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Synthesis toward the Lindenane-type Sesquiterpenoid Monomer of Chloraholide A†

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An investigation toward the synthesis of the lindenane-type sesquiterpenoid monomer of Chloraholide A using a Yamamoto rearrangement, intramolecular cyclopropanation reaction, 1,3-dipolar cyclization, and an intramolecular Heck reaction gave the pivotal intermediate **20**. This gives a practical synthetic route that could generate further natural products of the Chloranthaceae family.

Keywords lindenane-type sesquiterpenoid, intramolecular Heck reaction, Julia-Kocienski methylenation

Introduction

Chloraholide A (**1**), a highly complex lindenane-type sesquiterpenoid dimer, was first isolated by Yue and co-workers in 2007 from South China Chloranthus holostegius.[1] It exhibits potent and selective inhibition of the delayed rectifier (I_K) K^+ current with an IC_{50} of 10.9 μmol/L, which is 96-fold more potent than the positive control, tetraethylammonium chloride (IC_{50} = 1.05 mmol/L), a classical blocker of the delayed rectifier (I_K) K^+ current. However, the unique octacyclic core that is characteristic of Chloraholide A is unprecedented among known natural products.

The obvious synthetic challenge posed by chloraholide A coupled with its impressive biological activity has generated significant interest from the synthetic community. Chloraholide A was proposed as a Diels-Alder cycloaddition product of two lindenane-type sesquiterpenoids in a biogenic reaction. Several efforts toward the total synthesis of Chloraholide A have focused on the stereoselective synthesis of lindenane-type sesquiterpenoids,[2] while some efforts have been reported to construct the core structure through Diels-Alder cycloaddition.[3] In our previous paper,[2a] we reported the synthesis of pivotal intermediate **21**. Compared with the desired key intermediate **20** for the synthesis of Chloraholide A, its 14-methyl group is epimeric. Herein, we would like to present our efforts to construct a lindenane-type sesquiterpenoid framework of Chloraholide A with all configurations correct through a flexible synthetic strategy, which we believe may be applied to the synthesis of other members of the intriguing Chloranthaceae family.

Results and Discussion

In line with the previous work by Kawabata's group[4] and Yue's group,[1] our retrosynthetic analysis of Chloraholide A is outlined in Scheme 1. Chloraholide A could be assembled using segment **22** with expedient and practical conversion via a suitable functional group transformation and Diels-Alder cycloaddition, followed by oxidation and rearrangement. Compound **22** would be accessed from compound **20** in view of the chemical reactivity of the butenolide.[5] Further disconnection of this pivotal intermediate, using an intramolecular Heck reaction, 1,3-dipolar cyclization, intramolecular cyclopropanation, and Yamamoto rearrangement led to intermediate **3**, which could be disconnected to give 3-butyn-1-ol as the starting material.

As shown in Scheme 2, our synthesis commenced with alcohol **2**, which was prepared from commercially accessible 3-butyn-1-ol according to the literature in six steps.[6] According to the protocol reported by Yamamoto and co-workers,[7] rearrangement of silyl ether **3**, catalyzed by MABR (methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide)), the (*R*)-configured *β*-siloxy aldehyde **4** was obtained in 94% yield over two steps. Then Wittig methylenation of **4** could afford **5** in 95% yield. Treatment of **5** with TBAF in THF at room temperature gave alcohol **6** in 96% yield, which was then transformed to **7** using glyoxylic acid chloride *p*-toluenesulfonyl hydrazone[8] in 81% yield over two steps. Copper-catalyzed intramolecular cyclopropanation of diazoacetate **7** afforded the important intermediate bicyclic lactone **8a** as the main product (**8a**∶**8b** = 2∶1, which are inseparable in this step)[9] in 74% over-

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† Dedicated to the Memory of Professor Weishan Zhou.

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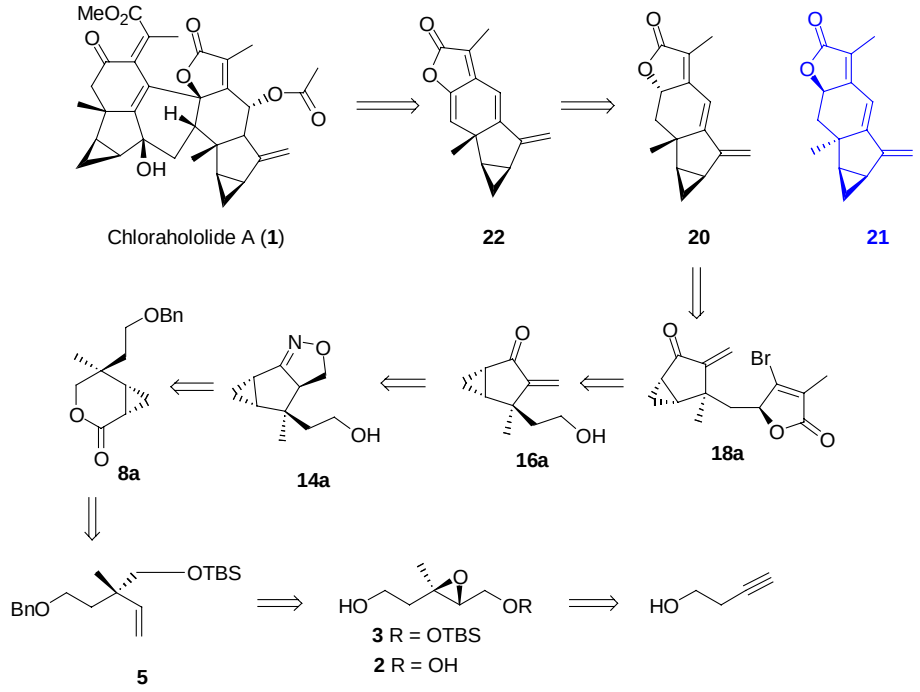
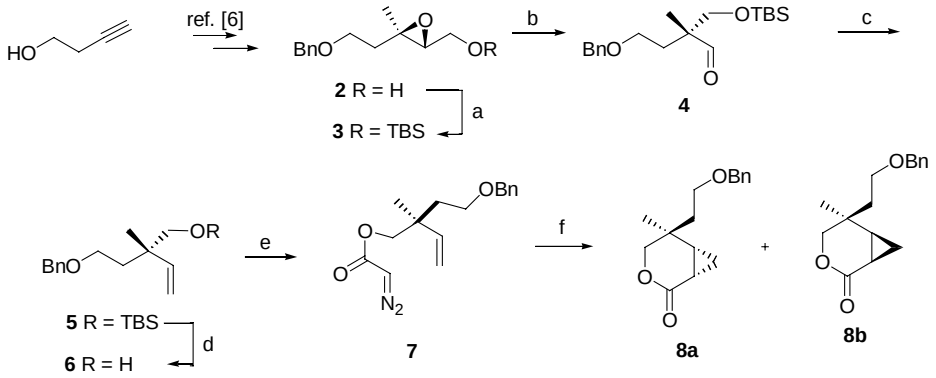
Scheme 1 Retrosynthetic analysis of chlorahololide A (**1**)



Scheme 2 Preparation of intermediate **8a**



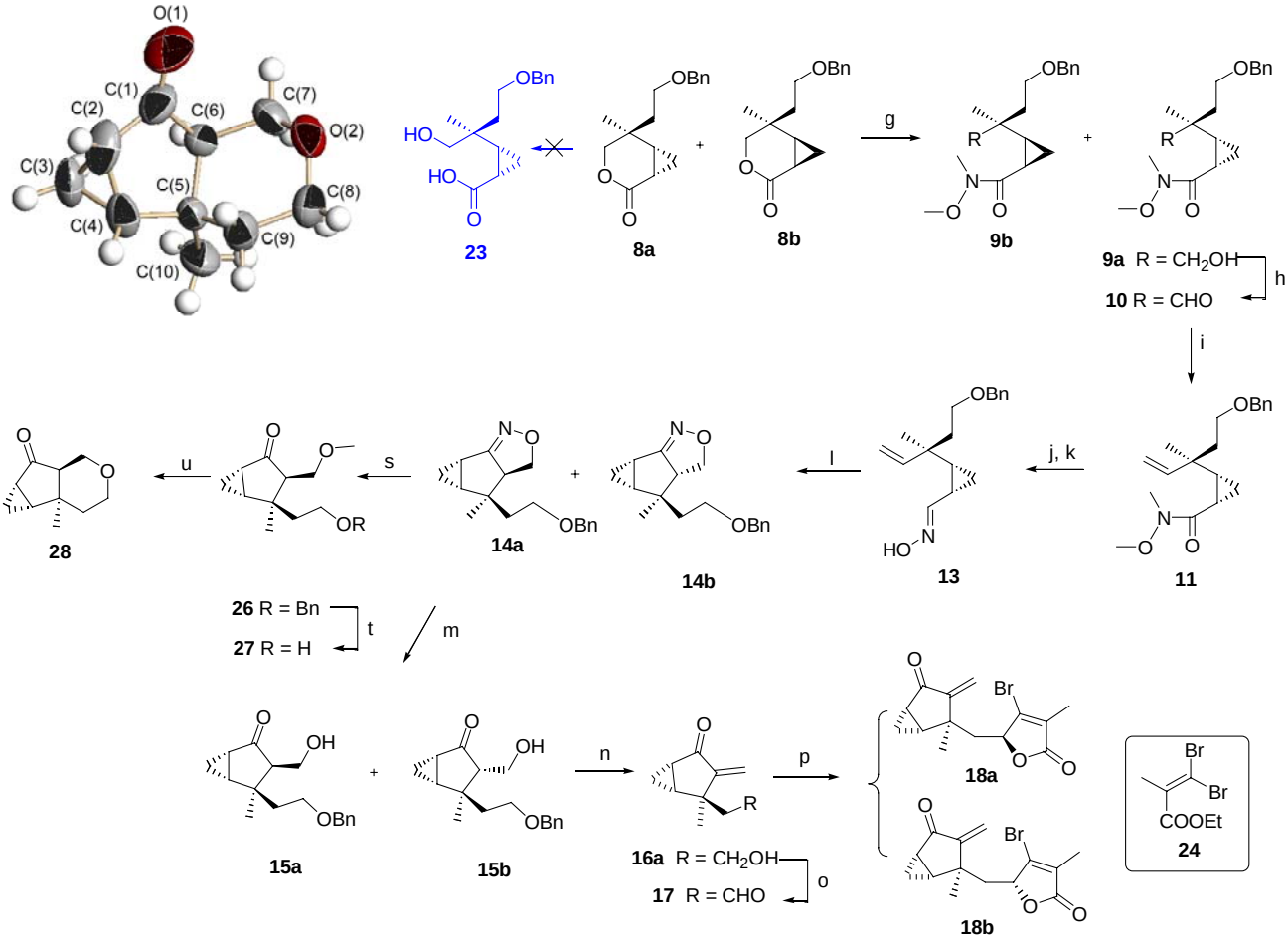
Reagents and conditions: (a) TBSCl, imidazole, DMF, r.t., 5 h; (b) MABR, CH_2Cl_2, –78 to –40 ℃, 2 h, 94% over two steps; (c) Ph_3PCH_3Br, *n*-BuLi, THF, –78 ℃ to r.t., overnight, 95%; (d) 1 mol/L TBAF in THF, THF, r.t., 3 h, 96%; (e) *p*-TsNHNHCOCl, dimethylaniline, CH_2Cl_2, then Et_3N, 0 ℃ to r.t., 30 min, 81% over two steps; (f) $Cu(TBS)_2$, PhMe, reflux, 30 min, 74%.

all yield (Scheme 2). It is worth mentioning that the *cis*-cyclopropane was constructed in a cyclic stereocontrolled manner without the use of a chiral catalyst.

Once the desired bicyclic lactone **8a** was available, the crucial lactone opening was attempted. Initially, we intended to selectively transform it to the hydroxy acid **23**. However, the transformation was problematic, although several attempts were made. Finally, the ring opening occurred smoothly with methoxymethylamine hydrochloride in the presence of $AlMe_3$[10] to afford the Weinreb amides **9a** and **9b** (**9a** and **9b** could be separated by silica gel column chromatography in this step) in 98% yield based on 62% conversion (Scheme 3).

DMP (Dess-Martin periodinane) oxidation of alcohol **9a** followed by a Wittig methylenation yielded ene **11** in 81% yield over two steps. Subsequent DIBAL-H reduction[11] of the Weinreb amide gave aldehyde **12** and oxime formation with hydroxylamine hydrochloride in pyridine[12] gave oxime **13**. Oxime **13** underwent intramolecular [3＋2] cycloaddition to give a mixture of the two diastereomeric isoxazolines **14a** and **14b** in 79% yield over three steps. Isoxazolines **14a** and **14b** were transformed to *α*-hydroxy ketones **15a** and **15b** by catalytic hydrogenation over 10% Pd/C in a 4∶1 mixture of methanol and water containing 3 equiv. of boric acid[13] in 76% yield. After debenzylation of *α*-hydroxy ketones **15a** and **15b**, ready acetylation and careful saponification led to the primary alcohol **16a** in 78% yield over three steps. Swern oxidation of **16a** led to aldehyde **17** in excellent yield. Then aldehyde **17** was treated with

Scheme 3 Preparation of the pivotal intermediate **18**



Reagents and conditions: (g) MeNHOMe•HCl, $AlMe_3$, CH_2Cl_2, r.t., 98% (62%, BORSM); (h) DMP, CH_2Cl_2, 3 h, r.t., 90%; (i) Ph_3PCH_3Br, NaHMDS, THF, 0 ℃, 1 h, 90%; (j) DIBAL-H, THF, –78 ℃, 1 h; (k) H_2NOH•HCl, Pyr., r.t.; (l) 5% NaClO, CH_2Cl_2, r.t., 79% over three steps; (m) H_2, 10% Pd/C, H_3BO_3, MeOH/H_2O (4∶1), r.t., 76%; (n) H_2, 10%Pd/C, MeOH, then Ac_2O, DMAP, Et_3N, CH_2Cl_2, then Na_2CO_3, MeOH/H_2O (2∶1), r.t., 78% over three steps; (o) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 ℃, 30 min then r.t. 30 min; (p) **24**, *i*-PrMgCl, THF, –78 ℃, 30 min, then 0 ℃, 3 h, 63% over two steps; (s) Raney Ni, AcOH, MeOH/H_2O (4∶1), r.t.; (t) H_2, 10% Pd/C, MeOH; (u) *p*-TsOH, Benzene, reflux, overnight, 95%.

Grignard reagent which was derived from **24**[14] to afford the precursors of the intramolecular Heck reaction **18a** and **18b** in 63% overall yield over two steps (diastereomer ratio >3∶1), which could be separated by silica gel column chromatography (Scheme 3).

With the desired precursors **18** in hand, we then turned our attention to assembling the skeleton of the lindenane-type sesquiterpenoid. Although an *exo*-type intramolecular Heck reaction is impossible for this substrate,[15] the *endo*-type ring closure was still problematic. After screening many reaction conditions, tetracyclic ketone **19** was produced in 31% yield based on 69% conversion under ligand-free conditions. Finally, the methylenation reaction was achieved under modified Julia-Kocienski conditions[2c,16] in moderate yield to give compound **20**, which possesses a typical lindenane-type sesquiterpenoid framework (Scheme 4).

The stereochemistry of the final product was confirmed by the X-ray crystallographic analysis of **28**, which was derived from isoxazoline **14a** as outlined in Scheme 3. Isoxazoline **14a** was transformed to *α*-methoxy ketone **26** by catalytic hydrogenation over Raney Ni and acetic acid in a 4∶1 mixture of methanol and water. After debenzylation, demethylation and spontaneous cyclization of **27** led to the solid **28**, which was crystallized from petroleum and ethyl acetate.

Experimental

Starting materials, reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. Anhydrous THF, toluene, benzene and CH_2Cl_2 were obtained from a distillation over sodium wire or CaH_2. All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. The progress of reactions was monitored by silica gel thin layer

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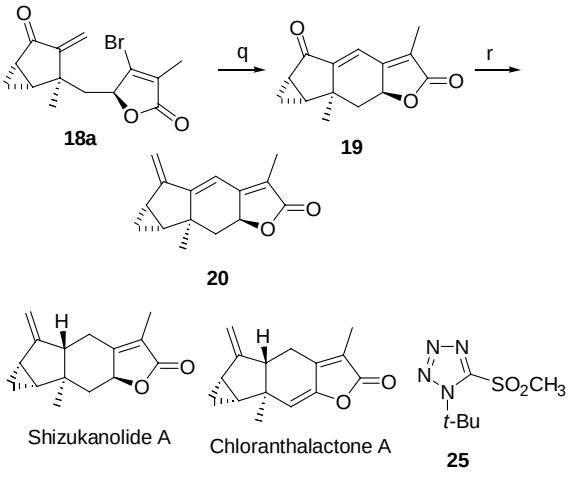
Scheme 4 Preparation of lindenane-type sesquiterpenoid framework **20**



Reagents and conditions: (q) $Pd(OAc)_2$, Et_3N, DMF, 80 ℃, 4 h, 31% (69%, BORSM); (r) Julia's reagent **25**, NaHMDS, THF, –78 ℃, 6 h, 47%.

chromatography (TLC) plates, visualized under UV and charred using phosphomolybdic acid solution followed by heating. Products were purified by flash column chromatography (FCC) on 200－400 mesh silica gel. Petroleum ether refers to the fraction with boiling range 60－90 or 30－60 ℃. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a spectrometer operating at 300 MHz. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a spectrometer operating at 75 MHz.

((2*R*,3*R*)-3-(2-(Benzyloxy)ethyl)-3-methyloxiran-2-yl)methanol (2) Colorless liquid, $[\alpha]_D^{20}$ =5.1 (c= 4.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39－7.28 (m, 5H), 4.51 (s, 2H), 3.86－3.81 (m, 1H), 3.72－3.66 (m, 1H), 3.60－3.55 (m, 2H), 3.06－3.03 (m, 1H), 1.93－2.01 (m, 2H), 1.33 (s, 3H); HR-ESIMS calcd for $C_{13}H_{18}O_3Na^+$ $[M+Na]^+$ 245.1168, found 245.1154.

(((2*R*,3*R*)-3-(2-(Benzyloxy)ethyl)-3-methyloxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (3) To a soln. of alcohol **2** (13.9 g, 62.6 mmol) and 1*H*-imidazole (9.38 g, 137.7 mmol) in 75 mL of DMF was added a soln. of TBSCl (10.38 g, 68.8 mmol) in 25 mL of DMF over a period of 25 min, and the mixture was then stirred at r.t. for 5 h. The reaction was quenched with 250 mL of H_2O, and the mixture was stirred for 30 min at r.t. The mixture was then poured into 150 mL of EtOAc. The org. phase was washed with sat. aq. NaCl soln. (50 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=100∶1 to 60∶1) to afford **3** (21.0 g) as a colorless oil in quantitative yield. $[\alpha]_D^{20}$ =–10.32 (c = 3.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37－7.28 (m, 5H), 4.50 (s, 2H), 3.82－3.68 (m, 2H), 3.60－3.55 (m, 2H), 2.988 (t, J=5.4 Hz, 1H), 1.99－1.89 (m, 1H), 1.85－1.78 (m, 1H), 1.29 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.52, 128.62, 127.86, 127.83, 73.28, 66.84, 63.45, 62.47, 59.27, 38.61, 26.14, 18.56,17.58, –4.92, –5.08; HR-ESIMS calcd for $C_{19}H_{32}O_3SiNa^+$ $[M+Na]^+$ 359.2018, found 359.2031.

(*R*)-4-(Benzyloxy)-2-((*tert*-butyldimethylsilyloxy)-methyl)-2-methylbutanal (4) To a soln. of methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide), which was prepared from 4-bromo-2,6-di(*tert*-butyl) phenol (53.6 g, 0.188 mol) and Me_3Al (94 mL, 0.094 mol; 1.0 mol/L in hexane) in 300 mL of CH_2Cl_2 at 0 ℃, was added a soln. of **3** (15.8 g, 0.047 mol) at –78 ℃ over a period of 30 min. The mixture was then stirred at –78 ℃ for 1 h then at –40 ℃ for 1 h. The resulting mixture was carefully poured into 1 mol/L HCl solution and then stirred vigorously for 30 min at r.t. The org. phase was washed with sat. aq. NaCl soln. (50 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc =100∶1 to 30∶1) to afford **4** (14.82 g) as a yellow oil in 94% yield. $[\alpha]_D^{20}$ =2.4 (c=1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.34－7.27 (m, 5H), 4.44 (s, 2H), 3.63 (dd, J=28.0, 9.9 Hz, 2H), 3.53－3.46 (m, 2H), 2.06－1.96 (m, 1H), 1.79－1.68 (m, 1H), 1.06 (s, 3H), 0.86 (s, 9H), 0.014 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.77, 138.34, 128.57, 127.86, 127.79, 73.31, 67.24, 66.28, 50.39, 33.26, 25.97, 18.38, 16.55, –5.44, –5.46; HR-ESIMS calcd for $C_{19}H_{32}O_3SiNa^+$ $[M+Na]^+$ 359.2018, found 359.2006.

(*S*)-(2-(2-(Benzyloxy)ethyl)-2-methylbut-3-enyloxy)-(*tert*-butyl)dimethylsilane (5) To a stirred suspension of (methyl)(triphenyl) phosphonium Bromide powder (56.94 g, 0.1593 mol) in 600 mL of dry THF at –78 ℃ was added *n*-BuLi (90 mL, 0.1434 mol; 1.6 mol/L in hexane) over 1 h, then slowly warmed to –40 ℃ (*ca.* 1.5 h). Then a soln. of **4** (29.8 g, 0.0885 mol) in 50 mL of THF was added dropwise over 30 min, and the resulting mixture was stirred for 2 h and warm to r.t. naturally. Acetone (3 mL) was added to the mixture to consume the excess Wittig reagent. The mixture was treated with sat. aq. NH_4Cl soln. and extracted with EtOAc (100 mL×3). The org. phase was washed with sat. aq. NaCl soln. (50 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=50∶1) to afford **5** (28.07 g) as a yellow oil in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34－7.28 (m, 5H), 5.79 (dd, J=17.5, 10.9 Hz, 1H), 4.98 (t, J=13.6 Hz, 2H), 4.46 (s, 2H), 3.48 (t, J=7.4 Hz, 2H), 3.33 (q, J=9.4 Hz, 2H), 1.74 (q, J= 9.4 Hz, 2H), 0.98 (s, 3H), 0.87 (s, 9H), 0.07 (s, 6H); HR-ESIMS calcd for $C_{20}H_{34}O_2SiNa^+$ $[M+Na]^+$ 357.2225, found 357.2214.

(*S*)-2-(2-(Benzyloxy)ethyl)-2-methylbut-3-en-1-ol

(6) To a soln. of **5** (28.2 g, 0.0843 mol) in 300 mL of THF was added TBAF (101 mL, 0.101 mol; 1 mol/L in THF) at 0 ℃. The mixture was stirred at r.t. for 3 h. After the completion of the reaction, The mixture was treated with sat. aq. NH_4Cl soln. and extracted with EtOAc (100 mL×2). The org. phase was washed with sat. aq. NaCl soln. (30 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=30∶1 to 10∶1) to afford **6** (17.83 g) as a colorless oil in 96% yield. $[\alpha]_D^{20}=-3$ ($c=2.36$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36−7.28 (m, 5H), 5.80 (dd, J=17.7, 11.1 Hz, 1H), 5.06 (ddd, J=12.9, 11.4, 1.2 Hz, 2H), 4.50 (s, 2H), 3.55 (t, J=5.9 Hz, 2H), 3.47−3.33 (m, 2H), 2.70 (t, J=6.9 Hz, 1H), 1.74−1.68 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.53, 138.20, 128.69, 127.98, 113.55, 73.43, 69.90, 67.25, 41.45, 37.32, 21.70; HR-EIMS calcd for $C_{14}H_{20}O_2^+$ [M^+] 220.1463, found 220.1464.

(*S*)-2-(2-(Benzyloxy)ethyl)-2-methylbut-3-enyl-2-diazoacetate (7) A suspension of glyoxylic acid *p*-toluenesulfonyl hydrazone (4.95 g, 20.43 mmol) in a solution of 50 mL of anhydrous benzene and 4.45 mL of thionyl chloride (61.29 mmol) was refluxed with stirring for 2 h under an argon atmosphere. The solvent was placed on a high-vacuum line for 1 h to remove residual thionyl chloride. This material was used immediately without purification. The crude glyoxylic acid chloride *p*-toluenesulfonyl hydrazone in 40 mL of CH_2Cl_2 was dropped into a solution of **6** (3.0 g, 13.62 mmol) in 130 mL of anhydrous CH_2Cl_2 in an ice bath under an argon atmosphere. Dimethylaniline (2.42 mL,19.07 mmol) in 17 mL of CH_2Cl_2 was added with stirring for 15 min prior to addition of Et_3N (3.8 mL, 27.24 mmol) in 15 mL of CH_2Cl_2. The resulting dark orange solution was stirred for 10 min at 0 ℃ and then 20 min at room temperature. The CH_2Cl_2 solution was evaporated. Flash column chromatography (PE∶EtOAc=40∶1 to 20∶1) provided **7** (3.18 g) as a yellow oil in 81% yield over two steps. $[\alpha]_D^{20}=7.04$ (c=2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.27 (m, 5H), 5.75 (dd, J=17.6, 10.9 Hz, 1H), 5.05 (dd, J=18.7, 14.2 Hz, 2H), 4.73 (s, 1H), 4.47 (s, 2H), 4.01 (q, J=15.1 Hz, 2H), 3.49 (t, J=7.2 Hz, 2H), 1.75 (t, J=7.2 Hz, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.88, 138.58, 128.62, 127.80, 114.17, 73.27, 71.40, 67.04, 46.37, 39.76, 37.03, 21.16; HR-ESIMS calcd for $C_{16}H_{20}N_2O_3Na^+$ [M+Na]$^+$ 311.1372, found 311.1391.

(1*S*,5*S*,6*R*)-5-(2-(Benzyloxy)ethyl)-5-methyl-3-oxabicyclo[4.1.0]heptan-2-one (8) To a refluxing solution of bis(*tert*-butylsalicylal diminato)copper(II) [$Cu(TBS)_2$] (116.6 mg, 0.281 mmol) in 240 mL anhydrous, deoxygenated toluene was added a solution of **7** (1.62 g, 5.62 mmol) in 60 mL deoxygenated toluene over 5 h under an argon atmosphere. The resulting mixture was refluxed for a further 30 min and then allowed to cool to room temperature. It was concentrated under reduced pressure and then purified by flash chromatography (PE∶EtOAc=5∶1 to 3∶1) to give 1.04 g of an inseparable 1.9∶1.0 mixture of **8** as a yellow oil in 74% yield. The stereochemistry of **8a** and **8b** (separated by reverse semi-preparative column: Agilent 1200HPLC using an Agilent 20RBAX Eclipse XDB-C18, 5 μm reversed-phase column measuring 4.6 mm×150 mm with 50% MeOH∶50% H_2O over 30 min. t_R(**8a**)= 11.32 min, t_R(**8b**)=12.42 min) was determined by extensive spectroscopic studies along with a single crystal X-ray diffraction analysis of relate compoud. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41−7.26 (m, 5H), 4.48 (s, 2H), 3.90 (dd, J=17.6, 7.0 Hz, 1H), 3.80−3.68 (m, 1H), 3.61 (dt, J=15.6, 4.8 Hz, 2H), 1.91−1.80 (m, 2H), 1.67 (dd, J=11.2, 5.2 Hz, 1H), 1.64−1.55 (m, 1H), 1.33 (dd, J=10.3, 5.6 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.62, 138.44, 128.68, 128.62, 127.96, 127.83, 73.43, 73.29, 73.15, 72.26, 66.71, 66.40, 37.72, 37.65, 31.22, 30.77, 26.18, 26.03, 23.74, 22.04, 16.36, 15.82, 9.07, 8.28; HR-ESIMS calcd for $C_{16}H_{21}O_3^+$ [M+H]$^+$ 261.1491, found 261.1480.

(1*S*,2*R*)-2-((*S*)-4-(Benzyloxy)-1-hydroxy-2-methylbutan-2-yl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (9a) and (1*R*,2*S*)-2-((*S*)-4-(benzyloxy)-1-hydroxy-2-methylbutan-2-yl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (9b) Trimethylaluminum (26.7 mL, 26.7 mmol; 1 mol/L in heptane) was slowly added over 20 min to *N*,*O*-dimethyl hydroxylamine hydrochloride (2.608 g, 26.73 mmol) in 70 mL anhydrous CH_2Cl_2 at 0 ℃. The bath was removed, and the solution was allowed to stir at r.t. for 1 h. Upon cooling the solution to 0 ℃, **8** (2.32 g, 8.91 mmol) in 50 mL anhydrous CH_2Cl_2 was cannulated in over a 30 min period. The cooling bath was removed, and the solution was stirred for several hours. The solution was cooled to 0 ℃, then treated with sat. aq. Rochelle's soln. and extracted with EtOAc (30 mL×2). The org. phase was washed with sat. aq. NaCl soln. (10 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=5∶1 to 2∶1) to afford **9** (1.73 g) as a yellow oil in 98% yield based on 0.892 g **8** recovery (62%, BORSM).

9a and **9b** were separated by normal semi-preparative column: Agilent 1200HPLC using an Agilent 20RBAX Zorbax SB-C18, 5 μm normal-phase column measuring 4.6 mm×250 mm with 90% hexane∶10% isopropyl alcohol over 50 min; t_R(**9b**)=16.18 min, t_R(**9a**)=20.52 min.

9a Colorless liquid, $[\alpha]_D^{20}=-35.46$ (c = 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34−7.28 (m, 5H), 4.50 (s, 3H), 3.75 (s, 3H), 3.65−3.57 (m, 2H), 3.35 (s, 3H), 3.19 (s, 3H), 1.94 (br, 1H), 1.81−1.66 (m, 3H), 1.36−1.21 (m, 2H), 0.92 (td, J=8.1, 3.6 Hz, 1H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.95, 128.67, 128.03, 127.97, 73.48, 70.69, 67.10, 61.58, 39.37, 34.12, 38.26, 29.75, 20.51, 17.70, 7.91; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 128.67, 128.03, 127.97,

73.48, 70.69, 67.10, 61.58, 39.37, 34.12, 29.75, 20.51, 17.70, 7.91; HR-ESIMS calcd for $C_{18}H_{27}NO_4Na^+$ [M+Na]$^+$ 344.1838, found 344.1835.

9b Colorless liquid, $[\alpha]_D^{20}$ =63.4 (c=0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38−7.24 (m, 5H), 4.51 (s, 2H), 3.72 (d, J=1.8 Hz, 3H), 3.60 (dddd, J=13.7, 12.2, 8.2, 4.1 Hz, 2H), 3.34 (s, 3H), 3.18 (s, 2H), 1.99 (d, J=25.6 Hz, 2H), 1.86−1.73 (m, 2H), 1.59 (ddd, J=14.9, 6.7, 4.0 Hz, 1H), 1.44 (t, J=6.9 Hz, 1H), 1.39 (ddd, J=12.3, 6.2, 4.3 Hz, 1H), 0.95−0.85 (m, 1H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.95, 128.68, 128.04, 128.01, 73.53, 70.54, 67.16, 61.48, 38.33, 37.98, 33.26, 30.00, 21.10, 17.22, 8.62; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 128.68, 128.04, 128.01, 73.53, 70.54, 67.16, 61.48, 38.33, 33.26, 30.00, 21.10, 17.22, 8.62.

(1*S*,2*R*)-2-((*S*)-4-(Benzyloxy)-2-methyl-1-oxobutan-2-yl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (10) Alcohol **9a** (4.75 g, 14.78 mmol) was dissolved in 200 mL CH_2Cl_2, then treated with DMP (7.522 g, 17.73 mmol) at 0 ℃, the solution became cloudy immediately until a colourless emulsion formed. The bath was removed, and the solution was allowed to stir at r.t. for 3 h, then hydrolysis was achieved by addition of 150 mL of a 1∶1 mixture of sat. aq $NaHCO_3$ soln. and sat. aq $Na_2S_2O_3$ soln. The mixture was stirred until two clear layers formed. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (50 mL×2). The org. phase was washed with sat. aq. NaCl soln. (20 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=2∶1) to afford **10** (4.26 g) as a yellow oil in 90% yield. $[\alpha]_D^{20}$ =−20 (c=0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.49 (s, 1H), 7.35−7.22 (m, 5H), 4.45 (s, 2H), 3.71 (s, 3H), 3.57 (t, J=6.5 Hz, 2H), 3.16 (s, 3H), 2.02 (dd, J=14.2, 7.1 Hz, 1H), 1.83 (dt, J=14.2, 6.0 Hz, 1H), 1.37 (dt, J=12.4, 6.6 Hz, 2H), 1.12 (s, 3H), 1.03 (dd, J=7.9, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.30, 172.61, 138.44, 128.58, 127.85, 113.80, 73.26, 66.53, 61.65, 37.33, 32.92, 28.41, 20.49, 16.54, 9.47. HR-ESIMS calcd for $C_{18}H_{25}NO_4Na^+$ [M+Na]$^+$ 342.1681, found 342.1669.

(1*S*,2*R*)-2-((*R*)-5-(Benzyloxy)-3-methylpent-1-en-3-yl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (11) To a stirred suspension of (methyl)(triphenyl) phosphonium Bromide powder (11.91 g, 33.25 mmol) in 100 mL of dry THF at 0 ℃ was added NaHMDS (29.9 mL, 29.9 mmol; 1.0 mol/L in THF) over 30 min. The bath was removed, and the solution was allowed to stir at r.t. for 30 min. Upon cooling the solution to −78 ℃, a soln. of **10** (4.26 g, 13.3 mol) in 60 mL of THF was added dropwise over 30 min, and the resulting mixture was stirred at 0 ℃ for another 1 h. Then the mixture was treated with sat. aq. NH_4Cl soln. and extracted with EtOAc (50 mL×3). The org. phase was washed with sat. aq. NaCl soln. (20 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc = 20∶1 to 5∶1) to afford **11** (3.8 g) as a yellow oil in 90% yield. $[\alpha]_D^{20}$ =−28.8 (c=0.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.28 (m, 5H), 5.80 (dd, J=17.4, 10.9 Hz, 1H), 4.95−4.87 (m, 2H), 4.47 (s, 2H), 3.71 (s, 3H), 3.57−3.50 (m, 2H), 3.16 (s, 3H), 1.89−1.75 (m, 2H), 1.37−1.23 (m, 2H), 1.01 (s, 3H), 0.93−0.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.79, 128.56, 127.82, 127.69, 111.60, 73.16, 67.54, 61.40, 42.43, 38.79, 32.09, 31.16, 21.82, 18.03, 8.21. HR-ESIMS calcd for $C_{19}H_{27}NO_3Na^+$ [M + Na]$^+$ 340.1889, found 340.1877.

(1a*S*,3a*S*,4*R*,5a*R*)-4-(2-(Benzyloxy)ethyl)-4-methyl-1a,3a,4,5a-tetrahydrocyclopropa-3*H*-cyclopenta[*c*]-isoxazole (14a) and (1a*S*,3b*S*,4*R*,5a*R*)-4-(2-(benzyloxy)-ethyl)-4-methyl-1a,3b,4,5a-tetrahydrocyclopropa-3*H*-cyclopenta[*c*]isoxazole (14b) To the cyclopropyl amide **11** (3.8 g, 11.97 mmol) in dry THF (120 mL) under nitrogen at −78 ℃, DIBAL-H (15.6 mL, 15.6 mmol; 1 mol/L in hexane) was added. The reaction was completed in 2 h. Reaction mixture was poured into a sat. aq. potassium sodium tartarate soln. (10 mL) and stirred for 1 h, then extracted with EtOAc (40 mL×2). The combined organic solution was washed with brine (20 mL×2) and dried over Na_2SO_4, concentrated to give 3.09 g (quantitative) of yellow liquid **12**.

Hydroxylamine hydrochloride (1.0 g, 14.36 mmol) was added to a solution of the aldehyde **12** in pyridine (36 mL). The reaction mixture was stirred at room temperature until the disappearance of the aldehyde as shown on TLC. Concentration of the solvent under reduced pressure and then purification with flash chromatography on silica gel (PE∶EtOAc=5∶1) to remove pyridinium chloride gave 3.2 g of colorless liquid oxime **13**.

To a stirred solution of oxime **13** (3.2 g, 11.7 mmol) in CH_2Cl_2 (140 mL) was added an aqueous NaClO soln. (17.5 mmol, 25 mL) and the mixture was stirred at room temperature for 9 h. The reaction was diluted with water and extracted with CH_2Cl_2 (30 mL×2), The org. phase was washed with sat. aq. NaCl soln. (10 mL×3) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc = 10∶1 to 5∶1) to afford **14** (2.58 g) as a yellow oil in 79% yield over three steps.

14a Colorless liquid, $[\alpha]_D^{20}$ = 47.8 (c = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35−7.27 (m, 5H), 4.50 (s, 2H), 4.26 (dd, J=11.0, 8.4 Hz, 1H), 3.99 (dd, J=12.0, 8.4 Hz, 1H), 3.62 (tdd, J=7.2, 4.2, 1.4 Hz, 2H), 3.24−3.14 (q, J=12 Hz, 1H), 2.09−2.04 (m, 2H), 1.78−1.70 (m, 2H), 1.13 (s, 3H), 1.03 (dd, J=9.0, 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.39, 138.42, 128.65, 128.01, 127.88, 127.86, 73.39, 69.31, 66.67, 59.41, 38.36, 36.75, 35.63, 24.82, 14.83, 10.26; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 128.65, 127.86, 73.39, 69.31, 66.67, 59.41, 36.75, 35.63, 24.82, 14.83, 10.26.

HR-ESIMS calcd. for $C_{17}H_{22}NO_2^+$ [M + H] $^+$ 272.2651, found 272.1654.

14b ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36－7.28 (m, 5H), 4.48 (s, 2H), 4.13－4.00 (m, 2H), 3.62－3.49 (m, 2H), 2.05－1.93 (m, 2H), 1.91－1.84 (m, 2H), 1.15－1.01 (m, 2H), 0.94－0.88 (m, 1H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.84, 138.24, 128.70, 128.00, 127.96, 127.88, 73.56, 73.40, 71.86, 70.17, 67.66, 67.51, 43.92, 37.57, 37.42, 19.48, 15.92, 12.74; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 128.70, 128.00, 127.96, 73.56, 73.40, 71.86, 70.17, 67.66, 43.92, 37.42, 19.48, 15.92, 12.74.

(1*S*,3*R*,4*S*,5*R*)-4-(2-(Benzyloxy)ethyl)-3-(hydroxymethyl)-4-methylbicyclo[3.1.0]hexan-2-one (15a) and (1*S*,3*S*,4*S*,5*R*)-4-(2-(benzyloxy)ethyl)-3-(hydroxymethyl)-4-methylbicyclo[3.1.0]hexan-2-one (15b) To a solution of isoxazoline **14** (607 mg, 2.229 mmol) in MeOH (28 mL) and water (7 mL) were added H_3BO_3 (346 mg, 5.572 mmol) and Pd/C (10%, 61 mg, 10% wt). The reaction flask was evacuated and refilled with H_2 five times, and stirring was continued at room temperature for 1.5 h. The reaction mixture was filtered through a pad of Celite, the organic solvents were removed under vacuum, and the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic phases were washed with sat. aq. $NaHCO_3$ soln. (10 mL×2) and NaCl soln. (10 mL), then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=5∶1 to 3∶1) to afford hydroxyketone **15** (465 mg) as a colorless liquid in 76% yield.

15a Colorless liquid, $[\alpha]_D^{20} = -14$ (c = 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34－7.27 (m, 5H), 4.47 (s, 2H), 3.87 (ddd, J=14.0, 8.4, 4.1 Hz, 1H), 3.57 (m, 3H), 2.82－2.74 (m, 1H), 2.11－2.01 (m, 2H), 1.90－1.80 (m, 1H), 1.65 (dt, J=14.8, 7.3 Hz, 2H), 1.19 (s, 3H), 1.19－1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.29, 128.63, 127.90, 122.30, 73.40, 66.83, 59.10, 52.39, 39.44, 37.39, 30.84, 27.60, 24.41, 13.53; HR-ESIMS calcd for $C_{17}H_{22}O_3Na^+$ [M + Na] $^+$ 297.1467, found 297.1472.

15b ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37－7.27 (m, 5H), 4.47 (s, 2H), 3.87 (dd, J=14.2, 5.4 Hz, 0.5H), 3.77－3.68 (m, 0.5H), 3.64－3.50 (m, 3H), 2.46 (s, OH), 2.26 (t, J=6.0 Hz, 1H), 1.95－1.80 (m, 4H), 1.66 (dd, J=13.9, 7.2 Hz, 1H), 1.13 (s, 3H), 1.10－1.05 (m, 1H).

(1*S*,4*S*,5*R*)-4-(2-Hydroxyethyl)-4-methyl-3-methylenebicyclo[3.1.0]hexan-2-one (16) Pd/C (10%, 270 mg, 20% wt) was suspended in a solution of hydroxyketone **15** (1.346 g, 4.906 mmol) in MeOH (50 mL). The reaction flask was evacuated and refilled with H_2 five times, and stirring was continued at room temperature for 8 h. The reaction mixture was filtered through a pad of Celite, the organic solvents were removed under vacuum to afford diol **M1** as an oil. The diol **M1** was taken directly to the next reaction.

To a solution of diol **M1** (904 mg, 4.907 mmol), DMAP (120 mg, 0.981 mmol), and Et_3N (4.1 mL, 29.44 mmol) in 50 mL of CH_2C1_2 was added acetic anhydride (1.39 mL, 14.72 mmol) at –20 ℃. The reaction mixture was stirred for 3 h and warmed to 0 ℃, before being quenched with sat. aq. $NaHCO_3$ soln. (10 mL). The aqueous phase was extracted with CH_2C1_2 (20 mL×2), and the combined organic phases were washed with H_2O (10 mL×2) and NaCl soln. (10 mL), then dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford **M2**, which was directly subjected to hydrolysis.

To a solution of **M2** in MeOH (48 mL) and H_2O (16 mL) was added Na_2CO_3 (96 mg, 9.814 mmol) in 8 mL of H_2O at room temperature. The resulting mixture was stirred for 1.5 h. Then methanol was removed under reduced pressure, and the residue was extracted with EtOAc (20 mL×2). The org. phase was washed with sat. aq. NaCl soln. (10 mL×2) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=2∶1) to afford **16a** (634 mg) as a colorless oil in 78% yield over three steps. $[\alpha]_D^{20}$ =31.43 (c=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.96 (s, 1H), 5.19 (s, 1H), 3.72－3.58 (m, 2H), 2.01 (br, 1H, OH), 1.99－1.89 (m, 2H), 1.77 (ddd, J=8.0, 6.6, 2.9 Hz, 2H), 1.20 (s, 3H), 1.19－1.11 (m, 1H), 0.71－0.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.09, 151.21, 119.19, 59.18, 46.03, 42.44, 29.43, 26.90, 23.38, 13.34. HR-EIMS calcd for $C_{10}H_{14}O_2^+$ [M^+] 166.0994, found 166.0987.

(*S*)-4-Bromo-3-methyl-5-(((1*R*,2*S*,5*S*)-2-methyl-3-methylene-4-oxobicyclo[3.1.0]hexan-2-yl)methyl)-furan-2(5*H*)-one (18a) and (*R*)-4-bromo-3-methyl-5-(((1*R*,2*S*,5*S*)-2-methyl-3-methylene-4-oxobicyclo-[3.1.0]hexan-2-yl)methyl)furan-2(5*H*)-one (18b) DMSO (0.42 mL, 6 mmol) in CH_2Cl_2 (10 mL) was slowly added to oxalyl chloride (0.29 mL, 3 mmol) in CH_2Cl_2 (20 mL) at –78 ℃. After stirring for 20 min, alcohol **16a** (332 mg, 2 mmol) in CH_2Cl_2 (20 mL) was cannulated into the solution over a 5 min period. The heterogeneous solution was stirred for 60 min, whereupon triethylamine (1.4 mL, 10 mmol) was added. The resulting mixture was stirred for 30 min then warmed to room temperature and stirred for another 30 min. Then the mixture was treated with sat. aq. NH_4Cl soln. and extracted with EtOAc (20 mL×2). The org. phase was washed with sat. aq. NaCl soln. (10 mL×2) and then dried (Na_2SO_4). After concentration, the oil was diluted with CH_2Cl_2 and Et_2O and then filtered through silica gel. This solution was concentrated again to afford aldehyde **17**, which was directly subjected to the next reaction.

i-PrMgCl (3.36 mL, 6.71 mmol) in THF (20 mL) was slowly added to dibromo ester **24** (1.921 g, 7.064 mmol) in THF (40 mL) at 0 ℃. After stirring for 30 min, the reaction mixture was cooled to –78 ℃, aldehyde **17** (580 mg, 3.532 mmol) in THF (20 mL) was cannulated into the solution over a 5 min period, the reaction mixture was stirred for 30 min and warmed to 0

℃. After 3 h, the mixture was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc (20 mL×2). The org. phase was washed with sat. aq. NaCl soln. (10 mL×2) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=6∶1 to 4∶1) to afford **18** (745 mg) as a yellow solid in 63% yield over two steps.

18a White solid, $[\alpha]_D^{20}$ =88.9 (c=0.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.11 (s, 1H), 5.35 (s, 1H), 4.90 (d, J=10.2 Hz, 1H), 2.15−2.07 (m, 2H), 2.07−2.02 (m, 1H), 1.89 (s, 3H), 1.69−1.59 (m, 2H), 1.38 (s, 3H), 1.28−1.19 (m, 2H), 0.81−0.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.93, 170.91, 149.99, 144.79, 129.39, 120.68, 81.01, 79.75, 47.32, 44.76, 42.97, 29.97, 26.50, 22.43, 13.74, 10.50; HR-ESIMS calcd for $C_{14}H_{15}O_3NaBr^+$ $[M+Na]^+$ 333.0102, found 333.0111.

18b White solid, $[\alpha]_D^{20}$ =24.6 (c=0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.16 (s, 1H), 5.36 (s, 1H), 4.73 (d, J=10.5 Hz, 1H), 2.27−2.19 (m, 2H), 2.18−2.09 (m, 2H), 1.89 (d, J=1.8 Hz, 3H), 1.68 (dd, J=9.6, 5.2 Hz, 1H), 1.33 (s, 3H), 1.29−1.23 (m, 1H), 0.79−0.73 (m, 1H).

(4a*S*,5a*S*,6a*R*,6b*S*,7a*S*)-3,6b-Dimethyl-6,6a,7,7a-tetrahydrocyclopropa[2,3]indeno[5,6-*b*]furan-2(6b*H*)-one (19) A solution of **18a** (160 mg, 0.514 mmol), $Pd(OAc)_2$ (34.6 mg, 30 mol%) and Et_3N (0.15 mL, 1.03 mmol) in DMF (10 mL) was stirred at 80 ℃ for 4 h under arogon atmosphere. The reaction mixture was allowed to cool to room temperature, quenched with water (10 mL), and extracted with EtOAc (20 mL×2). The org. phase was washed with water (5 mL×2) and sat. aq. NaCl soln. (10 mL×2) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶EtOAc=6∶1 to 3∶1) to afford **19** (26 mg) as a yellow solid in 31% yield based on 50 mg **18** recovery (69%, BORSM). $[\alpha]_D^{20}$ =−16.5 (c=0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.91 (s, 1H), 5.28−5.19 (m, 1H), 2.60 (dd, J=11.3, 4.7 Hz, 1H), 2.19−2.12 (m, 2H), 1.98 (s, 3H), 1.95−1.90 (m, 1H), 1.76−1.68 (m, 1H), 1.32 (s, 3H), 1.31−1.21 (m, 1H), 0.86−0.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.56, 154.50, 153.61, 127.76, 119.76, 109.39, 77.01, 44.66, 39.75, 29.90, 29.64, 24.05, 14.86, 9.40; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 119.76, 109.39, 77.01, 44.66, 29.90, 29.64, 24.05, 14.86, 9.40; HR-ESIMS calcd for $C_{14}H_{14}O_3Na^+$ $[M+Na]^+$ 253.0840, found 253.0845.

(4a*S*,5a*S*,6a*R*,6b*S*,7a*S*)-3,6b-Dimethyl-5,5a,6,6a,7,7a-hexahydrocyclopropa[2,3]indeno[5,6-*b*]furan-2(6b*H*)-one (20) NaHMDS (0.2 mL, 0.2 mmol; 1.0 mol/L in THF)) was slowly added to a solution of ketone **19** (30 mg, 0.13 mmol) and Julia's reagent **25** (37.2 mg, 0.182 mmol) in THF (2.5 mL) under argon. The mixture was stirred for 6 h at −78 ℃, then quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc (5 mL×2). The org. phase was washed with sat. aq. NaCl soln. (2 mL×2) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (PE∶Benzene=1∶2 to PE∶EtOAc=12∶1) to afford **20** (14 mg) as a white solid in 47% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.535 (s, 1H), 5.337 (s, 1H), 5.126 (s, 1H), 5.033−4.985 (m, 1H), 2.43 (dd, J=11.5, 5.0 Hz, 2H), 1.99−1.91 (m, 2H), 1.90 (s, 3H), 1.467−1.568 (m, 2H), 1.264 (s, 3H), 0.78 (td, J=7.7, 5.4 Hz, 2H), 0.14 (dd, J=8.4, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.90, 156.44, 154.93, 149.63, 119.54, 113.65, 107.21, 77.00, 40.14, 28.62, 26.21, 20.51, 12.20, 8.73; ^{13}C NMR-dept (75 MHz, $CDCl_3$) δ: 113.65, 107.21, 77.00, 45.65, 40.14, 28.62, 26.21, 20.51, 12.20, 8.73; HR-EIMS calcd for $C_{15}H_{16}O_2^+$ $[M^+]$ 228.1150, found 228.1154.

(4a*S*,5*R*,6*S*,7a*S*)-4a-Methyl-4a,5,5a,6,6a,7a-hexahydrocyclopropa[2,3]cyclopenta[*c*]pyran-7(3*H*)-one (28) $[\alpha]_D^{20}$ =25.8 (c=0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.25 (d, J=12.1 Hz, 1H), 3.72 (dd, J=11.5, 4.0 Hz, 1H), 3.41 (dd, J=12.1, 4.0 Hz, 1H), 3.31 (dd, J=11.3, 1.5 Hz, 1H), 1.86 (ddd, J=7.7, 6.7, 4.0 Hz, 2H), 1.80−1.66 (m, 1H), 1.58−1.50 (m, 2H), 1.28 (s, 3H), 1.22−1.13 (m, 1H), 1.13−1.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.19, 77.74, 77.31, 76.89, 63.54, 61.23, 45.49, 37.57, 35.20, 33.05, 26.53, 22.21, 13.05; HR-EIMS calcd for $C_{10}H_{14}O_2^+$ $[M^+]$ 166.0994, found 166.0985.

Conclusions

In summary, we have developed a practical synthesis of the lindenane-type sesquiterpenoid framework **20** in a linear sequence of 21 steps and an overall yield of 1.8% from easily accessible starting materials. The flexible synthetic route could generate further natural products of the Chloranthaceae family such as Shizukanolides A and Chloranthalactone A[17] (Scheme 4).

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