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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-BUCIDARASINS A AND C

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Abstract – In this paper, the first total synthesis of (+)-bucidarasins A and C is described. The chiral starting material was successfully obtained via reduction using a CBS catalyst and selective mono-TBS ether formation of *trans*-2-benzyloxymethyl-2-methylcyclohexane-1,3-diol, which was crucial to the successful enantioselective total synthesis of (+)-bucidarasins A and C. A synthetic approach towards (+)-bucidarasin C, based on the Barton-McCombie protocol, using V-70 as a radical promoter at low temperature to remove the C6-hydroxy moiety is also described.

INTRODUCTION

In 2002, Lee's group isolated bucidarasins A-D (Figure 1) from a crude extract of *Bucida buceras*.[1] Bucidarasins A-D belong to clerodane diterpene, a large family of molecules comprised of *cis*- and *trans*-fused members as well as *ent*-members.[2] Clerodane diterpenes feature the characteristic scaffold

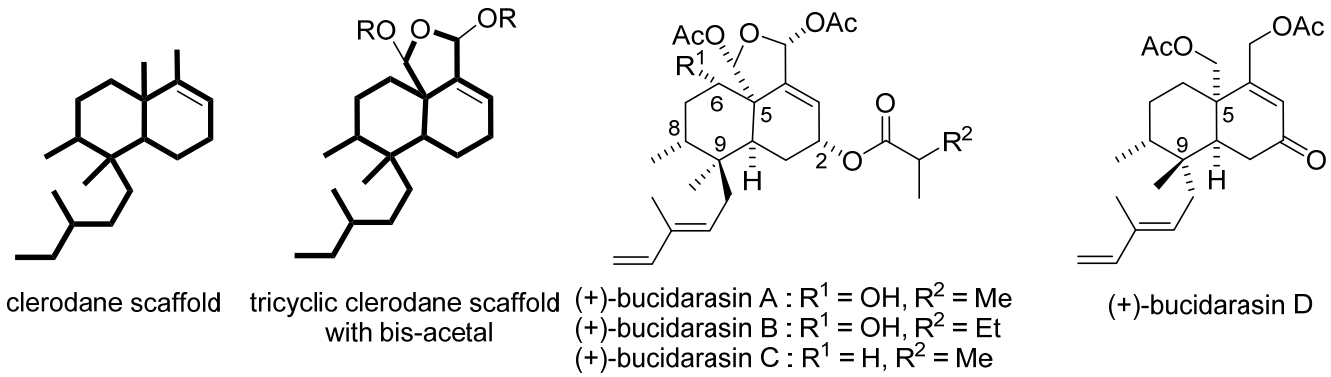


Figure 1. Structures of tricyclic clerodane scaffold, clerodane scaffold, and (+)-bucidarasin A-D

shown in Figure 1, while bucidarasins A-C possess a tricyclic scaffold composed of *cis*-dehydrodecalin fused to a tetrahydrofuran (THF) ring with two acetyloxy groups at the C18 and C19 positions. The tricyclic scaffold includes up to eight stereogenic centers, of which six are contiguous and two all-carbon quaternary stereogenic centers are involved. A number of similar tricyclic *cis*-clerodane diterpenes have been reported and were primarily isolated from the tropical genus Casearia;[3,4] many of these compounds have been shown to exhibit a wide range of bioactivities,[1,3a,f,h,l-u,w-y,4a,b,e,h,i,k-p] including cytotoxicity.[1,3a,f,h,n-r,t,u,w-y,4a,b,e,h,i,k-p] Specifically, recent biological studies revealed that some members of this family exhibit apoptotic activities[5] and synergistic effects with TRAIL (tumor necrosis factor-α-related apoptosis-inducing ligand), which lead to cell death.[4m]

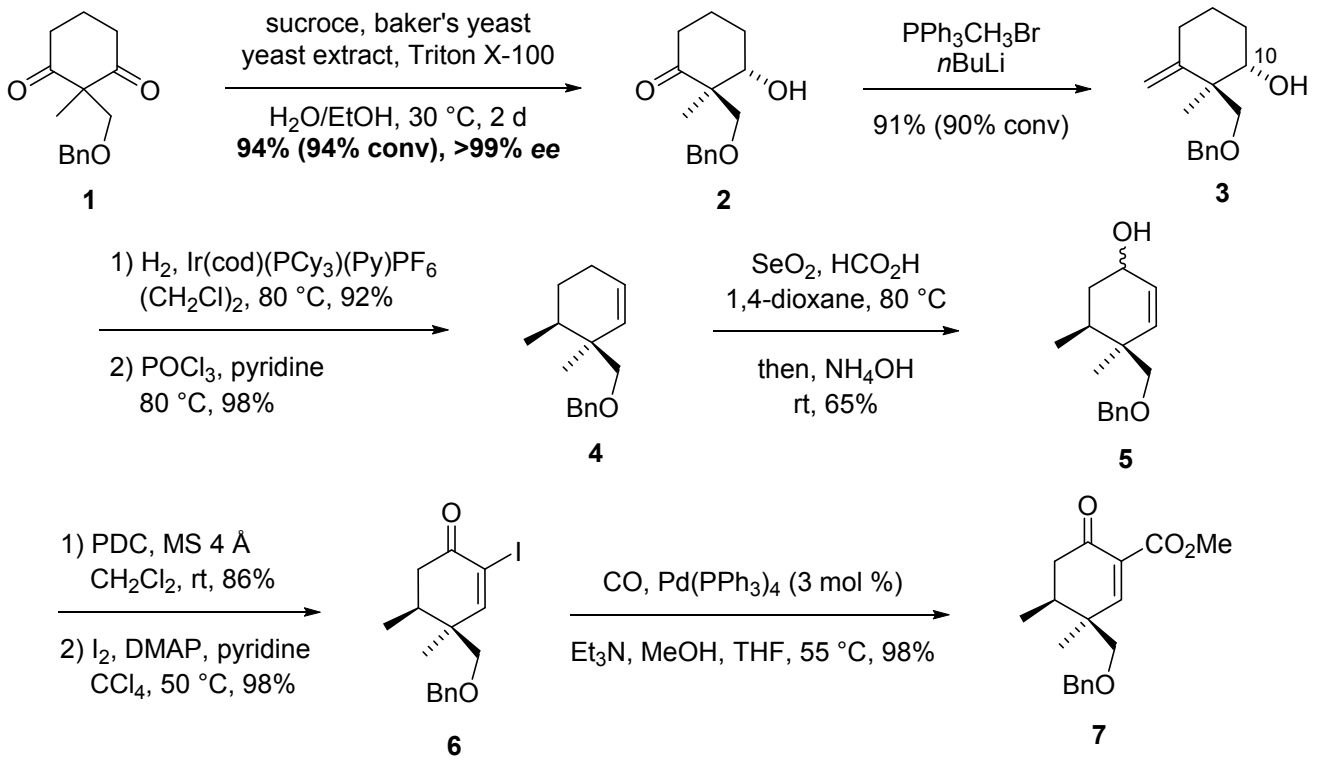
Bucidarasins A-C have been reported to be inhibitors of human tumor cell replication, and have also been reported to show various potent and wide spectrum activities. The IC_{50} values of bucidarasins A-C range from 0.5 to 1.9 μM against nine human tumor cell lines, and the potency is retained against drug resistant cell lines. On the other hand, bucidarasin D exhibits no bioactivity, suggesting that the acetal moiety is required for cytotoxicity.[1] The potent bioactivity and complex structure of bucidarasins A-C and related compounds make them attractive synthetic targets. Notably, our group succeeded in the first total synthesis of (–)-bucidarasin A.[6] To the best of our knowledge, the total syntheses of the THF ring-fused tricyclic *cis*-clerodane diterpenes have never been reported prior to our synthesis, though a number of clerodane diterpenes have been synthesized.[7]

Unfortunately, (–)-bucidarasin A synthesized by our group was the enantiomer of naturally occurring (+)-bucidarasin A, because it was difficult to identify the absolute configuration of (+)-bucidarasin A before beginning the total synthesis of naturally occurring bucidarasins, even though the absolute configurations of many congeners have been reported. Hence, in pursuit of carrying out structure-activity relationship (SAR) studies in addition to elucidating their modes of action, we began synthetic studies of natural bucidarasins. Herein, we report the enantioselective total synthesis of (+)-bucidarasins A and C.

RESULTS AND DISCUSSION

Scheme 1 shows the preparation of previously reported chiral dienophile **7**, which was used in the enantioselective total synthesis of (–)-bucidarasin A. The baker's yeast reduction of **1** afforded **2** as the sole product in excellent yield (94%, 94% conv) in a highly enantioselective manner (>99% ee).[8] Moreover, **2** contained an all-carbon quaternary stereogenic center, which was the same configuration as that of C9 in (–)-bucidarasin A. Consequently, **2** was used as the chiral starting material for the total synthesis of (–)-bucidarasin A. Accordingly, **2** was converted to **4** via **3** by Wittig methylenation, followed by the stereoselective hydroxy-directed hydrogenation of C10 using Crabtree's catalyst and

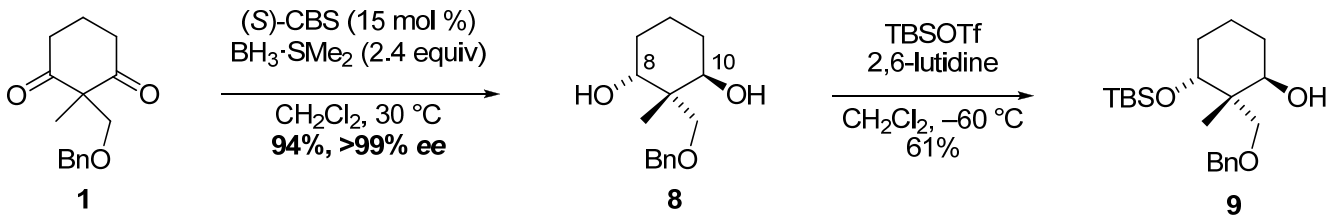
dehydration using $POCl_3$ to afford **4**. Compound **4** was successfully transformed to the requisite dienophile **7** through allylic oxidation, PDC oxidation, iodination, and Pd-catalyzed carbonylation.



Scheme 1. Enantioselective preparation of **7**[6]

If baker's yeast could be modified for use in the reduction of **1** to afford ***ent*-2**, ***ent*-7** could be easily prepared to achieve the total synthesis of (+)-bucidarasin A. Unfortunately, to the best of our knowledge, a baker's yeast reduction that can convert **1** to ***ent*-2** has not been reported to date. However, we reported the highly enantio- and stereoselective CBS (Corey-Bakshi-Shibata) reduction of **1**, which afforded the corresponding *trans*-1,3-diol with excellent ee (>99% ee) and yield (94%).[8] This catalytic asymmetric reduction was expected to be a suitable alternative in the preparation of ***ent*-7**, which could not be prepared via baker's yeast reduction.

One potential issue in the preparation of ***ent*-7** is the generation of the C8 stereogenic center. Since compound **3** was successfully converted to **4** via the stereoselective hydroxy-directed hydrogenation of C10 with Crabtree's catalyst,[9] the preparation of ***ent*-3** was proposed from **8** (Scheme 2), which possesses the *R* configuration at C10. However, the two hydroxy groups in **8**, which were generated using $BH_3 \cdot SMe_2$ and a catalytic amount of (*S*)-CBS catalyst, had to be chemically differentiated in order to prepare ***ent*-3**. Nevertheless, it was expected that one of the two hydroxy groups would selectively react with TBSOTf, because cyclohexane derivative **8** should assume the most stable chair conformation, which would contain one hydroxy group in the equatorial position.



Scheme 2. Reduction of **1** with (*S*)-CBS and $BH_3 \cdot SMe_2$, and selective formation of mono-TBS ether **9**

Indeed, although the selective oxidation of one hydroxy group of **8** was unsuccessful, the reaction of **8** with TBSOTf afforded **9** in 61% yield with the concomitant formation of the bis-TBS ether of **8** (20%) (Scheme 2). Although the formation of diastereomeric mono-TBS ether was observed via TLC during the reaction, it readily converted to the bis-TBS ether.

In this reaction, the slow addition of TBSOTf to a solution of **8** and 2,6-lutidine in CH_2Cl_2 at –60 °C using a syringe pump over 5 h, was crucial to afford **9** as the major product. The byproduct, the bis-TBS ether of **8,** was successfully separated via flash silica gel column chromatography and could be recycled upon treatment with TBAF.

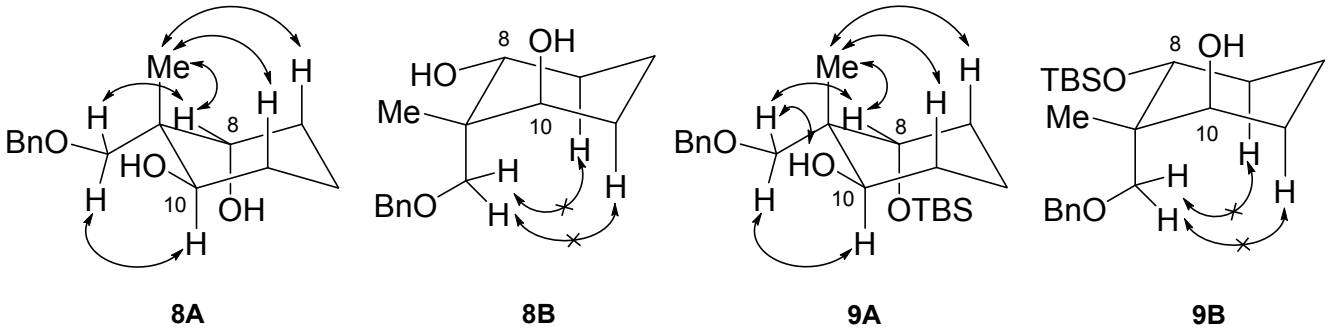
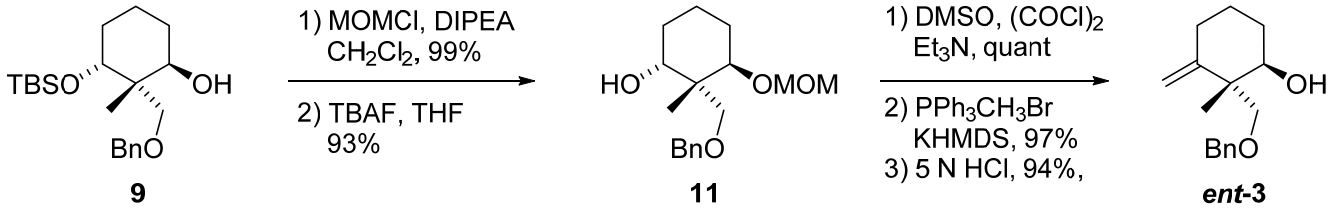


Figure 2. Structures of **8A** and **9A** elucidated by NMR studies

NMR studies of **8** and **9** indicated that their structures in $CDCl_3$ solution were exclusively those of **8A** and **9A**, respectively (Figure 2). The observed NOE correlations indicated that both compounds existed in the chair conformation, and the C8 and C10 substituents in **8A** and **9A** were axial and equatorial positions, respectively.

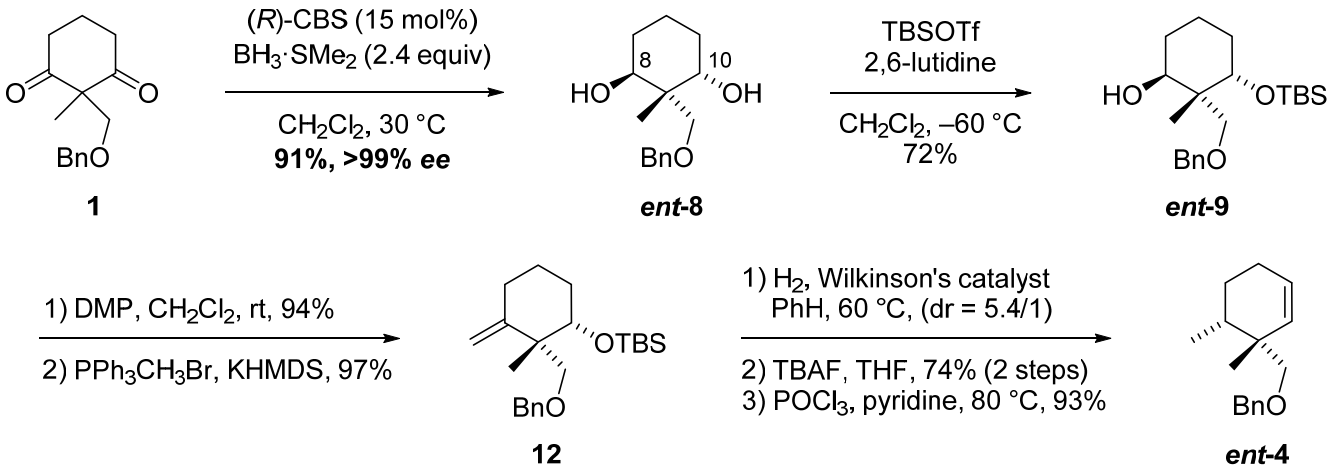
Before performing the reaction of **8**, it was expected that the C10 TBS ether would be preferentially formed because the equatorial hydroxy group is generally more reactive than the sterically hindered axial hydroxy group. However, interestingly, mono TBS ether **9** bearing an axial TBSO group at C8 was isolated.

The TBS ether formation of the equatorial C10 hydroxy group may be slow because the bulky TBS group could suffer from steric strain owing to the presence of the vicinal equatorial $BnOCH_2$ group. However, the possibility that the equatorial C8 hydroxy group in the minor conformer **8B** preferentially reacted with TBSOTf, followed by a conformational change from **9B** to **9A**, which possessed the axial C8 TBSO group, could not be ruled out.



Scheme 3. Enantioselective preparation of ***ent*-3** from **9**

Compound **9** was successfully converted to ***ent*-3** (Scheme 3). Specifically, the reaction of **9** with MOMCl (99%) and the removal of the TBS ether afforded **11** (93%). Swern oxidation of **11** (quant), Wittig methylenation (97%), and removal of the MOM ether under acidic conditions (94%) afforded ***ent*-3**, which proved to be the enantiomer of previously reported **3** by our group (^{1}H- and ^{13}C-NMR, IR, and HRMS).[6]



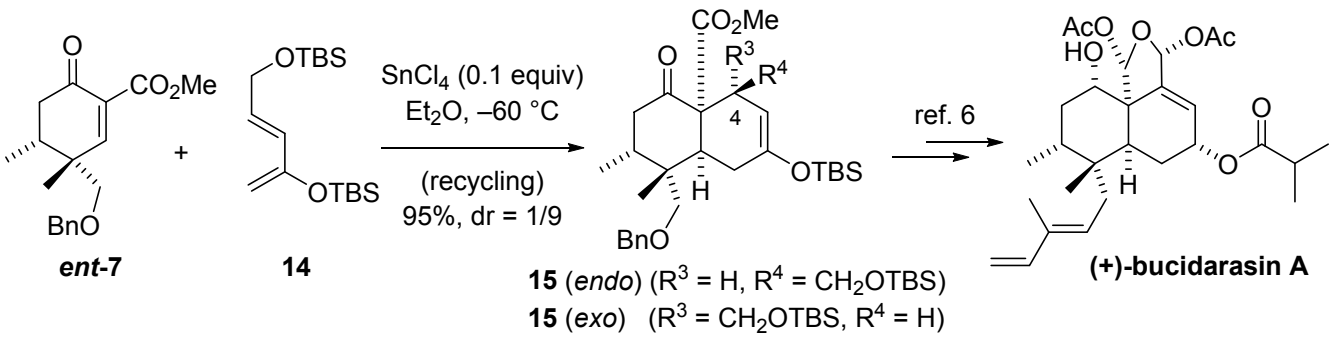
Scheme 4. Enantioselective preparation of ***ent*-4** via the reduction using (*R*)-CBS and $BH_3 \cdot SMe_2$

Compound ***ent*-3** was prepared from **1** in an overall yield of 48% via 7 steps, but the selective protection of **8** with TBSOTf affording **9** prompted us to develop a shorter route to the enantiomer of the reported intermediate. Thus, an alternative synthesis of ***ent*-4** commenced with the reduction of **1** using $BH_3 \cdot SMe_2$

in the presence of a catalytic amount of (*R*)-CBS catalyst to afford ***ent*-8** (91%, >99% ee), which was followed by the mono-TBS ether formation (72%), Dess-Martin oxidation (94%), and Wittig methylenation (97%) to afford **12** (Scheme 4).

To generate the C8 stereogenic center with the desired configuration, suitable catalysts for the stereoselective hydrogenation of **12** that do not catalyze the cleavage of the benzyl ether were surveyed. After several attempts, hydrogenation with the Wilkinson catalyst was found to afford the desired isomer as the major product in a ratio of 5.4/1. The isomers were inseparable at this stage, but could be purified after treatment of the mixture with TBAF (74%, 2 steps). Subsequent dehydration with $POCl_3$ in pyridine at 80 °C afforded ***ent*-4** in 93% yield, which proved to be the enantiomer of previously reported **4** by our group (^{1}H- and ^{13}C-NMR, IR, and HRMS).[6]

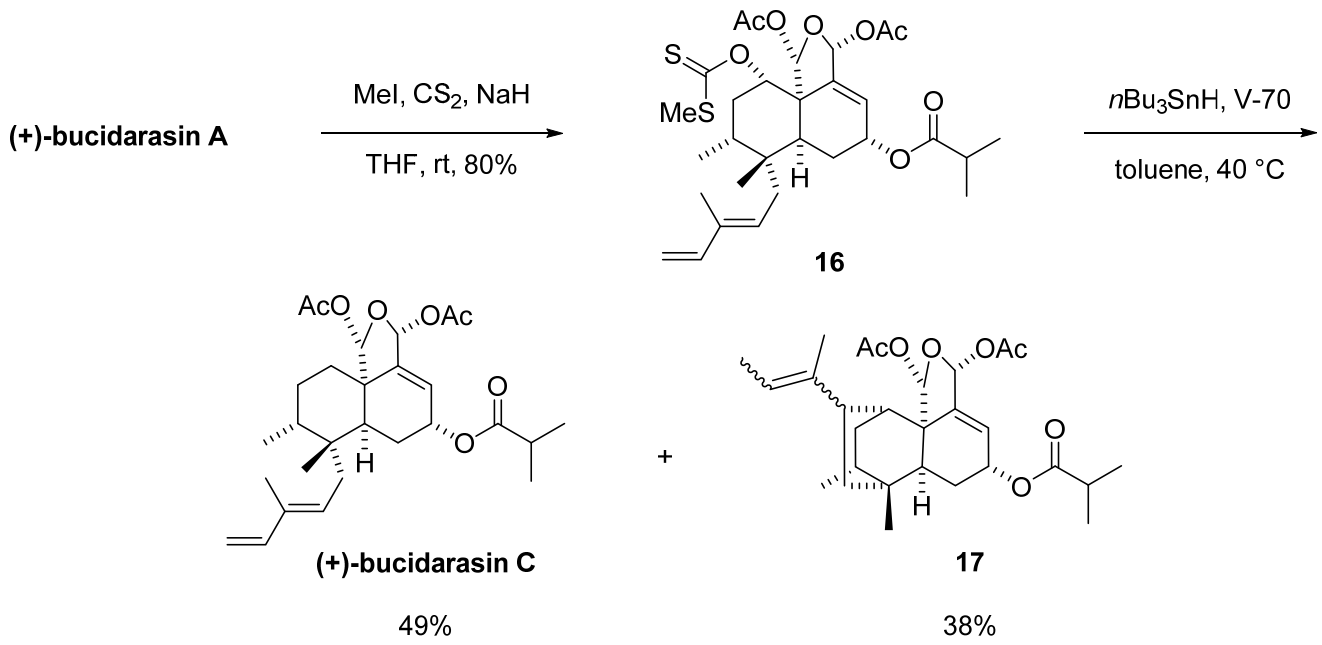
In the latter approach (Scheme 4), ***ent*-4** was prepared from **1** in an overall yield of 41% via 7 steps, and ***ent*-4** could be prepared from **1** via ***ent*-3** in an overall yield of 43% via 9 steps using the former approach (Schemes 2 and 3). Although the total number of steps in the former approach is greater, the undesired isomer was not formed in the hydrogenation of ***ent*-3**, which was advantageous for the scale-up synthesis.



Scheme 5. First enantioselective total synthesis of (+)-bucidarasin A

Since two enantioselective approaches toward (+)-bucidarasins A and C have been developed, ***ent*-4** was converted to (+)-bucidarasin A via the highly stereoselective Diels-Alder reaction of ***ent*-7** with **14**[10] affording **15** (Scheme 5), which was in line with the synthetic methods reported by our group. The final product proved to be (+)-bucidarasin A, which was the enantiomer of (–)-bucidarasin A, previously reported by our group (^{1}H- and ^{13}C-NMR, IR, HRMS, and $[\alpha]_D$).[6]

The conversion of (+)-bucidarasin A to (+)-bucidarasin C was also investigated (Scheme 6). The structural difference between (+)-bucidarasins A and C is only at the C6 position; i.e., (+)-bucidarasin C does not possess a hydroxy group at the C6 position, suggesting that the selective removal of the C6 hydroxy moiety in (+)-bucidarasin A can yield (+)-bucidarasin C.



Scheme 6. First enantioselective total synthesis of (+)-bucidarasin C

The C6 hydroxy group was found to be reactive though it was seemingly hindered by the C5 all-carbon quaternary center. Indeed, methyl xantate **16** was prepared in 80 % yield from (+)-bucidarasin A. The reaction of **16** with nBu$_3$SnH was expected to afford (+)-bucidarasin C, but the generated radical at the C6 position could undergo cyclization with the C9 diene. Indeed, the reaction of **16** with nBu$_3$SnH using V-70[11] proceeded at 40 °C to afford (+)-bucidarasin C in 49% yield, and the cyclized product was also formed in 38% yield. The synthesized (+)-bucidarasin C proved to be identical to naturally occurring (+)-bucidarasin C in all respects (^{1}H- and ^{13}C-NMR, IR, HRMS, $[\alpha]_D$).[1]

CONCLUSION

In summary, the first total synthesis of (+)-bucidarasins A and C was achieved. The chiral starting material was successfully obtained via the reduction using CBS catalyst, and the selective mono-TBS ether formation of *trans*-2-benzyloxymethyl-2-methylcyclohexane-1,3-diol was key to the successful enantioselective total synthesis of (+)-bucidarasins A and C. We also established a synthetic approach towards (+)-bucidarasin C, which utilizes the Barton-McCombie protocol, using V-70 as a radical promoter at low temperature. The synthetic approach towards (+)-bucidarasins established in this study has the potential to be useful in the synthesis of a vast number of congeners, and may lead to novel artificial analogs that could exhibit significant biological activities.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a JNM-ECS400 (400 MHz) spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS, δ scale), using residual protonated solvent as internal standard ($CDCl_3$ at ^{1}H: 7.26 ppm, ^{13}C: 77.2 ppm). The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). THF and Et_2O were distilled from sodium/benzophenone ketyl. MeOH was distilled with a small amount of magnesium and I_2. DMF was distilled prior to use. CH_2Cl_2 was distilled from CaH_2, and all other reagents were purchased from Aldrich, Wako Pure Chemical Industries, Ltd., Tokyo Chemical Industry Co., Ltd., or Kanto Chemical Co. Ltd.

(1*R*,3*R*)-2-Benzyloxymethyl-2-methylcyclohexane-1,3-diol (8). To a stirred mixture of (*S*)-CBS (1.0 M solution in toluene, 6.09 mL, 6.09 mmol) and 90% BH_3-SMe_2 (10.3 mL, 97.4 mmol) in CH_2Cl_2 (1850 mL) was added a solution of 2-benzyloxymethyl-2-methylcyclohexane-1,3-dione (10.0 g, 40.6 mmol) in CH_2Cl_2 (750 mL) at 30 °C via a syringe pump over 6 h. The reaction was quenched with MeOH (20 mL), and 2*N* HCl (120 mL) was added to the reaction mixture, and the resultant solution was stirred at room temperature for 10 h. After dilution with CH_2Cl_2 (100 mL), the organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 5/1) to afford **8** (9.55 g, 94%, >99% *ee*) as a white solid: R_f = 0.17 (hexane/EtOAc = 2/1); mp 77.2-78.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m), 4.60 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 4.15 (1H, dd, *J* = 11.0, 4.6 Hz), 3.80 (1H, t, *J* = 3.2 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.56 (1H, d, *J* = 9.2 Hz), 3.35 (1H, br s), 1.89 (1H, br), 1.90-1.70 (3H, m), 1.69-1.41 (4H, m), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ137.5 (Cq), 128.5 (CH), 127.9 (CH), 127.6 (CH), 77.3 (CH_2), 75.8 (CH), 73.6 (CH_2), 69.0 (CH), 43.0 (Cq), 29.8 (CH_2), 28.3 (CH_2), 18.7 (CH_2), 14.4 (CH_3); IR (neat) ν_{max} 3399, 2943, 2863, 1454, 1364, 1070, 1047, 998, 741, 694 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{15}H_{22}O_3Na$: 273.1461, found: 273.1461; $[\alpha]_D^{23}$ –18 (*c* 1.0, $CHCl_3$).

(1*R*,2*S*,3*R*)-2-Benzyloxymethyl-3-*tert*-butyldimethylsilyloxy-2-methylcyclohexanol (9); (2*R*,6*R*)-2,6-Bis(*tert*-butyldimethylsilyloxy)-1-methylcyclohexylmethoxymethylbenzene (9'). To a solution of **8** (16.1 g, 64.3 mmol) and 2,6-lutidine (15.0 mL, 129 mmol) in CH_2Cl_2 (700 mL) was added a

solution of TBSOTf (16.2 mL, 70.7 mmol) in CH_2Cl_2 (20 mL) at –60 °C via a syringe pump over 7 h, and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford **9** (14.2 g, 61%, a colorless oil), **9**' (6.23 g, 20%, a colorless oil), and starting material (2.54 g, 16%). **9**: R_f = 0.51 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.55 (1H, d, *J* = 11.8 Hz), 4.50, (1H, d, *J* = 11.8 Hz), 4.01 (1H, dd, *J* = 11.3, 4.5 Hz), 3.88 (1H, d, *J* = 8.6 Hz), 3.57 (1H, s), 3.36 (1H, s), 3.25 (1H, d, *J* = 8.6 Hz), 1.77-1.68 (1H, m), 1.68-1.56 (2H, m), 1.52-1.31 (3H, m), 0.99 (3H, s), 0.84 (9H, s), –0.013 (3H, s), –0.048 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Cq), 128.4 (CH), 127.7 (CH), 127.6 (CH), 79.9 (CH_2), 74.5 (CH), 73.8 (CH_2), 72.9 (CH), 43.4 (Cq), 29.3 (CH_2), 28.4 (CH_2), 25.8 (CH_3), 18.0 (Cq), 18.0 (CH_2), 14.2 (CH_3), –4.41 (CH_3), –5.27 (CH_3); IR (neat) ν_{max} 3436, 2930, 2856, 1471, 1360, 1252, 1075, 1026, 859, 773, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{36}O_3NaSi$: 387.2326, found: 387.2327; $[\alpha]_D^{23}$ –13 (*c* 0.58, $CHCl_3$).

9': R_f = 0.91 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m), 4.56 (1H, d, *J* = 11.9 Hz), 4.34, (1H, d, J = 11.9 Hz), 3.93 (1H, dd, *J* = 6.0, 1.8 Hz), 3.80 (1H, dd, *J* = 8.7, 3.7 Hz) , 3.50 (1H, d, *J* = 8.2 Hz) , 3.37 (1H, d, *J* = 8.2 Hz), 1.66-1.37 (6H, m), 0.97 (3H, s), 0.88 (9H, s), 0.82 (9H, s), 0.018 (3H, s), 0.0079 (3H, s), –0.0013 (3H, s), –0.032 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (Cq), 128.1 (CH), 127.4 (CH), 127.1 (CH), 73.7 (CH), 73.1 (CH), 72.2 (CH_2), 71.2 (CH_2), 44.9 (Cq), 29.9 (CH_2), 28.7 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 18.6 (CH_2), 18.1 (Cq), 18.0 (Cq), 16.0 (CH_3), –4.02 (CH_3), –4.32 (CH_3), –5.10 (CH_3), –5.27 (CH_3); IR (neat) ν_{max} 2928, 2856, 1471, 1360, 1251, 1079, 831, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{50}O_3NaSi_2$: 501.3191, found: 501.3192; $[\alpha]_D^{23}$ –18 (*c* 0.98, $CHCl_3$).

(1*R*,2*S*,3*R*)-(2-Benzyloxymethyl-3-methoxymethoxy-2-methylcyclohexyloxy)(*tert*-butyl)dimethylsilane (9a). To a stirred solution of **9** (15.4 g, 42.2 mmol) in CH_2Cl_2 (420 mL) was added DIPEA (29.4 mL, 169 mmol), MOMCl (6.42 mL, 84.5 mmol), and NaI (6.33 g, 42.2 mmol) successively at room temperature. The reaction mixture was stirred at 35 °C for 2 d, quenched with H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 40/1) to afford **9a** (17.1 g, 99%) as a colorless oil: R_f = 0.63 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 4.64 (1H, d, *J* = 6.9 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 6.9 Hz), 4.38 (1H, d, *J* = 11.9 Hz), 3.92 (1H, dd, *J* = 5.5, 2.3 Hz), 3.69 (1H, dd, *J* = 8.7, 4.1 Hz), 3.59 (1H, d, *J* = 8.2 Hz), 3.44 (1H, d, *J* = 8.2 Hz), 3.31 (3H, s), 1.80-1.69 (1H, m), 1.69-1.39 (5H, m), 1.05 (3H, s), 0.88 (9H, s), 0.021 (3H, s), 0.0090 (3H, s); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 139.1 (Cq), 128.1 (CH), 127.3 (CH), 127.2 (CH), 96.0 (CH_2), 77.5 (CH_2), 73.7 (CH), 73.1 (CH_2), 72.4 (CH), 55.4 (CH_3), 44.3 (Cq), 28.6 (CH_2), 26.6 (CH_2), 25.9 (CH_3), 18.5 (CH_2), 18.1 (Cq), 16.3 (CH_3), –4.41 (CH_3), –5.16 (CH_3); IR (neat) ν_{max} 2929, 2856, 1471, 1360, 1250, 1080, 1030, 833, 774, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{23}H_{40}O_4NaSi$: 431.2588, found: 431.2586; $[\alpha]_D^{22}$ –17 (*c* 0.96, $CHCl_3$).

(1*R*,2*R*,3*R*)-2-Benzyloxymethyl-3-methoxymethoxy-2-methylcyclohexanol (11). To a stirred solution of **9a** (17.1 g, 41.8 mmol) in THF (250 mL) was added TBAF (1.0 M solution in THF, 62.8 mL, 62.8 mmol), and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL), and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford **11** (11.4 g, 93%) as a colorless oil: R_f = 0.29 (hexane/EtOAc = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.63 (1H, d, *J* = 11.9 Hz), 4.61 (1H, d, *J* = 11.9 Hz), 4.53 (2H, s), 4.11 (1H, br s), 4.03 (1H, dd, *J* = 10.5, 4.6 Hz), 3.84 (1H, t, *J* = 2.7 Hz) , 3.75 (1H, d, *J* = 9.2 Hz), 3.36 (1H, d, *J* = 9.2 Hz), 3.34 (3H, s), 1.92-1.68 (2H, m), 1.66-1.43 (4H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (Cq), 128.5 (CH), 127.9 (CH), 127.7 (CH), 96.1 (CH_2), 76.6 (CH_2), 76.5 (CH), 74.5 (CH), 73.6 (CH_2), 55.3 (CH), 42.8 (Cq), 28.2 (CH_2), 27.3 (CH_2), 18.8 (CH_2), 15.3 (CH_3); IR (neat) ν_{max} 3472, 2939, 1453, 1362, 1213, 1143, 1032, 915, 735, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{26}O_4Na$: 317.1723, found: 317.1729; $[\alpha]_D^{22}$ +0.38 (*c* 1.6, $CHCl_3$).

(2*S*,3*R*)-2-Benzyloxymethyl-3-methoxymethoxy-2-methylcyclohexanone (11a). To a stirred solution of oxalyl chloride (5.07 mL, 58.15 mmol) and DMSO (5.50 mL, 77.4 mmol) in CH_2Cl_2 (192 mL) was added a solution of **11** (11.4 g, 38.7 mmol) in CH_2Cl_2 (30 mL) via a cannula at –78 °C. After 15 min, to the reaction mixture was added Et_3N (18.9 mL, 136 mmol), and the reaction mixture was stirred at the same temperature for 1 h, and at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 6/1) to afford **11a** (11.3 g, 100%) as a colorless oil: R_f = 0.36 (hexane/EtOAc = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m), 4.63 (1H, d, *J* = 13.3 Hz), 4.61 (1H, d, *J* = 13.3 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 4.47 (1H, d, *J* = 11.9 Hz), 4.05 (1H, dd, *J* = 9.2, 3.7 Hz), 3.71 (1H, d, *J* = 8.7 Hz), 3.37 (1H, d, *J* = 8.7 Hz), 3.35 (3H, s), 2.45-2.27 (2H, m), 2.11-2.01 (1H, m), 1.98-1.78 (2H, m), 1.70-1.60 (1H, m), 1.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8 (Cq), 138.3 (Cq), 128.2 (CH), 127.6 (CH), 127.5 (CH), 96.2 (CH_2), 77.5 (CH), 73.3 (CH_2), 71.4 (CH_2), 55.6 (CH), 55.5 (Cq), 37.9 (CH_2), 26.4 (CH_2), 19.7 (CH_2), 15.8

(CH_3); IR (neat) ν_{max} 2942, 2874, 1709, 1453, 1369, 1093, 1028, 916, 736, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{24}O_4Na$: 315.1567, found: 313.51569; $[\alpha]_D^{23}$ –15 (*c* 2.0, $CHCl_3$).

(1*S*,2*R*)-2-Methoxymethoxy-1-methyl-6-methylenecyclohexylmethoxymethylbenzene (11b). To a stirred suspension of PPh_3CH_3Br (38.7 g, 108 mmol) in THF (127 mL) was added KHMDS (0.5 M solution in toluene, 193 mL, 96.6 mmol) dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. Then, to the reaction mixture was added a solution of **11a** (11.3 g, 38.6 mmol) in THF (30 mL) via a cannula at 0 °C. After the addition, the mixture was stirred at room temperature for 1 h, and then was quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford **11b** (10.9 g, 97%) as a colorless oil: R_f = 0.64 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m), 4.86 (1H, d, *J* = 1.4 Hz), 4.82 (1H, d, *J* = 1.4 Hz), 4.64 (1H, d, *J* = 10.4 Hz), 4.62 (1H, d, *J* = 10.4 Hz), 4.54 (1H, d, *J* = 11.8 Hz), 4.48 (1H, d, *J* = 11.8 Hz), 3.72 (1H, dd, *J* = 8.2, 4.1 Hz), 3.52 (1H, d, *J* = 9.1 Hz), 3.39 (1H, d, *J* = 9.1 Hz), 3.35 (3H, s), 2.27-2.09 (2H, m), 1.88-1.78 (1H, m), 1.77-1.65 (2H, m), 1.48-1.35 (1H, m), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4 (Cq), 138.4 (Cq), 128.3 (CH), 127.7 (CH), 127.5 (CH), 109.5 (CH_2), 96.3 (CH_2), 78.5 (CH), 73.8 (CH_2), 73.3 (CH_2), 55.5 (CH), 46.2 (Cq), 32.4 (CH_2), 27.3 (CH_3), 23.2 (CH_2), 18.2 (CH_3); IR (neat) ν_{max} 2935, 2860, 1640, 1454, 1144, 1099, 1035, 892, 734, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{26}O_3Na$: 313.1774, found: 313.1774; $[\alpha]_D^{22}$ +2.2 (*c* 1.2, $CHCl_3$).

(1*R*,2*S*)-2-Benzyloxymethyl-2-methyl-3-methylenecyclohexanol (*ent*-3). To a stirred solution of **11b** (10.8 g, 37.2 mmol) in MeOH (186 mL) was added 5*N* HCl (18.6 mL), and the reaction mixture was stirred at 50 °C for 12 h. To the reaction mixture was added H_2O (200 mL), and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 15/1) to afford ***ent*-3** (8.58 g, 94%) as a colorless oil.

R_f = 0.39 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.74 (1H, s), 4.60 (1H, d, *J* = 12.4 Hz), 4.56 (1H, d, J = 12.4 Hz), 4.49 (1H, s), 3.73 (1H, d, *J* = 8.7 Hz), 3.68 (1H, ddd, *J* = 10.5, 4.1, 1.4 Hz), 3.65 (1H, d, *J* = 8.7 Hz), 3.61 (1H, d, *J* = 1.4 Hz), 2.22 (1H, ddd, *J* = 13.7, 13.7, 4.6 Hz), 2.06 (1H, ddd, *J* = 13.7, 3.2, 3.2 Hz), 1.85-1.70 (2H, m), 1.63-1.49 (1H, m), 1.37-1.22 (1H, m), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (Cq), 137.7 (Cq), 128.5 (CH), 127.8 (CH), 127.5 (CH), 107.7 (CH_2), 79.2 (CH_2), 76.3 (CH), 73.8 (CH_2), 44.6 (Cq), 32.5 (CH_2), 29.7 (CH_2), 24.2 (CH_2), 16.1 (CH_3); IR (neat) ν_{max} 3438, 2935, 2859, 1637, 1453, 1358, 1071, 895, 734, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}O_2Na$: 269.1512, found: 269.1512; $[\alpha]_D^{27}$ –13 (*c* 1.1, $CHCl_3$).

(1*S*,2*R*,3*S*)-2-Benzyloxymethyl-3-*tert*-butyldimethylsilyloxy-2-methylcyclohexan-1-ol (*ent*-9). To a solution of (1*S*,3*S*)-2-benzyloxymethyl-2-methylcyclohexane-1,3-diol (93.7 mg, 0.374 mmol) and 2,6-lutidine (87.2 μL, 0.749 mmol) in CH_2Cl_2 (15 mL) was added a solution of TBSOTf (0.129 mL, 0.561 mmol) in CH_2Cl_2 (15 mL) at –60 °C via a syringe pump over 5 h, and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford ***ent*-9** (98.4 mg, 72%) and its di-TBS ether ***ent*-9'** (24.7 mg, 13%) as a colorless oil. Starting material (14.0 mg, 15%) was recovered: R_f = 0.51 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m), 4.55 (1H, d, *J* = 11.9 Hz), 4.50, (1H, d, J = 11.9 Hz), 4.01 (1H, dd, *J* = 11.0, 4.1 Hz), 3.88 (1H, d, *J* = 8.7 Hz), 3.57 (1H, s), 3.36 (1H, s), 3.25 (1H, d, *J* = 8.7 Hz), 1.78-1.56 (3H, m), 1.52-1.32 (3H, m), 0.99 (3H, s), 0.83 (9H, s), -0.014 (3H, s), -0.049 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Cq), 128.4 (CH), 127.6 (CH), 127.6 (CH), 79.7 (CH_2), 74.4 (CH), 73.7 (CH_2), 72.8 (CH), 43.4 (Cq), 29.3 (CH_2), 28.3 (CH_2), 25.7 (CH_3), 18.0 (Cq), 18.0 (CH_2), 14.1 (CH_3), -4.46 (CH_3), -5.31 (CH_3); IR (neat) ν_{max} 3448, 2928, 2856, 1471, 1360, 1252, 1074, 1026, 859, 773, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{36}O_3NaSi$: 387.2326, found: 387.2325; $[\alpha]_D^{25}$ +14 (*c* 0.6, $CHCl_3$).

[(1*S*,3*S*)-2-Benzyloxymethyl-3-*tert*-butyldimethylsilyloxy-2-methylcyclohexyloxy](*tert*-butyl)-dimethyl-silane (*ent*-9'). R_f = 0.91 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m), 4.57 (1H, d, *J* = 11.9 Hz), 4.35, (1H, d, J = 11.9 Hz), 3.94 (1H, dd, *J* = 5.5, 1.8 Hz), 3.82 (1H, dd, *J* = 8.7, 4.1 Hz) , 3.51 (1H, d, *J* = 8.2 Hz) , 3.38 (1H, d, *J* = 8.2 Hz), 1.73-1.34 (6H, m), 0.99 (3H, s), 0.89 (9H, s), 0.83 (9H, s), 0.027 (3H, s), 0.017 (3H, s), 0.0079 (3H, s), -0.022 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (Cq), 128.1 (CH), 127.4 (CH), 127.1 (CH), 73.8 (CH), 73.2 (CH), 72.2 (CH_2), 71.2 (CH_2), 44.9 (Cq), 29.9 (CH_2), 28.7 (CH_2), 26.0 (CH_3), 25.9 (CH_3), 18.6 (CH_2), 18.1 (Cq), 18.0 (Cq), 16.1 (CH_3), -4.02 (CH_3), -4.31 (CH_3), -5.08 (CH_3), -5.25 (CH_3); IR (neat) ν_{max} 2928, 2856, 1471, 1360, 1251, 1078, 1070, 831, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{50}O_3NaSi_2$: 501.3191, found: 501.3192; $[\alpha]_D^{26}$ +18 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-2-Benzyloxymethyl-3-*tert*-butyldimethylsilyloxy-2-methylcyclohexan-1-one (*ent*-9a). To a solution of ***ent*-9** (189 mg, 0.518 mmol) in CH_2Cl_2 (13 mL) was added Dess-Martin periodinane (331 mg, 0.778 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and then, quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford ***ent*-9a** (177 mg, 94%) as a colorless

oil: R_f = 0.56 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 4.55 (1H, d, *J* = 12.4 Hz), 4.41 (1H, d, *J* = 12.4 Hz), 4.00 (1H, dd, *J* = 6.0, 2.7 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.63 (1H, d, *J* = 9.2 Hz), 2.47 (1H, ddd, *J* = 14.7, 9.6, 6.0 Hz), 2.36-2.24 (1H, m), 2.13-1.89 (2H, m), 1.86-1.75 (1H, m) , 1.74-1.62 (1H, m), 1.24 (3H, s), 0.86 (9H, s), 0.033 (3H, s), 0.024 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (Cq), 138.6 (Cq), 128.2 (CH), 127.4 (CH), 127.3 (CH), 75.5 (CH), 73.2 (CH_2) , 71.7 (CH_2), 55.1 (Cq), 37.8 (CH_2), 28.7 (CH_2), 25.8 (CH_3), 20.4 (CH_2), 19.4 (CH_3), 18.0 (Cq), -4.43 (CH_3), -5.27 (CH_3); IR (neat) ν_{max} 2928, 2855, 1707, 1462, 1360, 1249, 1078, 830, 774, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{34}O_3NaSi$: 385.2169, found: 385.2170; $[\alpha]_D^{25}$ +0.56 (*c* 0.71, $CHCl_3$).

[(1*S*,2*S*)-2-Benzyloxymethyl-2-methyl-3-methylidenecyclohexyloxy](*tert*-butyl)dimethylsilane (12). To a stirred suspension of PPh_3CH_3Br (482 mg, 1.35 mmol) in THF (6.0 mL) was added KHMDS (0.50 M solution in toluene, 2.25 mL, 1.12 mmol) dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added a solution of **2** (163 mg, 0.450 mmol) in THF (6.0 mL) via a cannula at 0 °C. After the addition, the reaction mixture was stirred at 60 °C for 1.5 h, and then was quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 100/1) to afford **12** (157 mg, 97%) as a colorless oil: R_f = 0.77 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m), 4.85 (1H, d, *J* = 1.8 Hz), 4.71 (1H, d, *J* = 1.8 Hz), 4.53 (1H, d, *J* = 12.4 Hz), 4.48 (1H, d, *J* = 12.4 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.49 (1H, d, *J* = 9.2 Hz), 3.47 (1H, dd, *J* = 8.7, 3.7 Hz), 2.24-2.09 (2H, m), 1.81-1.648 (2H, m), 1.63-1.49 (1H, m), 1.40-1.24 (1H, m), 1.19 (3H, s), 0.85 (9H, s) 0.00 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (Cq), 139.0 (Cq), 128.2 (CH), 127.4 (CH), 127.2 (CH), 109.3 (CH_2), 76.7 (CH), 73.2 (CH_2), 72.5 (CH_2), 46.7 (Cq), 32.5 (CH_2), 30.6 (CH_2), 25.8 (CH_3), 24.0 (CH_2), 20.8 (CH_3), 18.0 (Cq), -4.14 (CH_3), -5.08 (CH_3); IR (neat) ν_{max} 2930, 2855, 1638, 1461, 1360, 1250, 1080, 830, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{36}O_2NaSi$: 383.2377, found: 383.2376; $[\alpha]_D^{25}$ +31 (*c* 0.69, $CHCl_3$).

[(1*S*,2*S*)-2-Benzyloxymethyl-2,3-dimethylcyclohexyloxy](*tert*-butyl)dimethylsilane (12a). To a stirred solution of **12** (151 mg, 0.418 mmol) in benzene (8.4 mL) was added Wilkinson catalyst (19.4 mg, 5 mol %). The reaction mixture was stirred at 60 °C for 2 h under an atmosphere of hydrogen, and then, the reaction mixture was diluted with hexane/EtOAc (5/1, 10 mL), filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 100/1) to afford a mixture of **12a** and its isomer (150 mg, 99%) as a colorless oil. **Major product**: R_f = 0.76 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m), 4.46 (2H, s), 3.63 (1H, d, *J* = 9.2 Hz), 3.39 (1H, d, *J* = 9.2 Hz), 3.35 (1H, dd, *J* = 9.6, 5.0 Hz), 1.75-1.17 (7H, m), 1.03 (3H, d, *J* = 6.9 Hz), 0.97 (3H, s), 0.88 (9H, s), 0.024 (6H, s). **Minor product**: R_f = 0.76 (hexane/EtOAc = 10/1); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m), 4.54 (1H, d, *J* = 12.4 Hz), 4.36 (1H, d, *J* = 12.4 Hz), 3.84 (1H, br s), 3.48 (1H, d, *J* = 8.2 Hz), 3.25 (1H, d, *J* = 8.2 Hz), 1.87-1.76 (1H, m), 1.75-1.17 (6H, m), 0.90 (9H, s), 0.88 (3H, s), 0.74 (3H, d, *J* = 6.9 Hz), 0.0045 (6H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{38}O_2NaSi$: 385.2533, found: 385.2533.

[(1*S*,2*S*,3*R*)-2-Benzyloxymethyl-2,3-dimethylcyclohexyloxy](*tert*-butyl)dimethylsilane (12b). To a solution of **12a** (135 mg, 0.372 mmol) in THF (3.7 mL) was added TBAF (1.0 M solution in THF, 745 μL, 0.745 mmol), and the reaction mixture was stirred at 75 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 50/1) to afford **12b** (69.4 mg, 75%) and **12b'** (12.8 mg, 14%) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.49 (2H, s), 3.95 (1H, d, *J* = 9.2 Hz), 3.99-3.70 (1H, br), 3.55 (1H, d, *J* = 9.2 Hz), 3.24 (1H, dd, *J* = 11.9, 4.1 Hz), 1.90-1.80 (1H, m), 1.76-1.66 (1H, m), 1.65-1.43 (1H, m), 1.42-1.27 (3H, m), 1.26 (3H, s), 1.23-1.05 (1H, m), 0.83 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (Cq), 128.4 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 79.7 (CH), 74.0 (CH_2), 72.6 (CH_2), 41.3 (Cq), 40.7 (CH), 31.8 (CH_2), 30.3 (CH_2), 24.4 (CH_2), 21.7 (CH_3), 15.8 (CH_3); IR (neat) ν_{max} 3450, 2927, 2858, 1453, 1074, 1015, 733, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{24}O_2Na$: 271.1669, found: 271.1667; $[\alpha]_D^{25}$ +3.7 (*c* 0.60, $CHCl_3$).

[(1*S*,2*S*,3*S*)-2-Benzyloxymethyl-2,3-dimethylcyclohexyloxy](*tert*-butyl)dimethylsilane (12b'). R_f = 0.46 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m), 4.57 (1H, d, *J* = 11.9 Hz), 4.47 (1H, d, *J* = 11.9 Hz), 3.72 (1H, t, *J* = 2.7 Hz), 3.57 (1H, d, *J* = 11.9 Hz), 3.32 (1H, d, *J* = 11.9 Hz), 2.21-2.08 (1H, m), 1.83-1.68 (1H, m), 1.67-1.52 (2H, m), 1.48-1.36 (2H, m), 1.29-1.14 (1H, m), 0.76 (3H, d, *J* = 6.9 Hz), 0.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (Cq), 128.5 (CH), 127.8 (CH), 127.7 (CH), 78.1 (CH_2), 76.1 (CH), 73.6 (CH_2), 40.7 (Cq), 29.8 (CH_2), 28.9 (CH), 28.8 (CH_2), 20.0 (CH_2), 15.4 (CH_3), 15.2 (CH_3); IR (neat) ν_{max} 3483, 2932, 2856, 1454, 1071, 1014, 734, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{24}O_2Na$: 271.1669, found: 271.1667; $[\alpha]_D^{25}$ +1.0 (*c* 0.53, $CHCl_3$).

[(1*R*,6*R*)-1,6-Dimethylcyclohex-2-en-1-yl]methoxymethylbenzene (*ent*-4). To a stirred solution of **12b** (65.0 mg, 0.262 mmol) in pyridine (2.5 mL) was added $POCl_3$ (71.2 μL, 0.785 mmol) at 0 °C, and the mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with H_2O (5.0 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 100/1) to afford ***ent*-4** (56.1 mg, 93%) as a colorless oil: R_f = 0.77 (hexane/EtOAc = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (5H, m), 5.70 (1H, ddd, *J* = 10.1, 3.7, 3.7 Hz), 5.44 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz), 4.50 (2H, s), 3.28 (2H, s), 2.09-1.94 (2H, m), 1.65-1.53

(3H, m), 1.07 (3H, s), 0.94 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (Cq), 134.2 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 126.4 (CH), 76.0 (CH_2), 73.3 (CH_2), 38.5 (Cq), 36.8 (CH), 27.2 (CH_2), 25.0 (CH_3), 24.3 (CH_2), 15.8 (CH_3); IR (neat) ν_{max} 2957, 2921, 2859, 1453, 1365, 1095, 732, 695 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}ONa$: 253.1563, found: 253.1563; $[\alpha]_D^{26}$ +33 (c 2.0, $CHCl_3$).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10*S*,10a*S*)-1,3-Bis(acetyloxy)-10-hydroxy-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate ((+)-bucidarasin A). To a solution of the C2-hydroxy derivative of (+)-bucidarasin A (15.0 mg, 0.0345 mmol), which was synthesized from ***ent*-4** according to the procedure reported by our group,[1] in CH_2Cl_2 (1.5 mL) were added triethylamine (48.1 μL, 0.345 mmol) and isobutyryl chloride (10.9 μL, 0.104 mmol) successively at 0 °C, and the reaction mixture was stirred at 35 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5.0 mL) and ca.25% NH_4OH solution (5.0 mL) successively, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 3/1) to afford (+)-bucidarasin A (17.0 mg, 98%) as a white amorphous: R_f = 0.43 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, dd, J = 1.4, 1.4 Hz), 6.51 (1H, s), 6.27 (1H, dd, J = 17.4, 10.5 Hz), 5.99 (1H, dd, J = 4.1, 1.4 Hz), 5.47-5.41 (1H, m), 5.41-5.32 (1H, m), 5.09 (1H, d, J = 17.4 Hz), 4.93 (1H, d, J = 10.5 Hz), 3.80 (1H, ddd, J = 12.4, 9.6, 3.7 Hz), 2.64 (1H, qq, J = 6.9, 6.9 Hz), 2.36 (1H, dd, J = 11.4, 5.5 Hz), 2.24 (1H, dd, J = 16.5, 7.8 Hz), 2.10 (3H, s), 1.94 (3H, s), 1.92-1.83 (2H, m), 1.82-1.54 (4H, m), 1.66 (3H, s), 1.22 (3H, d, J = 6.9 Hz), 1.20 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (Cq), 170.1 (Cq), 169.4 (Cq), 145.3 (Cq), 141.2 (CH), 135.7 (Cq), 129.0 (CH), 121.8 (CH), 111.0 (CH_2), 97.0 (CH), 95.6 (CH), 72.8 (CH), 66.1 (CH), 53.5 (Cq), 37.6 (CH_2), 37.3 (Cq), 36.8 (CH), 36.7 (CH), 34.0 (CH), 30.3 (CH_2), 26.7 (CH_2), 25.0 (CH_3), 21.6 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_3), 15.6 (CH_3), 11.9 (CH_3); IR (neat) νmax 3469, 2969, 2933, 2878, 1749, 1728, 1605, 1371, 1225, 889, 735 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_8Na$: 527.2615, found: 527.2616; $[\alpha]_D^{25}$ +34 (c 0.85, MeOH).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10*S*,10a*S*)-1,3-Bis(acetyloxy)-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-10-methylsulfanylmethanethioyloxy-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate (16). To a stirred solution of (+)-bucidarasin A (14.0 mg, 0.0277 mmol) in THF (2.0 mL) was added CS_2 (10.1 μL, 0.166 mmol) and NaH (60%, 3.3 mg, 0.0832 mmol) successively at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 15 min, and then to the reaction mixture was added MeI (13.8 μL, 0.222 mmol). The reaction mixture was stirred at room temperature for 14 h, quenched with saturated aqueous NH_4Cl solution (5.0 mL), and the aqueous layer

was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20/1) to afford **16** (13.2 mg, 80%) as a colorless oil: R_f = 0.63 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, s), 6.53 (1H, dd, *J* = 1.7, 1.7 Hz), 6.29 (1H, dd, *J* = 17.0, 10.8 Hz), 6.00 (1H, br d), 5.96 (1H, dd, *J* = 11.9, 4.0 Hz), 5.49-5.43 (1H, m), 5.41-5.36 (1H, m), 5.11 (1H, d, *J* = 17.0 Hz), 4.95 (1H, d, *J* = 10.8 Hz), 2.64 (1H, qq, *J* = 6.8, 6.8 Hz), 2.58 (3H, s), 2.47 (1H, dd, *J* = 13.0, 3.4 Hz), 2.28 (1H, dd, *J* = 17.0, 8.5 Hz), 2.08 (3H, s), 2.11-1.99 (1H, m), 1.96 (3H, s), 1.98-1.87 (3H, m), 1.81-1.64 (2H, m), 1.68 (3H, s), 1.23 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1 (Cq), 176.3 (Cq), 170.0 (Cq), 169.4 (Cq), 143.6 (Cq), 141.1 (CH), 135.9 (Cq), 128.7 (CH), 123.4 (CH), 111.2 (CH_2), 97.1 (CH), 95.1 (CH), 82.2 (CH), 65.8 (CH), 52.2 (Cq), 37.7 (CH), 37.6 (Cq), 36.2 (CH), 34.0 (CH), 32.3 (CH_2), 30.3 (CH_2), 26.7 (CH_2), 25.0 (CH_3), 21.7 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_3), 18.5 (CH_3), 15.4 (CH_3), 12.0 (CH_3); IR (neat) νmax 2970, 2934, 1755, 1732, 1601, 1471, 1323, 1222, 1055, 836, 737 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{30}H_{42}O_8NaS_2$: 617.2213, found: 617.2212; $[\alpha]_D^{24}$ +54 (*c* 0.53, $CHCl_3$).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10a*S*)-1,3-Bis(acetyloxy)-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate ((+)-bucidarasin C). To a solution of **16** (10.0 mg, 0.0168 mmol) in degassed toluene (1.0 mL) were added a catalytic amount of V-70 and *n*-Bu_3SnH (44.1 μL, 0.168 mmol) successively at 0 °C. The reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 30/1) to afford (+)-bucidarasin C (4.0 mg, 49%) and **17** (3.1 mg, 38%, mixture of diastereomers (dr = 10/7)) as a colorless oil: R_f = 0.31 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, dd, *J* = 1.5, 1.5 Hz), 6.36 (1H, s), 6.28 (1H, dd, *J* = 17.2, 10.8 Hz), 5.89 (1H, dd, *J* = 4.6, 1.5 Hz), 5.42 (1H, br s), 5.38 (1H, br d), 5.08 (1H, d, *J* = 17.2 Hz), 4.92 (1H, d, *J* = 10.8 Hz), 2.63 (1H, qq, *J* = 6.9, 6.9 Hz), 2.23 (1H, dd, *J* = 16.1, 8.2 Hz), 2.22 (1H, br t), 2.10 (3H, s), 1.94 (3H, s), 1.92-1.87 (2H, m), 1.79-1.69 (2H, m), 1.67 (3H, s), 1.64-1.58 (1H, m), 1.53-1.41 (2H, m), 1.22 (3H, d, *J* = 6.9 Hz), 1.20 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.9 Hz), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (Cq), 170.3 (Cq), 169.7 (Cq), 147.0 (Cq), 141.3 (CH), 135.6 (Cq), 129.3 (CH), 120.3 (CH), 110.8 (CH_2), 98.8 (CH), 94.5 (CH), 66.3 (CH), 49.1 (Cq), 37.4 (Cq), 36.5 (CH), 34.7 (CH), 34.1 (CH), 30.4 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 26.1 (CH_2), 25.7 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 19.2 (CH_3), 18.7 (CH_3), 15.6 (CH_3), 12.0 (CH_3); IR (neat) νmax 2940, 1750, 1731, 1458, 1374, 1230, 1152, 1066, 935, 669 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_7Na$: 511.2666, found: 511.2679; $[\alpha]_D^{25}$ +17 (*c* 0.20, MeOH).

(1*R*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*)-3,5-Bis(acetyloxy)-14-(but-2-en-2-yl)-11,12-dimethyl-4-oxatetracyclo[9.2.2.0^{2,6}.0^{2,10}]pentadec-6-en-8-yl 2-methylpropanoate (17). **Major product**: R_f = 0.40 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (1H, dd, *J* = 1.8, 1.8 Hz), 6.33 (1H, br s), 6.02 (1H, br s), 5.65-5.56 (1H, m), 5.32-5.24 (1H, m), 2.66-2.57 (1H, m), 2.51-2.40 (1H, m), 2.28-2.20 (1H, m), 2.19 (3H, s), 2.20-2.16 (1H, m), 2.10 (3H, s), 1.81-1.58 (7H, m), 1.61 (3H, s), 1.58-1.49 (1H, m), 1.38-1.24 (1H, m), 1.21 (3H, d, *J* = 6.9 Hz), 1.21 (3H, d, *J* = 6.9 Hz), 0.86 (3H, s), 0.78 (3H, d, *J* = 6.0 Hz). **Minor product**: R_f = 0.40 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.66 (1H, dd, *J* = 1.8, 1.8 Hz), 6.01 (1H, br s), 5.47-5.34 (2H, m), 2.63-2.54 (1H, m), 2.39-2.29 (1H, m), 2.21-2.15 (1H, m), 2.14 (3H, s), 2.05 (3H, s), 1.88-1.81 (1H, m), 1.81-1.58 (2H, m), 1.70 (3H, s), 1.65 (3H, br d) 1.50-1.41 (1H, m), 1.38-1.24 (1H, m), 1.20 (6H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.9 Hz), 0.97 (3H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_7Na$: 511.2666, found: 511.2679.

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