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Shupeng Zhou, Kaifu Xia, Ang Li

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We have accomplished the asymmetric total synthesis of arcutinidine and arcutinine, two arcutine-type C20-diterpenoid alkaloids. A pentacyclic intermediate was rapidly assembled by using two Diels–Alder reactions. A cascade sequence of Prins cyclization and Wagner–Meerwein rearrangement was then developed to construct the core of arcutinidine, which was further elaborated into an oxygenated pentacycle through a scalable route. Chemoselective reductive amination followed by spontaneous imine formation furnished the pyrroline motif at a final stage.

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Asymmetric Total Synthesis of Arcutinidine and Arcutinine

Shupeng Zhou, Kaifu Xia, and Ang Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information Placeholder

ABSTRACT: We have accomplished the asymmetric total synthesis of arcutinidine and arcutinine, two arcutine-type C₂₀-diterpenoid alkaloids. A pentacyclic intermediate was rapidly assembled by using two Diels–Alder reactions. A cascade sequence of Prins cyclization and Wagner–Meerwein rearrangement was then developed to construct the core of arcutinidine, which was further elaborated into an oxygenated pentacycle through a scalable route. Chemoselective reductive amination followed by spontaneous imine formation furnished the pyrroline motif at a final stage.

The C₂₀-diterpenoid alkaloids¹ have long been attractive targets for chemical synthesis from the structural and biological perspectives.² Among them, members from the atisine,³ hetisine,⁴ denudatine,⁵ veatchine,⁶ napelline,⁷ and hetidine^{8,9} subclasses have been conquered by synthetic chemists. Nearly two decades ago, Bassonova and co-workers reported the discovery of two intricate C₂₀-diterpenoid alkaloids arcutine (**1**, Figure 1) and arcutinine (**2**) and their presumed biogenetic precursor arcutinidine (**3**). Their scaffold possesses two doubly fused bicyclo[2.2.2]octane moieties (Figure 1; highlighted in blue) and a congested pyrroline motif.¹⁰ Of note, a non-alkaloidal natural product atropurpuran (**4**) relevant to **1–3** was later discovered by Wang and colleagues.¹¹ Compared to the alkaloids, diterpenoid **4** has drawn considerable attention from the synthesis community.^{12–14} Suzuki et al. first disclosed an inspiring approach for construction of the core of **4**,^{12a} and the Qin¹³ and Xu¹⁴ groups recently accomplished elegant syntheses of this molecule in a racemic form, respectively. Obviously, the pyrroline and tertiary alcohol within the alkaloids pose an additional challenge for chemical synthesis. Right before our submission of this paper, Qin and co-workers disclosed a beautiful enantioselective synthesis of arcutinidine and arcutinine.¹⁵ During the course of our synthesis of hetidine type alkaloids,⁹ we were intrigued by the relationship between the hetidine and arcutine skeletons. Wang and Liang recognized the arcutine skeleton as a rearrangement product of the hetidine or hetisine skeleton.^{1a} More specifically, Sarpong and colleagues proposed a Wagner–Meerwein type 1,2-alkyl shift (Figure 1; key bonds highlighted in red) responsible for the biogenesis of the arcutine skeleton from the hetidine skeleton, and carried out DFT calculations to support this insightful hypothesis.¹⁶ Indeed, tongolinine (**5**) bearing a tertiary alcohol may serve as a precursor of the carbocation species required for initiating the

Wagner–Meerwein pathway. Our experience¹⁷ with Prins reaction suggested an opportunity to generate a carbocation species at the end of this powerful C–C bond forming reaction.¹⁸ Herein, we report an asymmetric total synthesis of **1** and **2**.¹⁹

Figure 1. The structures of representative arcutine type alkaloids (**1–3**) and related natural products [atropurpuran (**4**) and tongolinine (**5**)] and the postulated biogenetic relationship between the hetidine and arcutine skeletons.

We first undertook a retrosynthetic analysis of **1** (Figure 2). Disassembly of the pyrroline within **1** gave diketolaldehyde **6**; chemoselective reductive amination of the aldehyde functionality of **6** could be a challenge at a late stage of the synthesis.⁹ Compound **6** may arise from less oxygenated intermediate **7**. Position-selective C–H oxidation of the latter would furnish the corresponding lactone, and the quaternary C4 could be constructed through α -methylation. A key retrosynthesis step from **7** to compound **8** bearing a simplified hetidine framework relied on the design of a cascade sequence of Prins cyclization and Wagner–Meerwein rearrangement.²⁰ The MOM group of **8** was expected to serve as a precursor of the oxonium ion species that would initiate the 6-*endo-trig* cyclization. Upon formation of the C–C bond highlighted in blue (Figure 2), the resultant tertiary carbocation at C5 should induce the 1,2-alkyl shift to construct the C–C bond highlighted in red (Figure 2). On the basis of our experience of septedine synthesis,⁹ the bicyclo[2.2.2]octane

moiety of **8** could be assembled through an anionic Diels–Alder cycloaddition. Therefore, α,β -unsaturated enone **9** was considered a suitable precursor of **8**. Further simplification led to aldehyde **10**, which may result from an intermolecular Diels–Alder reaction²¹ of known diene **11**²² and dienophile **12**. The latter was traced back to known enantioenriched alcohol **13** that was readily available through lipase-mediated resolution.²³

Figure 2. Retrosynthetic analysis of **3**.

The synthesis commenced with scalable preparation of pentacyclic intermediate **8** (Scheme 1). Silylation of enantioenriched alcohol **13** (>99% ee) provided compound **14** in 93% yield. Treatment of **14** with *t*-BuLi generated the alkenyl lithium species, which was quenched by DMF to give aldehyde **12** in 91% yield. We then examined a variety of conditions for the intermolecular Diels–Alder reaction of **11** and **12**; acid lability of the ketal group of the former turned out to be a problem. To our delight, $\text{BF}_3 \cdot \text{OEt}_2$ was found to be an effective promoter for the cycloaddition at -78°C , and compound **10** was obtained in 68% isolated yield. One-pot vinyl lithium addition and MOM protection afforded allylic ether **15** in 85% yield as a single detectable diastereomer. Exposure to aq. HClO_4 resulted in selective hydrolysis of the ketal followed by $\text{C}=\text{C}$ bond migration, furnishing α,β -unsaturated enone **9** in 72% yield. Following from our experience with the anionic $[4+2]$ -cycloaddition,⁹ we subjected **9** to deprotonation with LiHMDS. The resultant 1,3-dienolate underwent an intramolecular Diels–Alder reaction at 22°C , and subsequent desilylation of the cycloadduct with TBAF provided alcohol **16** in 84% overall yield. Of note, complete removal of O_2 in the reaction system by the freeze–pump–thaw cycling was crucial to the success of this anionic cycloaddition. X-ray crystallographic analysis of **16** (Scheme 1) confirmed the stereochemical outcomes of the two Diels–Alder reactions. Dehydration of **16** with

$\text{SOCl}_2/\text{pyridine}$ gave trisubstituted olefin **8** in 76% yield.^{17a} Indeed, **8** could also serve as a versatile intermediate for the synthesis of hetidine type alkaloids.

Scheme 1. Construction of Pentacyclic Intermediate **8**

Table 1. Conditions for the Cationic Cascade Reaction

entry	conditions ^a	yield (%)
1	TFA, 0°C , 24 h	22
2	TESOTf, 0°C , 1 h	16
3	$\text{BF}_3 \cdot \text{OEt}_2$, -15°C , 6 h	37
4	TiCl_4 , -15°C , 1 h	24
5	SnCl_4 , -15°C , 1 h	63
6	SnCl_4 , TMSOAc, -15°C , 1 h	55

^a 1.0 equiv. acid. Reactions performed in CH_2Cl_2 .

With a large quantity of **8** in hand, we investigated the conditions for its conversion into **7**; the results are summarized in Table 1. In the presence of a suitable, stoichiometric acid promoter, **8** should undergo a Prins/Wagner–Meerwein cascade to give **7** bearing an arcutine scaffold, presumably via the intermediacy of two cationic species **17** and **18**. To our

delight, exposure of **8** to TFA gave **7** in 22% yield (entry 1), despite a significant amount of the alcohol resulting from MOM deprotection. TESOTf caused severe substrate decomposition (entry 2). $\text{BF}_3 \cdot \text{OEt}_2$ slightly increased the yield of **7** (entry 3), while TiCl_4 preferentially led to MOM removal (entry 4). SnCl_4 was then found to be an optimal promoter for the cascade reaction, and **7** was obtained in 63% yield on a gram scale (entry 5). We briefly explored the possibility of trapping the post-rearrangement carbocation species with an oxygen nucleophile (TMSOAc); however, proton elimination (leading to olefin **7**) remained the predominant reaction pathway (entry 6).

Scheme 2. Preparation of Oxygenated Pentacycle **6**

We then developed a robust route from **7** to oxygenated pentacycle **6** (Scheme 2). Face-selective Mukaiyama hydration of the trisubstituted olefin followed by position-selective C–H oxidation using the Sharpless protocol²⁴ ($\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4) afforded alcohol **19**, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 2). Of note, $\text{Mn}(\text{acac})_2$ ²⁵ was superior to $\text{Co}(\text{acac})_2$ as a precatalyst for this particular olefin hydration. The alcohol underwent one-pot Wittig methylenation and silylation to give compound **20** in 87% yield. α -Methylation of this lactone turned out to be a challenge; MeI was ineffective under various conditions. To our delight, MeOTf proved to be a more powerful reagent in this case.²⁶ The lithium enolate of **20** was methylated smoothly in the presence of HMPA, and desilylation with TBAF furnished alcohol **21** in one pot with good overall efficiency. The stereochemistry at C4 was secured by the rigid polycyclic system. Oxidation of **21** with SeO_2 /TBHP gave allylic alcohol **22** in 81% yield as an undesired diastereomer, which was then subjected to a sequence of LiAlH_4 reduction and $\text{CrO}_3 \cdot 2\text{pyr}$ oxidation.²⁷ Thus, diketolaldehyde **6** was obtained in 58% overall yield. We expected to address the stereochemical issue at C15 by face-selective ketone reduction at a final stage of the synthesis.

Scheme 3. Completion of the Synthesis of **3** and **2**

Completion of the synthesis of **3** and **2** relied on differentiating the reactivity of the three carbonyls of **6** (Scheme 3). Chemoselective condensation of the aldehyde with NH_2OH followed by face-selective 1,2-reduction of the α,β -unsaturated enone with NaBH_4 afforded compound **23** as a single diastereomer in 65% yield. The most hindered carbonyl group remained untouched through this reaction sequence. Exposure of **23** to TiCl_3 led to reductive cleavage of the N–O bond.²⁸ The resultant aldimine intermediate was further reduced in situ by NaBH_3CN to form primary amine **24**,²⁸ which underwent spontaneous cyclization upon aqueous workup to give **3** in 71% yield. Acylation of the allylic alcohol ($i\text{-PrCO}_2\text{H}$, DCC, DMAP) provided **2** in 77% yield. The structures of **2** and **3** were verified by X-ray crystallographic analysis (Scheme 3).

In summary, we have accomplished the asymmetric total synthesis of arcutinidine (**3**) and arcutinine (**2**). An expeditious and scalable route to a pentacyclic intermediate with hetidine features was established. A bioinspired Prins/Wagner–Meerwein cascade was then developed for conversion of the hetidine core structure into an arcutine core structure. These endeavors may facilitate studies of the biology of arcutine and hetidine type alkaloids.

AUTHOR INFORMATION

Corresponding Author

*ali@sioc.ac.cn

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The graphic entry for the TOC

arcutinidine; R = H
arcutinine; R = *i*-PrCO

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Asymmetric Total Synthesis of Arcutinidine and Arcutinine

Shupeng Zhou, Kaifu Xia, and Ang Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

*E-mail: ali@sioc.ac.cn

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I Experimental Procedures and Spectroscopic Data of Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium-benzophenoneketyl. Methylene chloride (CH_2Cl_2), *N,N*-dimethylformamide (DMF), *N,N*-diisopropylaminepyridine (*i*Pr₂NH), hexamethylphosphoramide (HMPA), *tert*-butanol (*t*-BuOH), triethylamine (Et_3N), and pyridine were distilled from calcium hydride and stored under an argon atmosphere. Methanol (MeOH) and ethanol (EtOH) was distilled from magnesium and stored under an argon atmosphere. Lipase acrylic resin from *Candida antarctica* was purchased from Sigma-Aldrich. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by Adamas-beta[®]. Reactions were monitored by thin layer chromatography (TLC) carried out on S-2 0.25 mm Merck silica gel plates (60F-254) using UV light for visualization and aqueous ammonium cerium nitrate/ammonium molybdate or basic aqueous potassium permanganate as developing agent. SiliaFlash[®] silica gel (P60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker AV III 400 or an Agilent 500/54/ASP spectrometer. The spectra were calibrated by using residual undeuterated solvents (for ¹H NMR) and deuterated solvents (for ¹³C NMR) as internal references: undeuterated chloroform ($\delta_{\text{H}} = 7.26$ ppm) and CDCl_3 ($\delta_{\text{C}} = 77.16$ ppm); undeuterated methanol ($\delta_{\text{H}} = 3.31$ ppm) and methanol-d₄ ($\delta_{\text{C}} = 49.00$ ppm); undeuterated acetone ($\delta_{\text{H}} = 2.05$ ppm) and acetone-d₆ ($\delta_{\text{C}} = 29.84$ ppm). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Melting points (m.p.) are uncorrected and were recorded on an SGW X-4 apparatus. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX III 7.0 Tesla ESI-FT mass spectrometer.

13

Enantioenriched alcohol 13: Racemic alcohol **13** was prepared from commercially available 1,3-cyclohexanedione through a two-step sequence according to the literature.^{1,2} To a stirred solution of racemic **13** (40.0 g, 226 mmol) in *t*-BuOMe (160 mL) were sequentially added vinyl acetate (23.4 g, 25.0 mL, 272 mmol) and lipase acrylic resin from *Candida antarctica* (400 mg) at 22 °C.³ The resultant mixture was stirred at that temperature for 58 h before it was filtered and concentrated under vacuum. The residue was purified by flash column chromatography with EtOAc/petroleum ether (1:5 → 1:2) to give enantioenriched alcohol **13** (16.8 g, 42%, 99.7% ee) as a pale yellow oil. **13**: $[\alpha]_D^{25} = -39.1$ ($c = 1.0$ in CHCl_3). The ee of **13** was determined by HPLC (*vide infra*). The spectra and physical properties of enantioenriched **13** are identical to those reported in the literature.²

14

Silyl ether 14: To a stirred solution of enantioenriched alcohol **13** (25.6 g, 145 mmol) in DMF (30 mL) were sequentially added imidazole (14.8 g, 217 mmol) and TBDPSCl (42.3 g, 40.0 mL, 154 mmol) at 22 °C. The resultant mixture was stirred at that temperature for 8 h before it was quenched with saturated aq. NaHCO_3 (300 mL). The mixture so obtained was extracted with petroleum ether (3 × 400 mL). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with EtOAc/petroleum ether (1:100) as eluent to give silyl ether **14** (56.2 g, 93%) as a white powder. **14**: $R_f = 0.27$ (silica, petroleum ether); $[\alpha]_D^{25} = -83.9$ ($c = 1.0$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3070, 3042, 2930, 2857, 1646, 1427, 1361, 1111, 1022, 972, 701 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.70\text{--}7.63$ (m, 4 H), 7.51–7.31 (m, 6 H), 5.98–5.93 (m, 1 H), 4.24–4.18 (m, 1 H), 2.51–2.38 (m, 1 H), 2.36–2.23 (m, 1 H), 1.97–1.83 (m, 1 H), 1.70–1.60 (m, 2 H), 1.59–1.48 (m, 1 H), 1.06 (s, 9 H) ppm; ^{13}C NMR (101

MHz, CDCl₃): δ = 135.93, 135.90, 134.2, 134.1, 132.3, 129.83, 129.82, 127.77, 127.75, 125.9, 68.6, 35.3, 30.9, 27.1, 20.8, 19.3 ppm; HRMS (m/z): [M + Na]⁺ calcd for C₂₂H₂₇BrOSiNa⁺ 437.0907, found 437.0906.

12

Aldehyde 12: To a stirred solution of silyl ether **14** (15.8 g, 38.0 mmol) in THF (200 mL) was added *t*-BuLi (50.0 mL, 80.0 mmol, 1.6 M in pentane) at -78 °C and the resultant mixture was stirred at that temperature for 30 min before DMF (6.04 g, 6.40 mL, 82.6 mmol) was added. The mixture was warmed to 22 °C and stirred for 30 min before it was quenched with saturated aq. NaHCO₃ (200 mL) and extracted with EtOAc (3 $\times$ 300 mL). The combined organic phases were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with EtOAc/petroleum ether (1:50 $\rightarrow$ 1:30) as eluent to give aldehyde **12** (12.6 g, 91%). **12:** R_f = 0.35 (silica, EtOAc:petroleum ether 1:40); $[\alpha]_D^{25}$ = -97.2 (c = 1.0 in CHCl₃); IR (film): $\nu_{\max}$ = 3070, 3049, 2931, 2857, 2708, 1690, 1471, 1427, 1172, 1110, 1080, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 9.37–9.34 (m, 1 H), 7.73–7.66 (m, 4 H), 7.49–7.43 (m, 2 H), 7.43–7.37 (m, 4 H), 6.51–6.46 (m, 1 H), 4.48–4.39 (m, 1 H), 2.19–2.01 (m, 2 H), 1.88–1.74 (m, 2 H), 1.74–1.62 (m, 1 H), 1.51–1.36 (m, 1 H), 1.08 (s, 9 H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 194.6, 151.4, 141.7, 135.9, 133.9, 133.8, 130.00, 129.97, 127.9, 127.8, 67.8, 31.9, 27.0, 21.3, 19.3, 18.9 ppm; HRMS (m/z): [M + Na]⁺ calcd for C₂₃H₂₈O₂SiNa⁺ 387.1751, found 387.1755.

10

Tricyclic aldehyde 10: To a stirred solution of aldehyde **12** (1.20 g, 3.29 mmol) and diene **11**⁴ (1.10 g, 6.58 mmol) in CH₂Cl₂ (10 mL) was added BF₃•OEt₂ (460 mg, 400 μ L, 3.24 mmol) at -78 °C. The

resultant mixture was allowed to stir at that temperature for 50 h before it was quenched with saturated aq. NaHCO_3 (50 mL). The resultant mixture was extracted with EtOAc (3×100 mL) and the combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography with $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{petroleum ether}$ (3:50:50) to give tricyclic aldehyde **10** (1.19 g, 68%) as a white foam. **10**: $R_f = 0.33$ (silica, $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{petroleum ether}$ 3:50:50); $[\alpha]_{\text{D}}^{25} = -109.7$ ($c = 1.0$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3069, 3047, 2930, 2856, 2698, 1722, 1427, 1375, 1261, 1106, 868, 702 \text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): $\delta = 9.19$ (s, 1 H), 7.70–7.63 (m, 4 H), 7.44–7.34 (m, 6 H), 5.50 (d, $J = 4.7$ Hz, 1 H), 4.06–3.89 (m, 4 H), 3.87–3.76 (m, 1 H), 2.53–2.40 (m, 1 H), 2.40–2.14 (m, 4 H), 1.88–1.78 (m, 1 H), 1.78–1.69 (m, 1 H), 1.61–1.51 (m, 3 H), 1.49–1.32 (m, 4 H), 1.33–1.24 (m, 1 H), 1.05 (s, 9 H), 1.02–0.92 (m, 1 H) ppm; ^{13}C NMR (101 MHz, CD_3COCD_3): $\delta = 207.7, 136.5, 136.4, 135.3, 134.72, 134.68, 130.6, 130.5, 128.5, 128.4, 119.6, 109.2, 71.6, 64.8, 64.7, 52.7, 46.2, 45.5, 36.17, 35.6, 29.5, 27.8, 27.5, 27.4, 21.7, 21.3, 19.8$ ppm; HRMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{33}\text{H}_{42}\text{O}_4\text{SiNa}^+$ 553.2745, found 553.2746.

Allylic ether 15: To a stirred solution of tricyclic aldehyde **10** (12.6 g, 23.7 mmol) in THF (240 mL) at -78 °C was added vinyl lithium⁵ (60.0 mL, 0.45 M in THF, 27.0 mmol) and the resultant mixture was stirred at that temperature for 30 min before a solution of MOMCl (2.97 g, 2.80 mL, 36.9 mmol) in THF (25 mL) was added. The resultant mixture was warmed to 22 °C and stirred for 30 min before it was quenched with saturated aq. NaHCO_3 (150 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×300 mL). The combined organic phases were washed with brine (200 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed under vacuum, and the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:15 $\rightarrow$ 1:10) to give allylic ether **15** (12.2 g, 85%) as a white foam. **15**: $R_f = 0.33$ (silica, EtOAc:petroleum ether 1:8); $[\alpha]_{\text{D}}^{20} = -80.5$ ($c = 1.0$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3070, 2929, 1471, 1425, 1260, 1104, 1032, 924, 876,$

702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.71–7.62 (m, 4 H), 7.46–7.32 (m, 6 H), 5.86 (ddd, *J* = 17.2, 10.2, 9.2 Hz, 1 H), 5.50–5.37 (m, 1 H), 5.24 (dd, *J* = 10.2, 1.1 Hz, 1 H), 5.13 (dd, *J* = 17.2, 1.1 Hz, 1 H), 4.34 (d, *J* = 6.3 Hz, 1 H), 4.22 (d, *J* = 6.3 Hz, 1 H), 4.20–4.12 (m, 1 H), 4.09–3.90 (m, 5 H), 3.10 (s, 3 H), 2.65 (br s, 1 H), 2.53–2.38 (m, 1 H), 2.32 (dd, *J* = 12.5, 2.5 Hz, 1 H), 2.29–2.13 (m, 3 H), 1.87 (dd, *J* = 13.1, 2.5 Hz, 1 H), 1.70–1.54 (m, 1 H), 1.58 (dd, *J* = 13.1, 3.8 Hz, 1 H), 1.53–1.24 (m, 6 H), 1.03 (s, 9 H), 0.98–0.89 (m, 1 H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 135.9, 135.4, 135.3, 135.2, 134.6, 129.53, 129.49, 127.53, 127.47, 119.7, 118.5, 109.6, 95.8, 81.0, 69.5, 64.6, 64.4, 56.0, 46.4, 42.7, 36.3, 33.7, 28.9, 28.2, 27.3, 27.1, 22.4, 19.5, 19.3 ppm; HRMS (*m/z*): [M + Na]⁺ calcd for C₃₇H₅₀O₅SiNa⁺ 625.3320, found 625.3325.

α,β-Unsaturated enone 9: To a stirred solution of allylic ether **15** (4.65 g, 7.71 mmol) in THF/acetone (60 mL, 5:1) was added aq. HClO₄ (20.0 mL, 3.0 M) at 22 °C. The resultant mixture was allowed to stir at that temperature for 1.5 h before it was quenched with saturated aq. NaHCO₃ (100 mL). The mixture so obtained was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:10 → 1:5) as eluent to give α,β-unsaturated enone **9** (3.10 g, 72%) as a white foam. **9**: *R*_f = 0.36 (silica, EtOAc:petroleum ether 1:3); [α]_D²⁰ = -40.5 (*c* = 1.0 in CHCl₃); IR (film): ν_{max} = 3071, 3047, 2932, 2888, 2822, 1669, 1609, 1471, 1426, 1256, 1105, 996, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.71–7.60 (m, 4 H), 7.47–7.39 (m, 2 H), 7.38–7.32 (m, 4 H), 5.95 (s, 1 H), 5.63 (ddd, *J* = 17.2, 10.3, 8.5 Hz, 1 H), 5.23 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.16 (d, *J* = 17.2 Hz, 1 H), 4.53 (d, *J* = 6.6 Hz, 1 H), 4.33 (d, *J* = 6.6 Hz, 1 H), 4.30–4.23 (m, 1 H), 3.90 (d, *J* = 8.5 Hz, 1 H), 3.72–3.53 (m, 1 H), 3.24 (s, 3 H), 3.02–2.87 (m, 1 H), 2.56–2.45 (m, 1 H), 2.41–2.20 (m, 3 H), 2.17–2.07 (m, 1 H), 2.00–1.85 (m, 2 H), 1.84–1.70 (m, 1 H), 1.69–1.55 (m, 2 H), 1.46–1.22 (m, 4 H), 1.05 (s, 9 H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 199.8,

169.2, 136.0, 135.9, 134.5, 133.9, 133.2, 129.75, 129.68, 127.57, 127.54, 126.4, 119.9, 93.8, 81.68, 74.4, 56.7, 43.7, 41.0, 40.4, 38.1, 31.9, 31.7, 27.3, 26.8, 22.5, 22.1, 19.5, 15.8 ppm; HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{46}O_4SiNa^+$ 581.3058, found 581.3060.

16

Cycloadduct 16: A solution of α,β -unsaturated enone **9** (9.10 g, 16.3 mmol) in THF (160 mL) was subjected to the freeze-pump-thaw cycling for three times. To the solution was added LiHMDS (50.0 mL, 1.0 M in THF, 50.0 mmol) at 22 °C. The reaction mixture was allowed to stir at that temperature for 7 h before TBAF (80.0 mL, 1.0 M in THF, 80.0 mmol) was added. The resultant mixture was heated to 70 °C and stirred at that temperature for 5 h before it was quenched with saturated aq. NH_4Cl (200 mL). The resultant mixture was extracted with EtOAc (3 $\times$ 300 mL) and the combined organic phases were washed with brine (200 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:5 $\rightarrow$ 1:2) to give cycloadduct **16** (4.38 g, 84%) as a white solid. **16**: R_f = 0.30 (silica, EtOAc:petroleum ether 1:2); $[\alpha]_D^{20}$ = -52.0 (c = 1.0 in $CHCl_3$); IR (film): ν_{max} = 3485, 2927, 1714, 1461, 1393, 1334, 1238, 1123, 1042, 922, 757 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ = 4.73 (d, J = 6.6 Hz, 1 H), 4.63 (d, J = 6.6 Hz, 1 H), 4.08 (s, 1 H), 3.46 (s, 1 H), 3.38 (s, 3 H), 2.70–2.62 (m, 1 H), 2.30 (d, J = 19.6 Hz, 1 H), 2.23–2.19 (m, 1 H), 2.18–2.10 (m, 1 H), 2.12 (d, J = 19.6 Hz, 1 H), 2.08–2.01 (m, 1 H), 1.94–1.89 (m, 1 H), 1.89–1.82 (m, 3 H), 1.82–1.78 (m, 1 H), 1.78–1.70 (m, 2 H), 1.70–1.62 (m, 1 H), 1.61–1.52 (m, 1 H), 1.52–1.41 (m, 3 H), 1.34–1.23 (m, 2 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 216.7, 96.9, 95.1, 74.6, 55.5, 46.7, 44.7, 44.1, 43.2, 42.0, 40.8, 39.2, 35.3, 35.1, 34.2, 31.9, 25.4, 24.9, 18.4 ppm; HRMS (m/z): $[M + Na]^+$ calcd for $C_{19}H_{28}O_4Na^+$ 343.1880, found 343.1884. CCDC 1914278 contains the supplementary crystallographic data of **16** [m.p.: 112–115 °C (EtOAc:petroleum ether 1:10)]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

8

Pentacyclic intermediate 8: To a stirred solution of cycloadduct **16** (3.80 g, 11.9 mmol) in CH₂Cl₂ (400 mL) were sequentially added pyridine (48.9 g, 50.0 mL, 618 mmol) and SOCl₂ (7.22 g, 4.40 mL, 60.6 mmol) at 0 °C. The resultant mixture was allowed to stir at that temperature for 1 h before it was quenched with saturated aq. NaHCO₃ (200 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organic phases were sequentially washed with aq. citric acid (4 × 200 mL, 10 wt%) and brine (200 mL), dried over anhydrous Na₂SO₄, and filtered. The solvent was evaporated under vacuum. The residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:10 → 1:5) as eluent to give pentacyclic intermediate **8** (2.73 g, 76%) as a white foam. **8**: *R*_f = 0.31 (silica, EtOAc:petroleum ether 1:4); [α]_D²⁰ = −156.9 (*c* = 1.0 in CHCl₃); IR (film): ν_{max} = 2927, 1730, 1453, 1398, 1327, 1288, 1128, 1105, 1030, 960, 861, 799 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 5.57–5.51 (m, 1 H), 4.76 (d, *J* = 6.8 Hz, 1 H), 4.66 (d, *J* = 6.8 Hz, 1 H), 3.63–3.58 (m, 1 H), 3.39 (s, 3 H), 2.78–2.68 (m, 1 H), 2.33 (d, *J* = 19.6 Hz, 1 H), 2.29–2.24 (m, 1 H), 2.12 (d, *J* = 19.6 Hz, 1 H), 2.15–2.02 (m, 2 H), 2.02–1.91 (m, 5 H), 1.90–1.84 (m, 1 H), 1.84–1.75 (m, 2 H), 1.70–1.60 (m, 3 H), 1.54–1.44 (m, 2 H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 215.6, 140.8, 121.6, 97.1, 95.9, 55.7, 48.8, 48.1, 44.4, 44.2, 44.1, 41.9, 37.9, 34.3, 30.6, 28.9, 25.7, 25.5, 20.9 ppm; HRMS (*m/z*): [*M* + Na]⁺ calcd for C₁₉H₂₆O₃Na⁺ 325.1774, found 325.1779.

7

Hexacyclic intermediate 7: To a stirred solution of pentacyclic intermediate **8** (2.57 g, 8.50 mmol) in CH₂Cl₂ (100 mL) was added SnCl₄ (9.00 mL, 1.0 M in CH₂Cl₂, 9.00 mmol) at −15 °C. The mixture was allowed to stir at that temperature for 1 h before it was quenched with saturated aq. NH₄Cl (100 mL)

and extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:10 → 1:5) as eluent to give hexacyclic intermediate **7** (1.45 g, 63%) as a white foam. **7**: *R*_f = 0.33 (silica, EtOAc:petroleum ether 1:3); [α]_D²⁰ = −69.2 (*c* = 1.0 in CHCl₃); IR (film): ν_{max} = 2930, 2858, 1729, 1460, 1460, 1400, 1259, 1153, 1043, 960, 806 cm^{−1}; ¹H NMR (400 MHz, CDCl₃): δ = 5.59–5.51 (m, 1 H), 4.30 (dd, *J* = 9.1, 7.8 Hz, 1 H), 3.61–3.51 (m, 1 H), 3.44 (dd, *J* = 9.1, 4.4 Hz, 1 H), 2.38–2.11 (m, 4 H), 2.20 (d, *J* = 18.8 Hz, 1 H), 2.01 (d, *J* = 18.8 Hz, 1 H), 1.97–1.91 (m, 2 H), 1.89–1.79 (m, 3 H), 1.79–1.67 (m, 2 H), 1.57–1.45 (m, 2 H), 1.42–1.31 (m, 1 H), 1.31–1.18 (m, 1 H), 1.18–1.05 (m, 1 H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 216.1, 146.3, 119.8, 89.9, 74.9, 47.2, 45.8, 43.8, 40.1, 39.7, 37.6, 36.4, 34.9, 32.9, 30.9, 28.1, 26.6, 24.3 ppm; HRMS (*m/z*): [*M* + Na]⁺ calcd for C₁₈H₂₂O₂Na⁺ 293.1512, found 293.1519.

Hexacyclic lactone 19: To a stirred solution of hexacyclic intermediate **7** (2.26 g, 8.36 mmol) and PhSiH₃ (8.77 g, 10.0 mL, 81.1 mmol) in EtOH (70 mL) was added Mn(acac)₂ (212 mg, 0.837 mmol) at 22 °C, through the suspension was bubbled O₂ for 30 min. The resultant mixture was allowed to stir under an oxygen atmosphere at 22 °C for 2 h. The volatiles were removed under vacuum, and the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:2 → 1:1) to give the tertiary alcohol (1.95 g, 81%) as a pale yellow oil. This oil was dissolved in acetonitrile/EtOAc (40 mL, 1:1). To the stirred solution were sequentially added phosphate buffer (30 mL, 1.0 M, pH = 7.0), NaIO₄ (7.23 g, 33.8 mmol), and RuCl₃•3H₂O (88.4 mg, 0.338 mmol) at 22 °C. The reaction mixture was stirred at that temperature for 24 h before it was quenched with saturated aq. NaHCO₃ (50 mL) and Na₂S₂O₃ (50 mL) and extracted with CH₂Cl₂ (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The

residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:1) as eluent to give lactone **19** (1.43 g, 70%) as a white powder. **19**: R_f = 0.34 (silica, EtOAc:petroleum ether 1:2); $[\alpha]_D^{25} = -82.7$ ($c = 1.0$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3473, 2928, 2867, 1747, 1727, 1456, 1330, 1261, 1092, 1019, 798 \text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): $\delta = 4.32$ (dd, $J = 5.7, 1.3$ Hz, 1 H), 2.38–2.34 (m, 1 H), 2.34–2.18 (m, 2 H), 2.26 (d, $J = 19.3$ Hz, 1 H), 2.06 (d, $J = 19.3$ Hz, 1 H), 2.11–1.92 (m, 4 H), 1.89–1.81 (m, 2 H), 1.80–1.67 (m, 3 H), 1.64–1.52 (m, 3 H), 1.51–1.43 (m, 3 H), 1.42–1.33 (m, 1 H). ppm; ^{13}C NMR (126 MHz, CDCl_3): $\delta = 214.9, 179.1, 86.1, 72.3, 49.0, 47.0, 45.4, 44.9, 42.8, 36.9, 34.8, 32.2, 31.7, 29.1, 27.2, 23.6, 22.7, 19.2$ ppm; HRMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}^+$ 325.1410, found 325.1412. CCDC 1914280 contains the supplementary crystallographic data of **19** [m.p.: 262–264 °C (CHCl_3 :petroleum ether 1:5)]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Silyl ether 20: To a stirred suspension of methyltriphenylphosphonium bromide (2.90 g, 8.12 mmol) in THF (20 mL) was added *t*-BuOK (8.00 mL, 1.0 M in THF, 8.00 mmol) at 22 °C. The mixture was stirred at that temperature for 15 min before the solution of hexacyclic lactone **19** (1.17 g, 3.87 mmol) in THF (10 mL) was added. The resultant mixture was allowed to stir at 22 °C for 30 min before it was cooled to 0 °C. Et_3N (3.92 g, 5.40 mL, 38.7 mmol) and TMSOTf (6.89 g, 5.60 mL, 31.0 mmol) were sequentially added, and the resultant mixture was allowed to stir at that temperature for 15 min before it was quenched with saturated aq. NaHCO_3 (100 mL). The resultant mixture was extracted with EtOAc (3 $\times$ 200 mL), and the combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:30 $\rightarrow$ 1:20) as eluent to give silyl ether **20** (1.23 g, 85%) as a white foam. **20**: R_f = 0.31 (silica, EtOAc:petroleum ether 1:10); $[\alpha]_D^{25} = -82.4$ ($c =$

1.0 in CHCl₃); IR (film): $\nu_{\max}$ = 3070, 2982, 2946, 2867, 1773, 1454, 1260, 1249, 1137, 1025, 835, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 4.75–4.70 (m, 1 H), 4.61–4.56 (m, 1 H), 4.22 (d, J = 5.6 Hz, 1 H), 2.32–2.27 (m, 1 H), 2.25–2.15 (m, 2 H), 2.08–2.02 (s, 1 H), 2.02–1.95 (m, 2 H), 1.94–1.85 (m, 1 H), 1.84–1.70 (m, 2 H), 1.69–1.63 (m, 3 H), 1.63–1.54 (m, 4 H), 1.54–1.49 (m, 1 H), 1.39–1.28 (m, 3 H), 0.14 (s, 9 H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 179.8, 150.6, 104.8, 87.0, 76.2, 48.3, 46.9, 45.3, 39.3, 36.4, 36.1, 34.9, 34.6, 31.3, 30.9, 29.6, 23.9, 23.5, 19.6, 2.6 ppm; HRMS (m/z): [M + H]⁺ calcd for C₂₂H₃₃O₃Si⁺ 373.2193, found 373.2195.

Methylated lactone 21: To a stirred solution of *i*-Pr₂NH (1.52 g, 2.10 mL, 15.0 mmol) in THF (20 mL) was added BuLi (6.80 mL, 2.13 M in hexane, 14.5 mmol) at 0 °C. The mixture was stirred at that temperature for 30 min before HMPA (10.0 mL) and a solution of lactone **20** (1.78 g, 4.78 mmol) in THF (10 mL) were sequentially added. The resultant mixture was allowed to stir at 0 °C for 2 h before TBAF (50.0 mL, 1.0 M in THF, 50.0 mmol) was added. The mixture was warmed to 22 °C and allowed to stir at that temperature for 3 h before it was quenched with saturated aq. NaHCO₃ (100 mL). The resultant mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with EtOAc/petroleum ether (1:10 → 1:5) to give methylated lactone **21** (1.10 g, 73%) as a white powder. **21**: R_f = 0.38 (silica, EtOAc:petroleum ether 1:3); $[\alpha]_D^{25}$ = -100.6 (c = 1.0 in CHCl₃); IR (film): $\nu_{\max}$ = 3504, 3066, 2930, 2864, 1753, 1655, 1463, 1379, 1260, 1100, 923, 872, 667 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 4.74–4.69 (m, 1 H), 4.60–4.54 (m, 1 H), 4.18 (dd, J = 5.8, 1.2 Hz, 1 H), 2.34–2.27 (m, 1 H), 2.24–2.16 (m, 1 H), 2.14–2.06 (m, 2 H), 2.05–1.98 (m, 1 H), 1.91–1.77 (m, 2 H), 1.76–1.68 (m, 2 H), 1.68–1.55 (m, 6 H), 1.51–1.43 (m, 1 H), 1.44–1.34 (m, 2 H), 1.20 (s, 3 H), 1.27–1.13 (m, 2 H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 182.14,

150.60, 104.65, 85.43, 73.64, 50.34, 48.32, 44.95, 39.02, 36.47, 35.94, 34.62, 34.11, 32.59, 31.86, 31.37, 29.67, 19.13, 18.67, 16.96 ppm; HRMS (m/z): $[M + H]^+$ calcd for $C_{20}H_{27}O_3^+$ 315.1955, found 315.1959.

Allylic alcohol 22: To a stirred solution of methylated lactone **21** (1.45 g, 4.61 mmol) in CH_2Cl_2 (40 mL) were sequentially added SeO_2 (5.11 g, 4.60 mmol) and TBHP (4.00 mL, 5.5 M in decane, 22.0 mmol) at 0 °C. The mixture was stirred at that temperature for 3 h before it was quenched with saturated aq. Na_2SO_3 (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , and filtered. The volatiles were removed under vacuum, and the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:2 → 1:1) to give allylic alcohol **22** (1.23 g, 81%) as a white foam. **22:** R_f = 0.37 (silica, EtOAc:petroleum ether 1:1); $[\alpha]_D^{25} = -89.8$ (c = 1.0 in acetone); IR (film): ν_{max} = 3401, 2970, 2943, 2864, 1759, 1689, 1445, 1302, 1047, 1029, 991, 730 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 5.01–4.98 (m, 1 H), 4.98–4.96 (m, 1 H), 4.23 (dd, J = 5.7, 1.5 Hz, 1 H), 3.83 (br s, 1 H), 2.44–2.37 (m, 1 H), 2.17–2.02 (m, 3 H), 2.02–1.93 (m, 1 H), 1.93–1.83 (m, 1 H), 1.80–1.67 (m, 2 H), 1.66–1.56 (m, 5 H), 1.55–1.40 (m, 3 H), 1.33–1.18 (m, 3 H), 1.21 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CD_3COCD_3): δ = 182.0, 156.2, 109.0, 85.8, 73.7, 73.3, 49.2, 48.2, 45.5, 38.9, 36.7, 34.3, 32.8, 32.4, 31.8, 31.5, 25.9, 19.8, 19.1, 17.7 ppm; HRMS (m/z): $[M + H]^+$ calcd for $C_{20}H_{27}O_4^+$ 331.1904, found 331.1911.

Diketoaldehyde 6: To a stirred solution of lactone **22** (1.21 g, 3.66 mmol) in THF (35 mL) was added $LiAlH_4$ (417 mg, 11.0 mmol) at 22 °C. The mixture was heated to 70 °C and allowed to stir at that

temperature for 4 h before it was quenched with saturated aq. NH_4Cl (100 mL). The resultant mixture was extracted with CH_2Cl_2 (3×150 mL), and the combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was evaporated under vacuum, and the residue was subjected to the next step without further purification. To a stirred solution of pyridine (7.24 g, 7.40 mL, 91.5 mmol) in CH_2Cl_2 (20 mL) were sequentially added celite (13.2 g) and CrO_3 (4.39 g, 43.9 mmol) at 22 °C.⁶ The resultant mixture was stirred at that temperature for 15 min before a solution of above residue in CH_2Cl_2 (35 mL) was added. The mixture was stirred at 22 °C for 20 min before it was filtered through a short pad of celite and washed with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , and filtered. The volatiles were removed under vacuum, and the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:4 $\rightarrow$ 1:2) to diketoaldehyde **6** (696 mg, 58% for the two steps) as a white foam. **6**: $R_f = 0.29$ (silica, EtOAc:petroleum ether 1:2); $[\alpha]_D^{25} = -50.3$ ($c = 1.0$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3482, 2959, 2923, 2853, 1701, 1626, 1465, 1378, 1261, 1096, 1018, 797 \text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): $\delta = 9.55$ (s, 1 H), 5.96 (d, $J = 1.3$ Hz, 1 H), 5.20 (d, $J = 1.3$ Hz, 1 H), 2.77–2.70 (m, 1 H), 2.51–2.42 (m, 1 H), 2.34–2.25 (m, 1 H), 2.21–2.14 (m, 1 H), 2.13–2.03 (m, 3 H), 2.03–1.96 (m, 1 H), 1.95–1.83 (m, 3 H), 1.83–1.72 (m, 3 H), 1.69–1.60 (m, 2 H), 1.60–1.51 (m, 2 H), 1.21 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CDCl_3): $\delta = 217.0, 205.6, 200.6, 146.7, 117.0, 77.7, 58.3, 48.5, 47.6, 46.5, 44.5, 36.1, 35.1, 32.2, 30.8, 28.4, 21.2, 20.0, 19.5, 16.5$ ppm; HRMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}^+$ 351.1567, found 351.1565.

Oxime 23: To a stirred solution of diketoaldehyde **6** (319 mg, 0.971 mmol) in MeOH (10 mL) were sequentially added NaOAc (95.6 mg, 1.17 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (68.8 mg, 0.990 mmol) at 22 °C. The mixture was allowed to stir at that temperature for 2 h before the solvent was evaporated under

vacuum. The residue was dissolved in THF/MeOH (11 mL, 10:1). To the stirred solution was added NaBH₄ (73.3 mg, 1.94 mmol) at −78 °C. The mixture was stirred at that temperature for 15 min before it was quenched with saturated aq. Na₂HCO₃ (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and filtered. The residue was subjected to flash column chromatography for purification using MeOH/CH₂Cl₂ (1:30 → 1:15) as eluent to give oxime **23** (218 mg, 65%) as a pale yellow oil. **23**: *R*_f = 0.32 (silica, MeOH:CH₂Cl₂ 1:15); [α]_D²⁵ = −21.6 (*c* = 1.0 in CH₃OH); IR (film): ν_{max} = 3447, 2960, 2925, 2870, 1702, 1647, 1461, 1261, 1097, 1036, 799 cm^{−1}; ¹H NMR (400 MHz, CD₃OD): δ = 7.52 (s, 1 H), 5.04–4.99 (m, 1 H), 4.94–4.89 (m, 1 H), 3.98–3.93 (m, 1 H), 2.40–2.24 (m, 2 H), 2.24–2.14 (m, 2 H), 2.08–1.97 (m, 2 H), 1.97–1.90 (m, 1 H), 1.90–1.80 (m, 1 H), 1.74–1.57 (m, 4 H), 1.54–1.37 (m, 5 H), 1.34 (s, 3 H) ppm; ¹³C NMR (126 MHz, CD₃OD): δ = 220.2, 160.8, 155.8, 107.7, 78.2, 73.98, 58.8, 47.8, 44.9, 41.4, 40.5, 37.2, 36.4, 35.4, 31.1, 30.1, 26.1, 23.9, 20.0, 18.0 ppm; HRMS (*m/z*): [*M* + *H*]⁺ calcd for C₂₀H₂₈NO₄⁺ 346.2013, found 346.2016.

3: arcutinidine

Arcutinidine (3): To a stirred solution of oxime **23** (197 mg, 0.570 mmol) and NH₄OAc (879 mg, 11.4 mmol) in MeOH (5.0 mL) were sequentially added NaBH₃CN (107 mg, 1.70 mmol) and TiCl₃ [1.30 mL, 20% w/v in aq. HCl (2.0 M), 1.70 mmol] at 0 °C. The mixture was stirred at that temperature for 1 h before 1N NaOH was added until pH = 10. The resultant mixture was allowed to stir at 22 °C for 10 min before it was extracted with EtOAc (4 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over anhydrous Na₂SO₄, and filtered. The volatiles were removed under vacuum, and the residue was purified by flash column chromatography with MeOH/CH₂Cl₂ (1:30) to give arcutinidine (**3**; 127 mg, 71%) as a white solid. **1**: *R*_f = 0.30 (silica, MeOH:CH₂Cl₂ 1:15); IR (film): ν_{max} = 3422, 3072, 2930, 2866, 1648, 1459, 1377, 1260, 1053, 972, 770 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 5.08–5.05

(m, 1 H), 5.01–4.97 (m, 1 H), 3.98 (s, 1 H), 3.71 (dd, $J = 15.3, 2.2$ Hz, 1 H), 3.45 (dd, $J = 15.3, 2.2$ Hz, 1 H), 2.35–2.26 (m, 2 H), 2.12–2.03 (m, 2 H), 1.98–1.90 (m, 2 H), 1.89–1.84 (m, 1 H), 1.78–1.67 (m, 3 H), 1.66–1.58 (m, 3 H), 1.57–1.51 (m, 2 H), 1.44–1.30 (m, 4 H), 0.95 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CDCl_3): $\delta = 186.4, 155.4, 108.6, 75.1, 73.6, 73.3, 58.9, 42.6, 41.0, 40.3, 37.2, 35.4, 32.7, 31.8, 30.7, 28.9, 26.1, 23.6, 20.2, 16.6$ ppm; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_2^+$ 314.2115, found 315.2117. CCDC 1914281 contains the supplementary crystallographic data of **1** [m.p.: 159–161 °C (EtOAc:petroleum ether 1:5)]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2: arcutinine

Arcutinine (2): To a stirred solution of *i*-PrCO₂H (9.3 mg, 0.106 mmol) and 4-DMAP (8.6 mg, 0.0704 mmol) in CH_2Cl_2 (100 μL) was added DCC (100 μL , 1.0 M in CH_2Cl_2 , 0.100 mmol) at 22 °C. The mixture was stirred at that temperature for 5 min before a solution of arcutinidine (**3**; 22.1 mg, 0.0705 mmol) in CH_2Cl_2 (600 μL) was added. The resultant mixture was allowed to stir at 22 °C for 3 h before it was quenched with saturated aq. NaHCO_3 (10 mL). The resultant mixture was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with acetone/ CH_2Cl_2 (1:10 $\rightarrow$ 1:5) to give arcutinine (**2**; 20.8 mg, 77%) as a white solid. **2:** $R_f = 0.26$ (silica, acetone: CH_2Cl_2 1:10); $[\alpha]_{\text{D}}^{25} = -15.4$ ($c = 0.50$ in CHCl_3); IR (film): $\nu_{\text{max}} = 3218, 2959, 2926, 2854, 1734, 1649, 1457, 1385, 1189, 1154, 1097, 1009, 975, 945$ cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 5.43\text{--}5.35$ (m, 1 H), 4.98–4.92 (m, 1 H), 4.90–4.83 (m, 1 H), 3.70 (dd, $J = 15.3, 2.2$ Hz, 1 H), 3.45 (dd, $J = 15.3, 2.2$ Hz, 1 H), 2.68–2.55 (m, 1 H), 2.48–2.38 (m, 1 H), 2.37–2.31 (m, 1 H), 2.06–1.95 (m, 3 H), 1.90–1.83 (m, 1 H), 1.81–1.71 (m, 3 H), 1.69–1.60 (m, 2 H), 1.60–1.51 (m, 3 H),

1.42–1.34 (m, 2 H), 1.34–1.24 (m, 2 H), 1.21 (d, $J = 3.9$ Hz, 3 H), 1.19 (d, $J = 3.9$ Hz, 3 H), 0.95 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CDCl_3): $\delta = 185.5, 177.1, 150.4, 110.2, 75.0, 73.7, 73.4, 58.7, 43.6, 41.0, 39.3, 37.1, 35.4, 34.4, 33.1, 32.2, 30.8, 28.6, 25.9, 23.3, 20.2, 19.3, 19.2, 16.7$ ppm; HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{34}\text{NO}_3^+$ 384.2533, found 384.2538. CCDC 1915624 contains the supplementary crystallographic data of **2** [m.p.: 245–247 °C (CH_2Cl_2 :petroleum ether 1:10)]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

II HPLC Traces for Measuring Enantiomeric Excess

13

The racemic and enantioenriched **13** were analyzed by HPLC (CHIRALPAK IG column, *i*-PrOH:hexane 2:98, 0.80 mL/min) to determine the retention time and enantiomeric excess. For **13**, ee = 99.7%.

PDA Ch1 230nm					
Peak#	Ret. Time	Area	Height	Area%	Conc.
1	28.419	6389737	204593	49.921	0.000
2	29.891	6410036	182303	50.079	0.000
Total		12799773	386896	100.000

PDA Ch1 230nm					
Peak#	Ret. Time	Area	Height	Area%	Conc.
1	27.738	11380435	320125	99.858	0.000
2	29.484	16146	531	0.142	0.000
Total		11396580	320656	100.000	

¹H NMR Spectrum of 14 (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 14 (101 MHz, CDCl_3)

¹H NMR Spectrum of 12 (400 MHz, CDCl₃)

^{13}C NMR Spectrum of 12 (101 MHz, CDCl_3)

^1H NMR Spectrum of 10 (400 MHz, CDCl_3)

^{13}C NMR Spectrum of 10 (101 MHz, CD_3COCD_3)

¹H NMR Spectrum of **15** (400 MHz, CDCl₃)

^{13}C NMR Spectrum of 15 (101 MHz, CDCl_3)

¹H NMR Spectrum of **9** (400 MHz, CDCl₃)

^{13}C NMR Spectrum of 9 (101 MHz, CDCl_3)

¹H NMR Spectrum of 16 (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 16 (126 MHz, CDCl_3)

¹H NMR Spectrum of **8** (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 8 (126 MHz, CDCl_3)

¹H NMR Spectrum of 7 (400 MHz, CDCl₃)

^{13}C NMR Spectrum of 7 (126 MHz, CDCl_3)

^1H NMR Spectrum of 19 (400 MHz, CDCl_3)

^{13}C NMR Spectrum of 19 (126 MHz, CDCl_3)

¹H NMR Spectrum of 20 (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 20 (126 MHz, CDCl_3)

¹H NMR Spectrum of 21 (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 21 (126 MHz, CDCl_3)

¹H NMR Spectrum of 22 (400 MHz, CDCl₃)

^{13}C NMR Spectrum of 22 (126 MHz, CD_3COCD_3)

^1H NMR Spectrum of 6 (400 MHz, CDCl_3)

^{13}C NMR Spectrum of 6 (126 MHz, CDCl_3)

^1H NMR Spectrum of 23 (400 MHz, CD_3OD)

^{13}C NMR Spectrum of 23 (126 MHz, CD_3OD)

¹H NMR Spectrum of 3 (500 MHz, CDCl₃)

^{13}C NMR Spectrum of 3 (126 MHz, CDCl_3)

¹H NMR Spectrum of 2 (400 MHz, CDCl₃)

¹³C NMR Spectrum of 2 (126 MHz, CDCl₃)

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