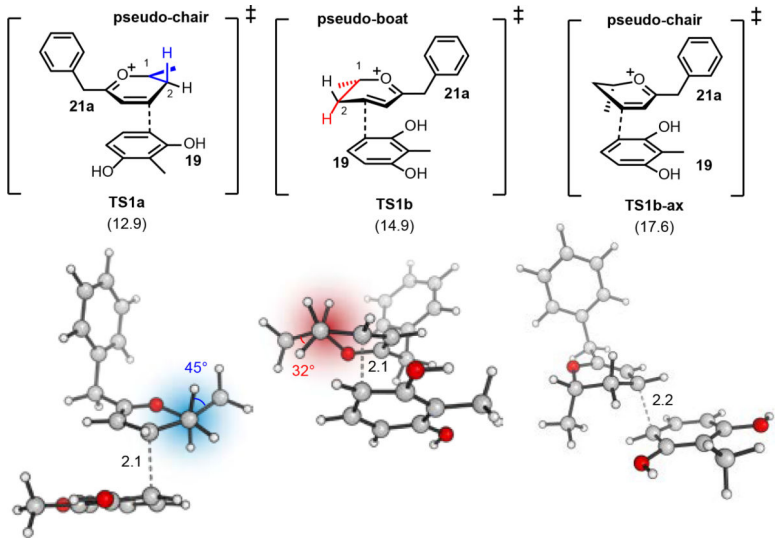

Figure 1.

Computed structures and relative free energies of stereoselective Michael addition transition states with ωB97X-D/def2svp/CPCM(THF) method. Free energies are in kcal/mol and relative to the separated species of **21a** and **19**.

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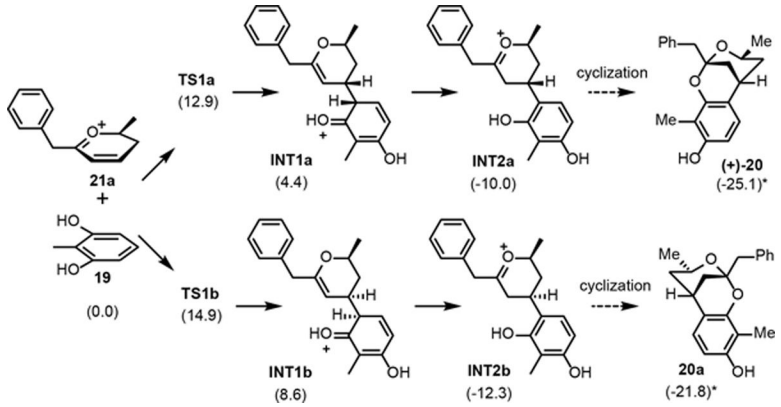

Figure 2.

Computed relative free energies of the key species along the reaction pathways. Free energies are in kcal/mol and relative to the separated species of **21a** and **19**. *Free energies relative to (+)-**21** and **19**.

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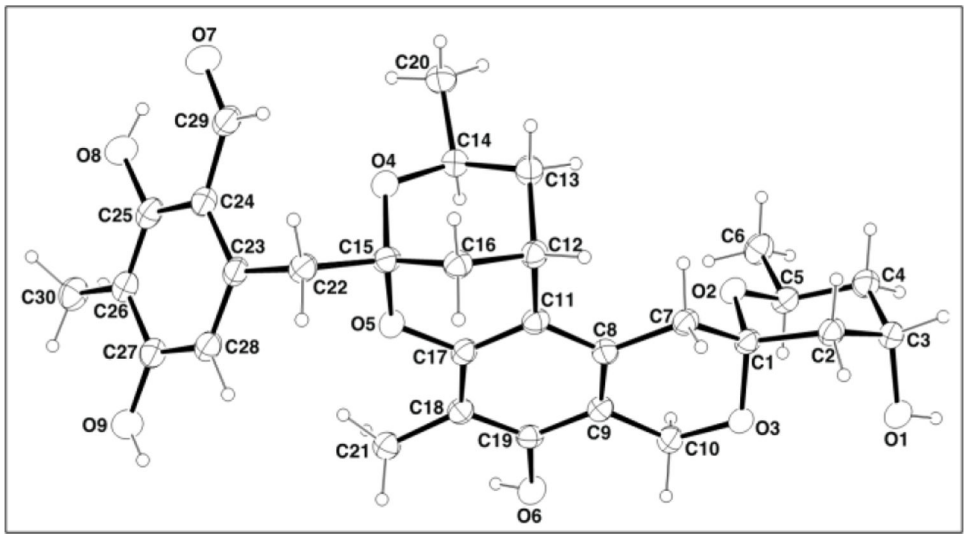

Figure 3.
X-Ray structure determination of (+)-**1**

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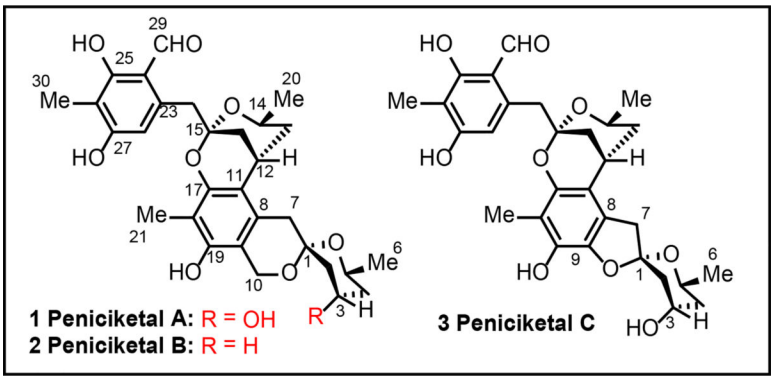

Scheme 1. (+)-Peniciketal A-C

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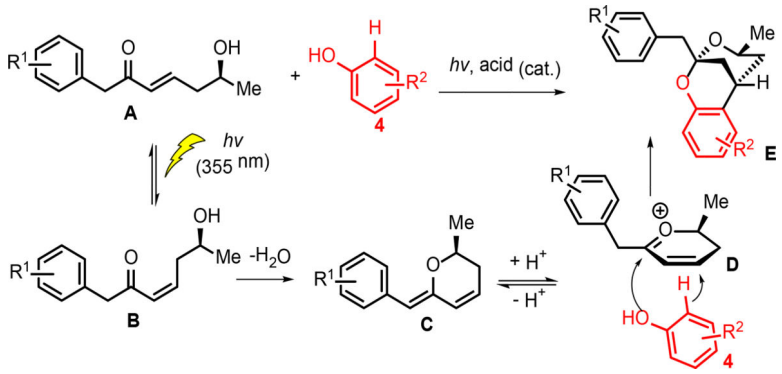

Scheme 2. The Proposed Photochemical Union Tactic for Peniciketals A-C

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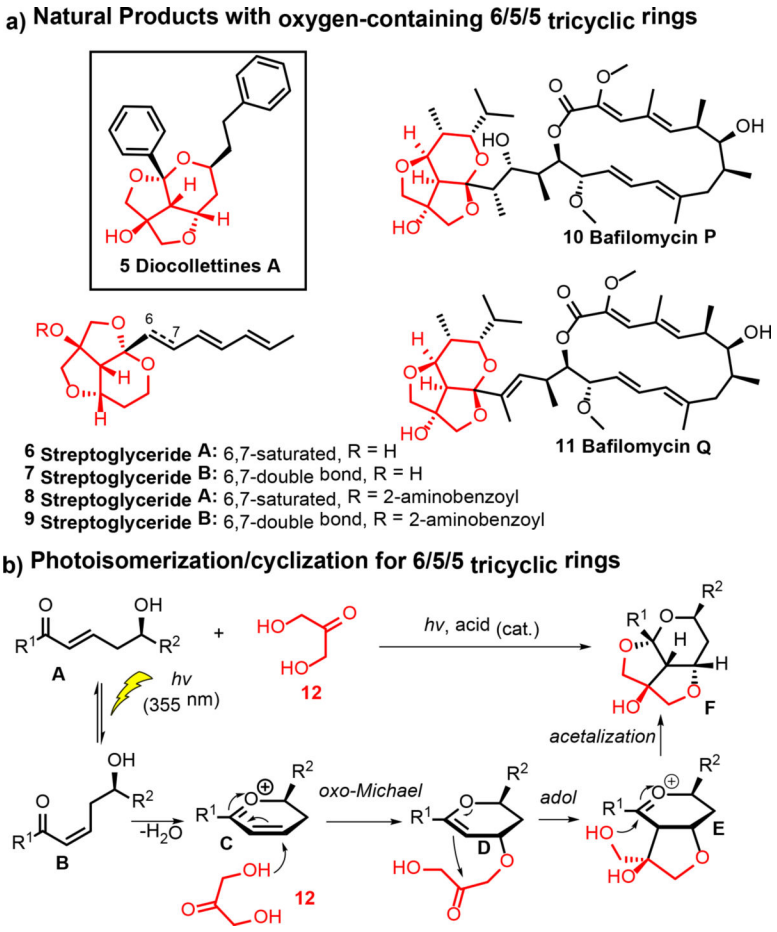
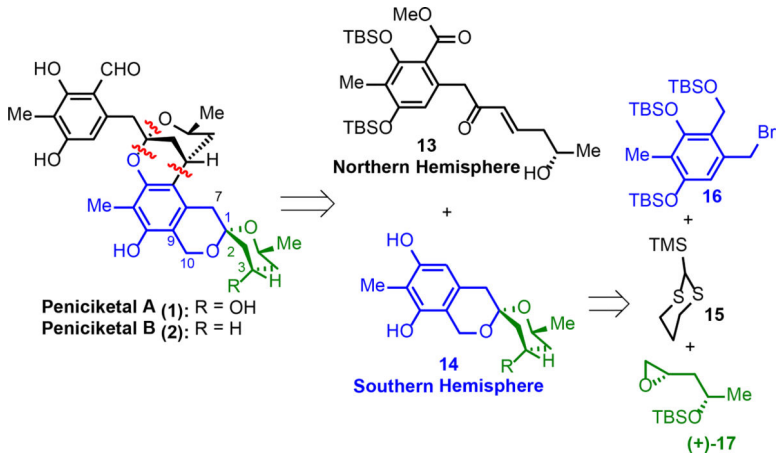


Scheme 3. Photoisomerization/cyclization Union Strategy for 6/5/5 Tricyclic Rings



Scheme 4. Retrosynthetic Analysis of the Unified Synthesis of Peniciketals A-C

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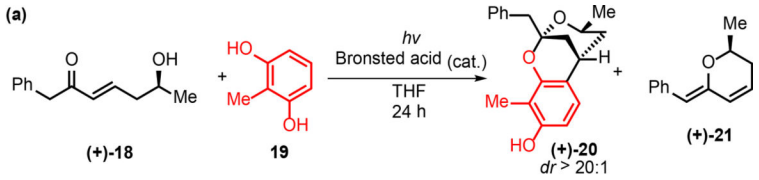
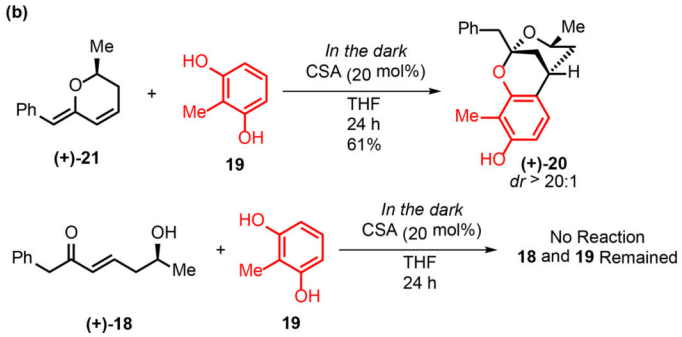
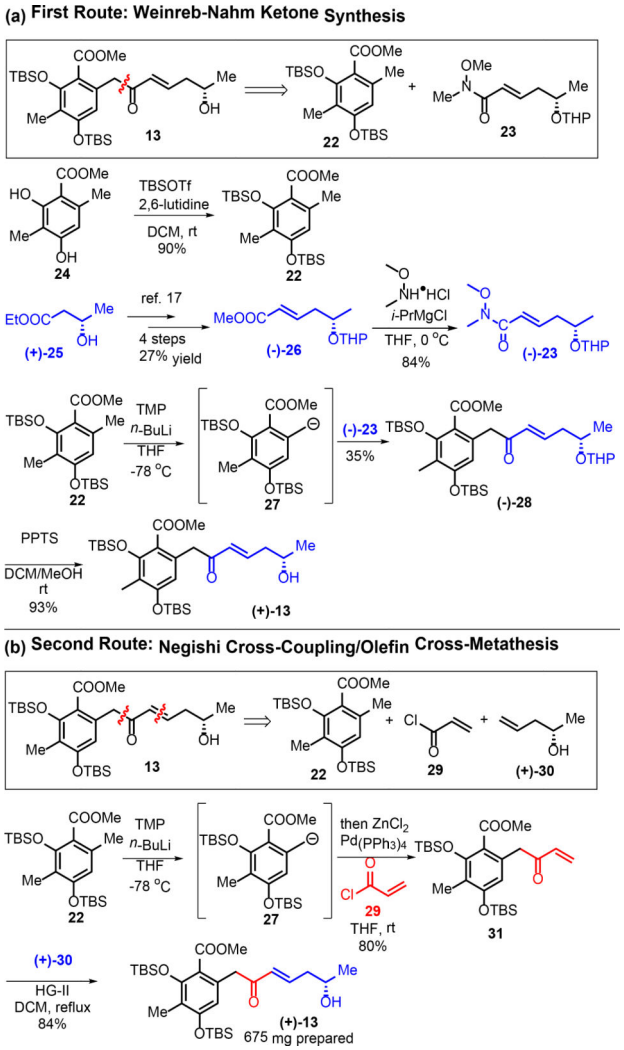


entry	concentration	Bronsted acid (cat.)	yield[a] (%) of **20**
1	0.1 M	PTSA (20 mol%)	45
2	0.2 M	PTSA (20 mol%)	71
3	**0.2 M**	**CSA (20 mol%)**	**80**
4	0.2 M	PPTS (50 mol%)	49

[a]Reaction conditions: All yields are isolated. Bronsted acid (cat.), (+)-**18** (0.2 mmol) and **19** (0.2 mmol) were irradiated by UV-A light (λ=355 nm) in THF at rt for 24 h. *dr* was measured by ^{1}H NMR.



Scheme 5. Model Studies and Control Experiments



Scheme 6. Synthesis of the Northern Hemisphere (+)-13

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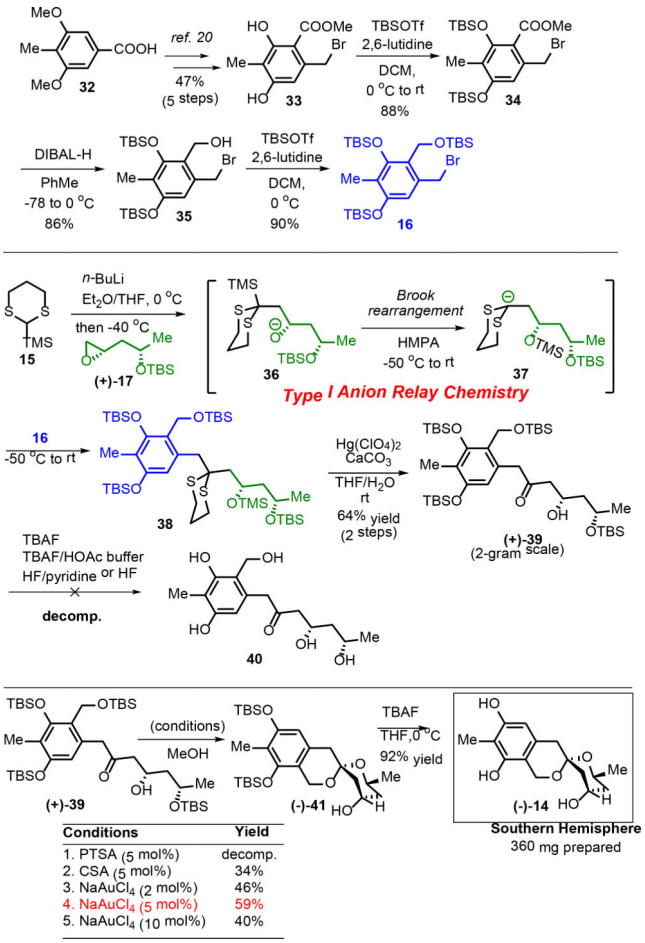

Scheme 7. Synthesis of the Southern Hemisphere (−)-14

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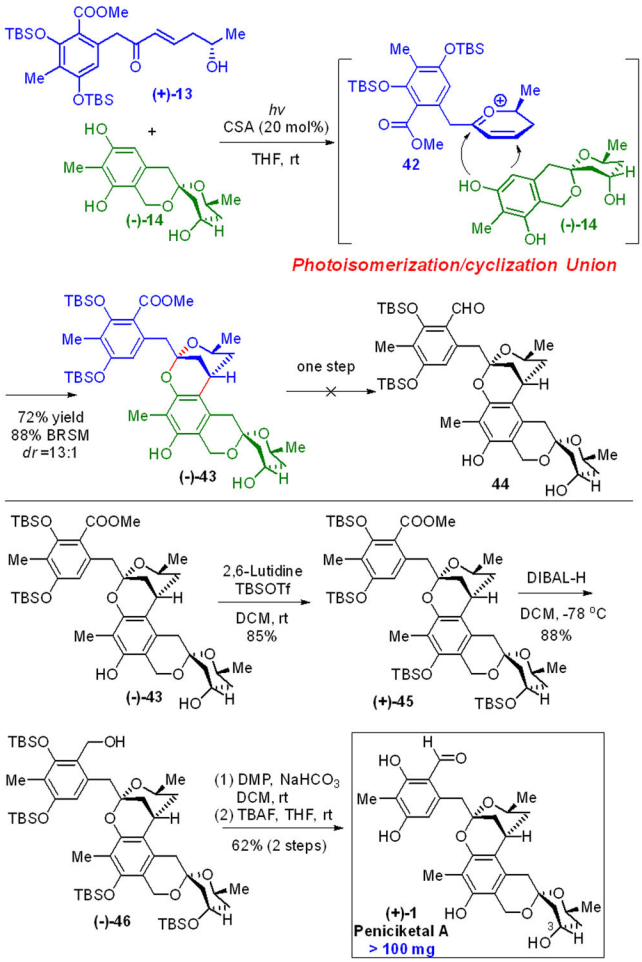

Scheme 8. Total Synthesis of (+)-Peniciketal A

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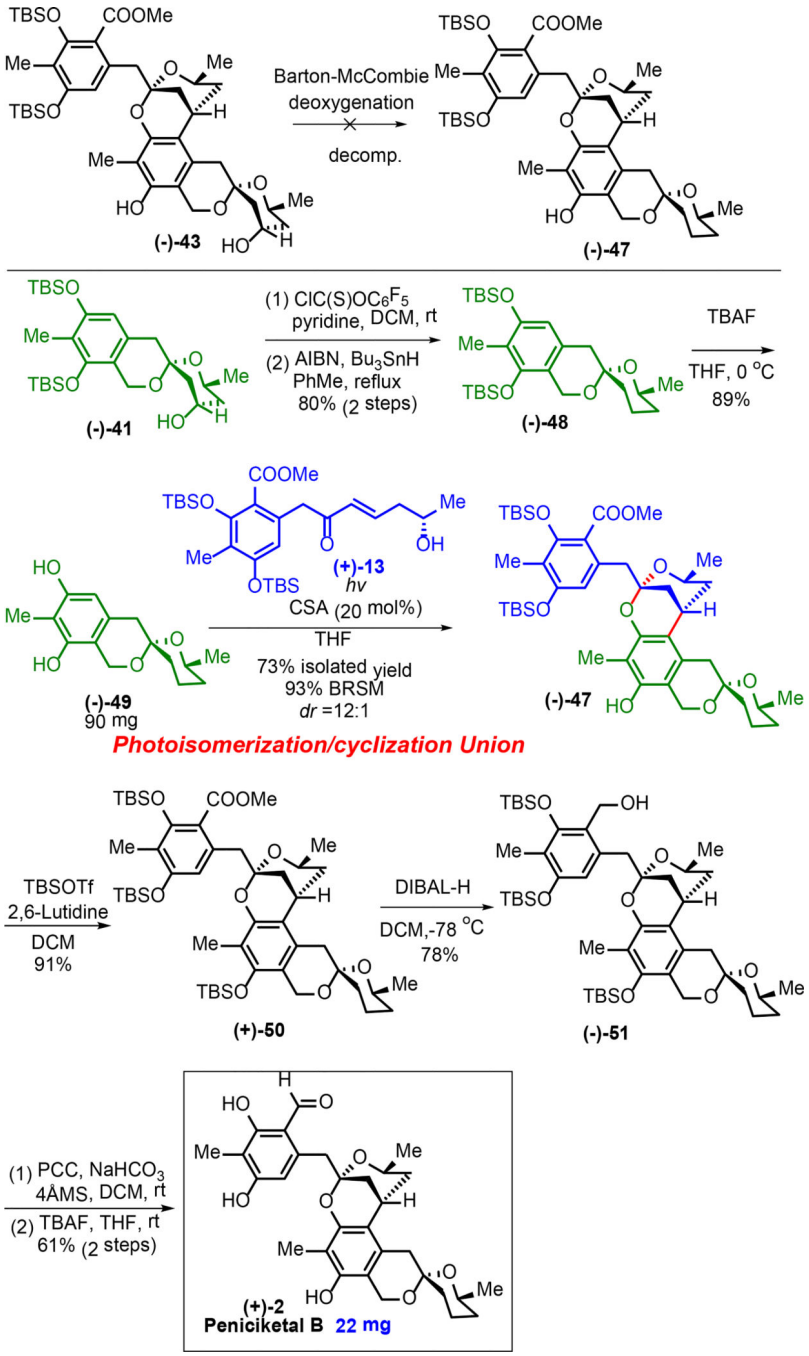
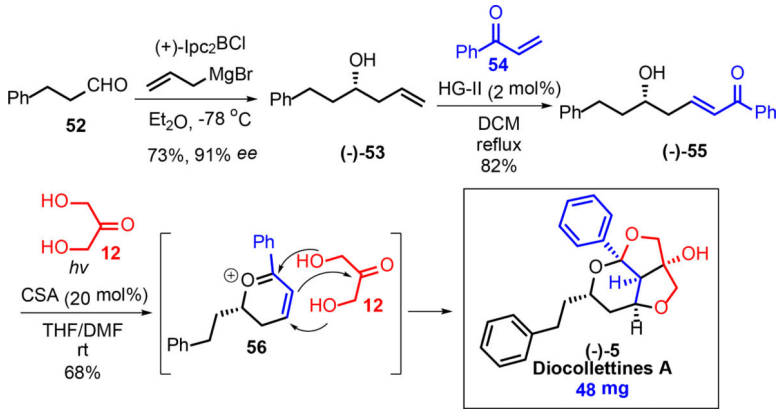


Scheme 9. Total Synthesis of (+)-Peniciketal B



Scheme 10. Total Synthesis of (−)-Diocollettines A

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Table 1.

Biological Evaluation of Synthetic Peniciketals

Cell Lines	**(+)-1**	**(+)-2**
Lung Cancer Cells A549	16.4 μM	6.8 μM
Lung Cancer Cells H1975	14.3 μM	7.3 μM
Lung Normal Cells IMR90	> 50 μM	38 μM