

## Total Synthesis of Paniculide A from D-Glucose

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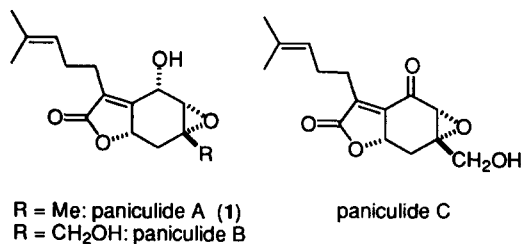
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**Abstract:** The chiral total synthesis of paniculide A (**1**), a highly oxygenated sesquiterpene possessing a bisabolane skeleton, starting from D-glucose is described. The two different approaches, both involved Ferrier's carbocyclization reaction to construct the cyclohexane unit in **1**, were explored. The first approach, employing the carbocyclization of bicyclic substrate furnished the formal total synthesis. The second approach, designed to suppress the undesired side reactions observed in the first one, adopted the carbocyclization of a monocyclic substrate, and Claisen rearrangement for the stereoselective carbon-carbon bond formation. The successful total synthesis of **1** revealed the effectiveness of the combination of Ferrier's carbocyclization and Claisen rearrangement for the chiral synthesis of highly oxygenated natural products possessing cyclohexane units. © 1999 Elsevier Science Ltd. All rights reserved.

### Introduction

Ferrier's carbocyclization reaction is one of the most useful transformation for the construction of optically pure cyclohexanone derivatives from aldohexoses<sup>1</sup> and is frequently used in the synthesis of cyclitols and aminocyclitols.<sup>2</sup> Chiral and highly oxygenated cyclohexanes derived from aldohexoses are potentially versatile chiral building blocks in natural product synthesis, however, not so many reports on the application of this reaction to the preparation of structurally more complex natural products have been appeared.<sup>3</sup> In this article, as a part of our continuous study to utilize Ferrier's carbocyclization reaction in the preparation of natural products containing a cyclohexane unit,<sup>4</sup> we report a total synthesis of paniculide A (**1**) starting from D-glucose. Paniculide A (**1**) is a sesquiterpene isolated by Overton from callus cultures derived from the hypocotyl and stem tissues of *Andrographis paniculate*.<sup>5</sup> Paniculide B and C were also isolated from the cultures. The structural study of paniculides by spectroscopic method<sup>5a</sup> and the X-ray analysis<sup>5b</sup> of paniculide B bis-*p*-bromobenzoate by Overton and co-workers revealed that paniculides have highly oxygenated bisabolene skeleton. The intriguing structures of paniculides stimulated synthetic interests and total synthesis of racemic paniculide A, B, and C was first achieved by Smith.<sup>6</sup> Alternative total syntheses of racemic paniculide A by



Kido and Yoshikoshi,<sup>7</sup> formal syntheses of racemic paniculide A by Jacobi,<sup>8</sup> paniculide B and C by Baker,<sup>9</sup> and synthesis of the precursor of paniculide B in optically active form by Tadano<sup>10</sup> have been reported to date. In 1994, the first asymmetric total synthesis of paniculide A has been achieved by Narasaka.<sup>11</sup>

Previous successful total synthesis of racemic paniculide A by Smith<sup>6</sup> revealed that the compound **2** is a suitable intermediate for the total synthesis, and compound **2** was easily prepared from the  $\gamma$ -lactone **3**. We planned to synthesize Smith's intermediates **2** or **3** in optically pure form from D-glucose using Ferrier's carbocyclization reaction as the key transformation (Fig. 1).

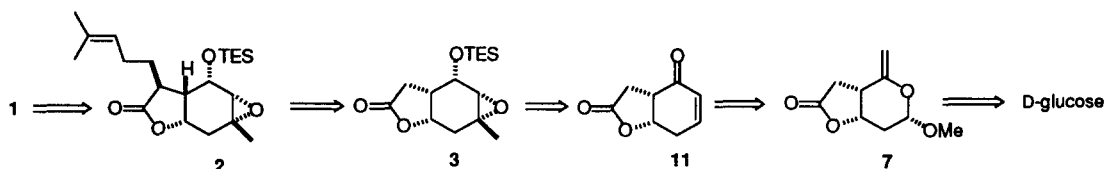
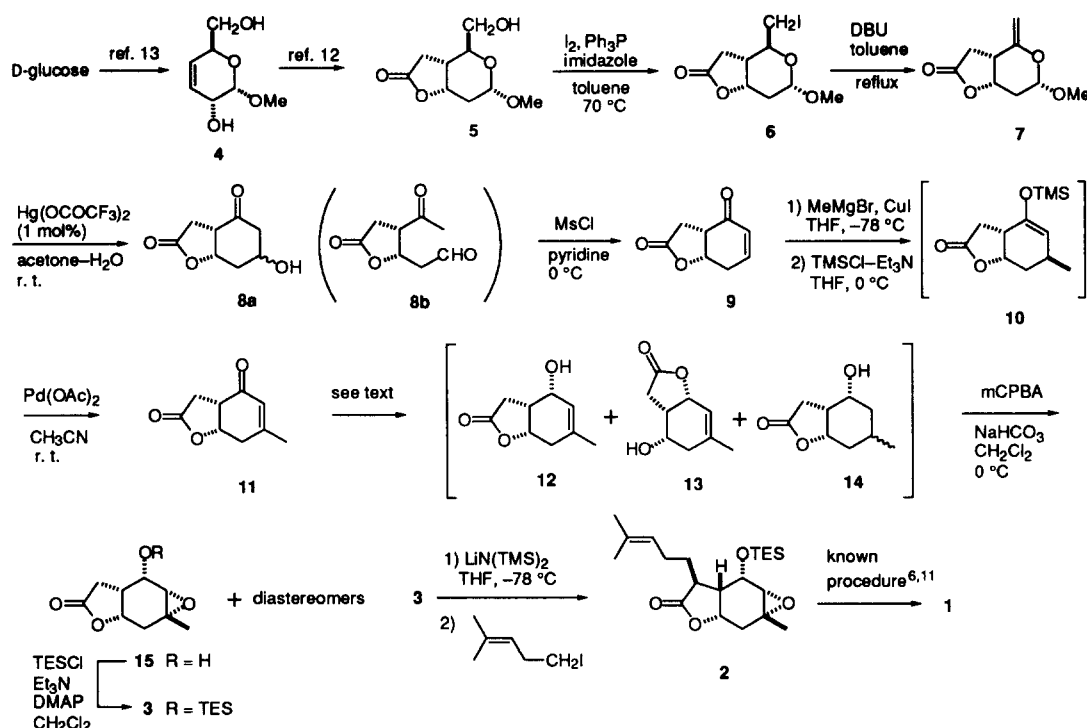


Fig. 1. Retrosynthetic analysis of paniculide A (TES = Et<sub>3</sub>Si-).

## Results and Discussion

**Synthesis of the Smith's intermediate (2) by way of Ferrier's carbocyclization of the bicyclic enopyranoside derivative (7):** Our initial approach to paniculide A involved the synthesis of Smith's intermediate **2** via **3** starting from D-glucose (Fig. 1). Retrosynthetically, compound **3** was planned to be derived from enone **11**, which was envisioned as arising by Ferrier's carbocyclization reaction of bicyclic enopyranoside derivative **7**. The synthesis began with the known  $\gamma$ -lactone **5**, prepared by the procedure reported by Corey and Shibasaki<sup>12</sup> from 3,4-enopyranoside **4**<sup>13</sup> (Scheme 1). The primary hydroxy group in **5** was converted into iodide to give **6** (85%), which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene to afford unstable bicyclic enopyranoside **7** in 82% yield. Although the attempted cyclization of **7** under the original conditions of Ferrier (1 equiv. HgCl<sub>2</sub>)<sup>1a</sup> led only to the decomposition of **7**, affording no desired product, treatment of **7** with catalytic amount of Hg(OCOCF<sub>3</sub>)<sub>2</sub> (1 mol%) in aqueous acetone at room temperature<sup>14a</sup> successfully induced the carbocyclization to provide **8a**. Unfortunately, the reaction was found to be somewhat capricious and the reproducibility was rather poor: the yield of **8a** varied in a range of 10–60%. Particularly, when the reaction was carried out in larger (5 ~ mmol) scale, considerable decomposition of **7** and the formation of many undesired products were observed, which rendered the yield of **8a** significantly lower (10–20%). One of the by-products in this step was assumed to be an unstable acyclic keto-aldehyde (**8b**), which rapidly decomposed. Since no retro-aldol reaction of **8a** was observed by TLC analysis, the formation of **8b** suggested that the bicyclic structure of **7** might inhibit the smooth carbocyclization. Thus, the low yield of **8a** and the lack of consistency upon scale-up should be due to the chemical instability of **7** as well as its bicyclic nature. Treatment of **8a** with methanesulfonyl chloride in pyridine caused  $\beta$ -elimination and provided enone **9** in 76% yield. Copper(I) catalyzed conjugate addition of methyl group and subsequent trap of the resulting enolate with TMSCl afforded silyl enol ether **10**, which was treated with stoichiometric amount of Pd(OAc)<sub>2</sub><sup>15</sup> to give compound **11** in 58% yield from **9**. With the chiral enone **11** in hand, reduction of the carbonyl group and introduction of the epoxide function, which would complete the formal synthesis of paniculide A, were next examined. Given the concave-convex nature of the bicyclo[4.3.0]nonane system in



**Scheme 1.** Ms = MeSO<sub>2</sub>-, TMS = Me<sub>3</sub>Si-, THF = tetrahydrofuran.

**11**, hydride reductions were expected to lead to the desired  $\alpha$ -alcohol. Reduction of compound **11** under the conditions of Luche (NaBH<sub>4</sub>-CeCl<sub>3</sub>, 0 °C in MeOH), however, afforded an inseparable mixture of allyl alcohol **12**, lactone-migrated compound **13**, and over-reduced compound **14** in a ratio of 4:1:1 (determined with 270 MHz <sup>1</sup>H NMR spectrum) in 90% yield. The structures of these compounds were assigned by <sup>1</sup>H NMR analysis with spin-spin decoupling experiments. Other reduction conditions to avoid the deleterious lactone migration and over-reduction proved to be unfruitful: with Zn(BH<sub>4</sub>)<sub>2</sub> in ether, compounds **12**, **13**, and **14** were obtained in a ratio of 2:1:0, in 60% yield; with LiBEt<sub>3</sub>H in THF at -78 °C, exclusive formation of compound **13** was observed (70% yield). Similar lactone migration had been reported by Tadano and co-workers<sup>10</sup> in their formal synthesis of paniculide B. Fortunately, epoxidation of the mixture of compounds **12**, **13**, and **14** with *m*-chloroperbenzoic acid (mCPBA), followed by chromatographic separation afforded the desired epoxide **15** in 38% isolated yield from **11**. Reaction of compound **15** with triethylsilyl chloride provided the known synthetic intermediate **3** for paniculide A in 75% yield. The spectral data were fully identical with those reported by Smith.<sup>6</sup> Reaction of compound **3** with lithium bis(trimethylsilyl)amide (LHMDS) at -78 °C, followed by treatment with 5-iodo-2-methyl-2-pentene<sup>16</sup> generated the alkylated product **2** in 24% yield along with the recovered starting material **3** (24%). The spectral data of **2** were also identical with those reported for the authentic compound<sup>6,11</sup> in all respects, and the specific rotational value  $[\alpha]_{\text{D}}^{23} - 39$  (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>) were in good agreement with those reported by Narasaka<sup>11</sup>  $[\alpha]_{\text{D}}^{26} - 39.77$  (*c* 1.115, CH<sub>2</sub>Cl<sub>2</sub>). Since compound **3** had been already converted into paniculide A in three steps by Smith<sup>6</sup> and Narasaka,<sup>11</sup> formal total synthesis of paniculide A **1** in optically active form has been completed.

**The alternative approach to paniculide A, combination of Ferrier's carbocyclization reaction and Claisen rearrangement:** As discussed above, synthesis of paniculide A in a formal sense has been achieved. However, poor reproducibility of the carbocyclization (7 to 8) and the problematic lactone migration in reduction step, which made the synthetic route not practical, promoted us to investigate another synthetic approach (Fig. 2). To establish the reproducibility in Ferrier's carbocyclization step, we decided to employ the mono-cyclic substrate, such as 20. In the lactone-migration event, we reasoned that the migration (12 → 13) had occurred because there would be an equilibration between 12 and 13 in the reduction step,<sup>17</sup> therefore affording the migrated 13 as the thermodynamically favored product. We also assumed that the reduction of the enone already possessing an alkyl substituent at C-3 position in  $\beta$ -orientation, like 34, would not cause the migration, since the migrated product has an alkyl group orienting the sterically disfavored concave face. These assumptions were supported by the computational analysis of compounds 12 and 13, and model compounds 12a and 12b. Thus, calculation of the heat of formations (Boltzmann-weighted average at 298 K)<sup>18</sup> of compounds 12 and 13 at the PM3 level revealed that migrated compound 13 is stable than compound 12 by 0.342 kcal/mol, implying that the migrated 13 is the thermodynamically favored product. On the other hand, calculation of model compounds possessing *S*-methyl group at C-3 suggested 12a is more stable than migrated compound 13a by 1.73 kcal/mol, predicting that the presence of the *S*-alkyl group at C-3 might suppress the lactone migration.

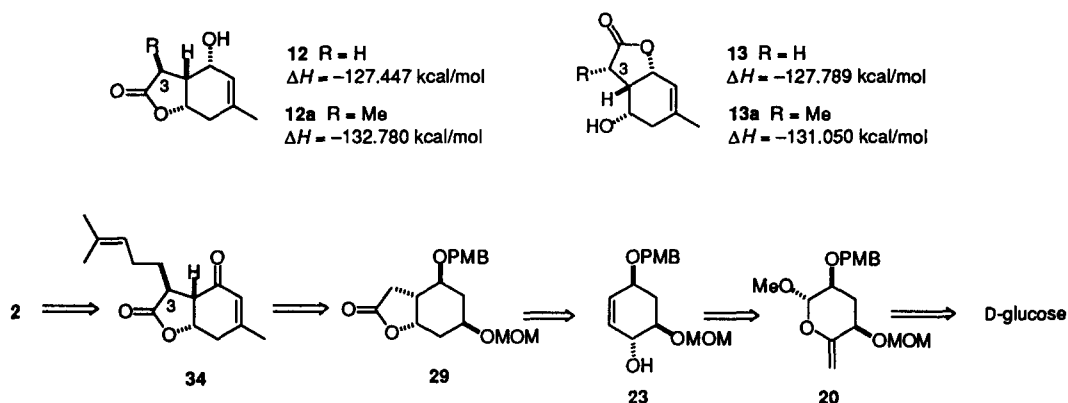
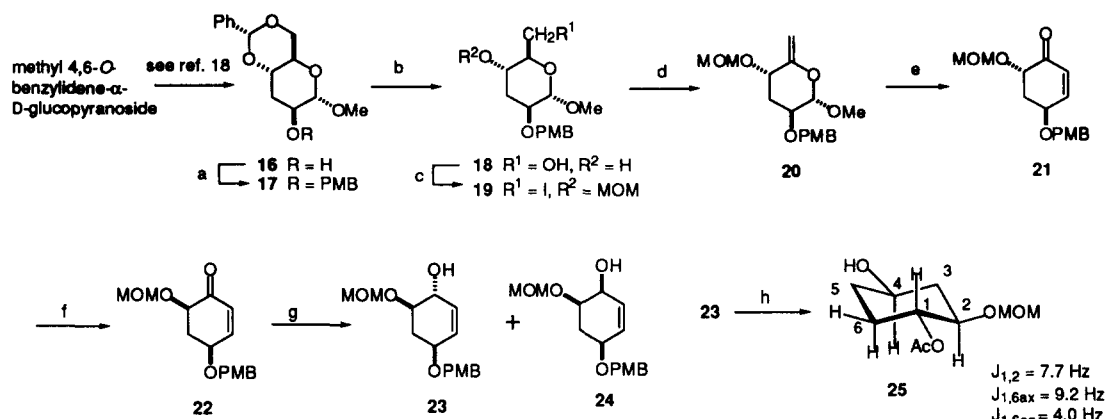


Fig. 2. PMB = 4-methoxybenzyl, MOM = MeOCH<sub>2</sub>-.

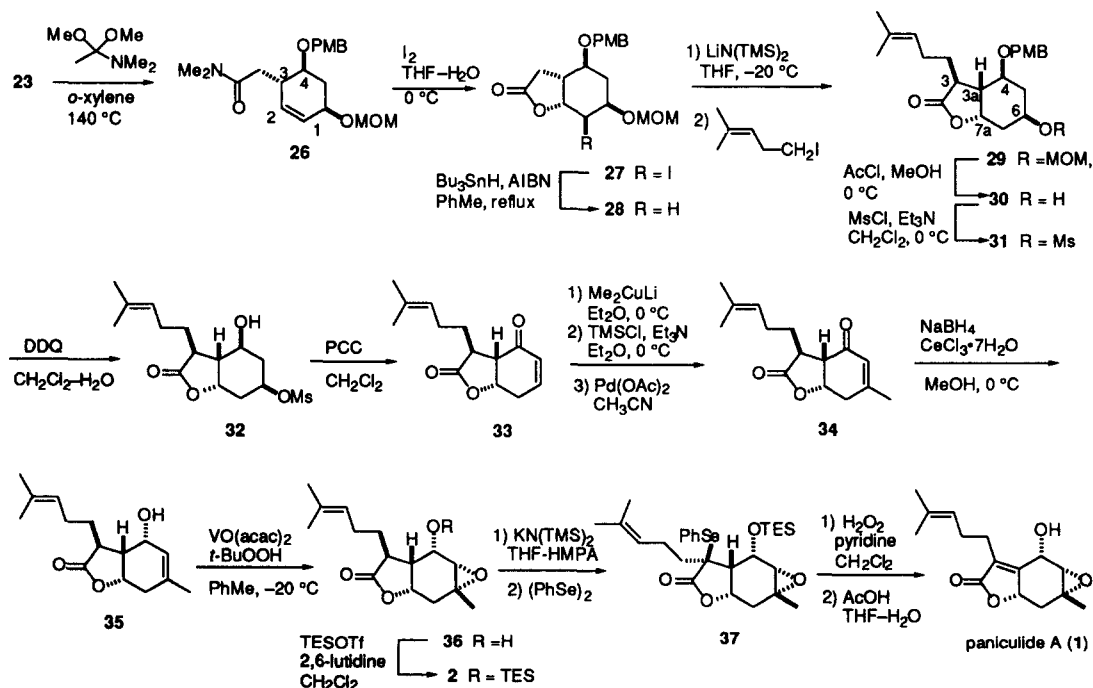
Based on these considerations, the revised synthetic plan was designed. Thus, compound 2 was envisioned to be derived by the reduction, followed by epoxidation, of enone 34 possessing a C<sub>6</sub> side chain orienting to the convex face at C-3. Compound 34 was planned to be prepared from  $\gamma$ -lactone 29, which was envisioned to be constructed by Claisen rearrangement followed by halo-lactonization of allyl alcohol 23.

The new approach to paniculide A commenced with the known 3-deoxy- $\alpha$ -D-arabinopyranoside<sup>19</sup> 16, which was obtained from commercially available methyl 4,6-*O*-benzylidene- $\alpha$ -D-glucopyranoside in 2 step reactions (Scheme 2). 4-Methoxybenzyl ether formation of 16 gave 17 (98%), whose benzylidene acetal was removed to afford diol 18 in 89% yield. The primary hydroxy group was replaced with iodide and the secondary one was protected as a methoxymethyl ether to give 19 in 82% yield. Treatment of 19 with *t*-BuOK in THF at room temperature gave hex-5-enopyranoside derivative 20 in 85% yield. Catalytic Ferrier's carbocyclization of 20 with Hg(OCOCF<sub>3</sub>)<sub>2</sub> (5 mol%) in aqueous acetone at room temperature, and subsequent



**Scheme 2.** Reagents and conditions: a) NaH, *N,N*-dimethylformamide (DMF), PMBCl, 0 °C ~ r.t.; b) AcOH·H<sub>2</sub>O (4:1), 70 °C; c) I<sub>2</sub>, Ph<sub>3</sub>P, imidazole, toluene, r.t., then MOMCl, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; d) *t*-BuOK, THF, r.t.; e) Hg(OACF<sub>3</sub>)<sub>2</sub> (5 mol%), acetone·H<sub>2</sub>O (2:1), r.t., then MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; f) DBU, toluene, r.t.; g) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, -78 °C; h) Ac<sub>2</sub>O, pyridine, r.t., then H<sub>2</sub>, 10% Pd/C, EtOH, r.t.

$\beta$ -elimination provided enone **21** in 67% yield. At this stage, methoxymethoxy function in **21** was epimerized with DBU to afford **22**, since the reduction of the ketone carbonyl group in **21** was found to show low stereoselectivity (with  $\text{NaBH}_4\text{-CeCl}_3$  at  $0\text{ }^\circ\text{C}$ , 1.6:1, in 82% yield; with diisobutylaluminium hydride (DIBAL-H) at  $-78\text{ }^\circ\text{C}$ , 2.6:1, in 78% yield).<sup>20</sup> Two cycles of the epimerization of **21** gave **22** in 62% yield (**21**, 23% recovered). Reduction of **22** with  $\text{NaBH}_4\text{-CeCl}_3$  at  $-78\text{ }^\circ\text{C}$  proceeded stereoselectively, and provided **23** and **24** in 86% and 6% isolated yields, respectively. The structure of **23** was confirmed by  $^1\text{H}$  NMR analysis of its



### Scheme 3.

corresponding saturated derivative **25**. The large spin-spin coupling constants observed in **25** ( $J_{1,2} = 7.7$ ,  $J_{1,6ax} = 9.2$  Hz) clearly supported the assigned structure. Claisen rearrangement of **23** with *N,N*-dimethylacetamide dimethyl acetal<sup>21</sup> in degassed *o*-xylene under Ar in the presence of molecular sieves **3A** successfully provided **26** as the sole product in 89% yield (Scheme 3). The observed large coupling constants in the <sup>1</sup>H NMR of **26** ( $J_{3,4} = 8.8$ ,  $J_{4,5ax} = 11.7$  Hz) showed that **26** has a half boat conformation with a quasi-equatorial carbon side-chain at C-3 and an equatorial 4-methoxybenzyloxy group at C-4, confirming that the carbon side-chain at C-3 was introduced in the suprafacial mode. Iodolactonization and subsequent deiodination afforded  $\gamma$ -lactone **28** in 94% yield. At this stage, introduction of a C<sub>6</sub> side chain of paniculide A was examined. Thus, deprotonation of **28** with LHMDs at –20 °C, followed by treatment with 5-iodo-2-methyl-2-pentene at –20 °C to 5 °C afforded alkylated product **29** in 71% yield. The *O*-MOM protecting group was detached with HCl-MeOH to give **30** in 93% yield. The observed NOE between H-3 and H-4 in compound **30** revealed that the stereochemistry at C-3 should be *S*, showing that the C<sub>6</sub> side chain had been introduced, as expected, from the convex face. After conversion of hydroxy group in **30** into methanesulfonyl ester, the remaining *O*-PMB group was deprotected to give **32** in 63% yield. Treatment of **32** with pyridinium chlorochromate (PCC) caused the oxidation of alcohol function as well as concomitant elimination of methanesulfonic acid to give the enone **33**, quantitatively. Introduction of a methyl group in 1,4-fashion was achieved by reaction of **33** with Me<sub>2</sub>CuLi, and the intermediary enolate was trapped with TMSCl-Et<sub>3</sub>N to give silyl enol ether, which, without isolation was oxidized with Pd(OAc)<sub>2</sub> to regenerate the enone function to provide **34** in 67% yield. With the trihydrobenzofuran skeleton possessing all the required carbons for paniculide A in hand, the introduction of an epoxide and a double bond were examined. As mentioned above, reduction of enone **34** was expected to give the desired allyl alcohol **35** as the major product. Indeed, treatment of **34** with NaBH<sub>4</sub>-CeCl<sub>3</sub> in MeOH at 0 °C afforded **35** as the sole product in 70% yield. The formation of the lactone-migrated product could not be detected in the reaction mixture. Stereoselective formation of the epoxide function was successfully achieved under the conditions of Sharpless, VO(acac)<sub>2</sub>-*t*-BuOOH system,<sup>22</sup> to generate **36** in 72% yield, along with enone **34** in 15% yield. Triethylsilyl ether formation of **36** provided **2** in 95% yield, whose spectroscopic data (<sup>1</sup>H and <sup>13</sup>C NMR) were fully identical with those of the compound, prepared by the first approach. Finally, introduction of the double bond into **2** was performed through the procedure reported by Smith and Narasaka.<sup>6,11</sup> Treatment of **2** with KHMDS at 0 °C, followed by addition of diphenyl diselenide afforded a selenide **37** in 58% yield. Oxidation of **37** with hydrogen peroxide in pyridine-CH<sub>2</sub>Cl<sub>2</sub>, followed by treatment with aqueous acetic acid in THF afforded paniculide A **1** in 94% yield. The spectral (<sup>1</sup>H and <sup>13</sup>C NMR) data of synthetic **1** were fully identical with those of the authentic paniculide A. Physical property of synthetic **1** (m.p. 116–117 °C) (lit. 120–121 °C,<sup>5a</sup> 118.8–121.1 °C<sup>11</sup>), and specific rotational value  $[\alpha]_D^{20} + 14.5$  (*c* 0.17, MeOH) (lit.<sup>11</sup>  $[\alpha]_D^{29} + 14.98$  (*c* 0.747, MeOH)) were also in good agreement with those reported previously.

## Conclusion

The synthesis of paniculide A, a highly oxygenated sesquiterpene, starting from D-glucose in two different ways is described. The first approach, which resulted in the formal total synthesis, revealed that catalytic Ferrier's carbocyclization is applicable to the bicyclic substrate **7**, although the lack of reproducibility is still unsolved. The successful total synthesis by the second approach showed that the combination of Ferrier's carbocyclization reaction and Claisen rearrangement is a potent procedure for the stereoselective formation of the carbon-carbon bonds, whose chirality could be effectively transferred from the carbon-oxygen bond. This

work proved that Ferrier's carbocyclization reaction is a useful key reaction for the construction of natural products having a highly substituted cyclohexane unit.

### Acknowledgments

We thank Professor Amos B. Smith, III (University of Pennsylvania, Philadelphia, U.S.A.) for providing us with the authentic sample of paniculide A and spectral data of his synthetic intermediates. Financial support of the Grant-in Aid for Scientific Research on Priority Area from the Ministry of Education, Science, Sports and Culture, of Japanese Government is gratefully acknowledged.

### EXPERIMENTAL

M.p.s were determined on a Mitamura-riken micro hot stage and are uncorrected.  $^1\text{H}$  NMR spectra were measured with a JEOL JNM-GSX 270 (270 MHz) or a JEOL JNM-LA 300W (300 MHz) spectrometers, with tetramethylsilane as the internal standard for solutions in deuteriochloroform, unless otherwise noted, and  $J$  values are given in Hz.  $^{13}\text{C}$  NMR spectra were taken on a JEOL JNM-GSX 270 (67 MHz) or a JEOL JNM-LA 300W (75 MHz) spectrometer. Low and high resolution mass spectra were measured by a JEOL GC Mate spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument with 1-dm tube and values of  $[\alpha]_D$  are recorded in units of  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ . IR spectra were taken with a JASCO FT/IR-200 spectrometer. Organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated below  $40^\circ\text{C}$  under reduced pressure.

**(1*S*,2*S*,4*S*,6*S*)-2-(Iodomethyl)-4-methoxy-3,7-dioxabicyclo[4.3.0]nonan-8-one (6).** A solution of (1*S*,2*S*,4*S*,6*S*)-2-hydroxymethyl-4-methoxy-3,7-dioxabicyclo[4.3.0]nonan-8-one<sup>8</sup> (5, 352 mg, 1.74 mmol), triphenylphosphine (913 mg, 3.48 mmol), imidazole (474 mg, 6.96 mmol) and iodine (839 mg, 3.31 mmol) in toluene (20 ml) was stirred at  $70^\circ\text{C}$  for 2 h. After cooling, the mixture was diluted with EtOAc and washed with a saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution, a saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (20 g), with acetone–toluene (1:10) as eluent, to afford compound 6 (461 mg, 85%) as crystals: M.p.  $149\text{--}149.5^\circ\text{C}$  (from EtOAc);  $[\alpha]_D^{27} + 59$  (c 0.5,  $\text{CHCl}_3$ ); IR (KBr)  $1760 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta = 2.11$  (ddd, 1 H,  $J = 4.8, 4.8, 15.4 \text{ Hz}$ ), 2.17 (ddd, 1 H,  $J = 3.1, 4.8, 15.4 \text{ Hz}$ ), 2.27 (dd, 1 H,  $J = 2.6, 17.6 \text{ Hz}$ ), 2.45 (dddd, 1 H,  $J = 2.6, 3.4, 4.8, 10.3 \text{ Hz}$ ), 2.72 (dd, 1 H,  $J = 7.7, 17.6 \text{ Hz}$ ), 3.18 (dd, 1 H,  $J = 7.0, 11.0 \text{ Hz}$ ), 3.39 (dd, 1 H,  $J = 2.9, 11.0 \text{ Hz}$ ), 3.43 (s, 3 H), 3.56 (ddd, 1 H,  $J = 2.9, 7.0, 10.3 \text{ Hz}$ ), 4.63 (ddd, 1 H,  $J = 4.8, 4.8, 4.8 \text{ Hz}$ ), 4.87 (dd, 1 H,  $J = 3.1, 4.8 \text{ Hz}$ ). Found: C, 34.68; H, 4.11%. Calcd for  $\text{C}_9\text{H}_{13}\text{O}_4\text{I}$ : C, 34.64; H, 4.20%.

**(1*S*,4*S*,6*S*)-4-Methoxy-2-methylene-3,7-dioxabicyclo[4.3.0]nonan-8-one (7).** A solution of compound 6 (1.65 g, 5.29 mmol) and DBU (2.37 ml, 15.9 mmol) in toluene (50 ml) was heated under reflux for 5 h. After cooling, the mixture was diluted with EtOAc and washed with water and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (50 g), with EtOAc–toluene (1:3; containing 1 vol%  $\text{Et}_3\text{N}$ ) as eluent, to afford compound 7 (794 mg, 82%) as crystalline residue: M.p.  $61\text{--}62^\circ\text{C}$ ;  $[\alpha]_D^{27} + 166$  (c 1.5,  $\text{CHCl}_3$ ); IR (neat)  $1780$  and  $1660 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta = 2.06$  (ddd, 1 H,  $J = 3.3, 5.5, 15.0 \text{ Hz}$ ), 2.20 (ddd, 1 H,  $J = 3.3, 3.3, 15.0 \text{ Hz}$ ), 2.76 (d, 2 H,  $J = 9.0 \text{ Hz}$ ), 3.45 (s, 3 H), 3.50 (td, 1 H,  $J = 9.0, 9.5 \text{ Hz}$ ), 4.24 (s, 1 H), 4.50 (d, 1 H,  $J = 1.1 \text{ Hz}$ ), 4.87 (dddd, 1 H,  $J = 1.1, 3.3, 5.5, 9.5 \text{ Hz}$ ), 4.95 (dd, 1 H,  $J = 3.3, 3.3 \text{ Hz}$ ). Found: C, 58.72; H, 6.96%. Calcd for  $\text{C}_9\text{H}_{12}\text{O}_4$ : C, 58.69; H, 6.57%.

**(3*aS*,7*aS*)-3,3*a*,7,7*a*-Tetrahydrobenzo[*b*]furan-2,4-dione (9).** To a solution of compound 7 (850 mg, 4.61 mmol) in acetone (12 ml) and water (6 ml) was added mercury(II) trifluoroacetate (21 mg, 0.046 mmol), and the mixture was stirred at room temperature for 13 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (10 g), with EtOAc– $\text{Et}_2\text{O}$  (1:1) as eluent, to afford syrupy (3*aS*,6*R*,7*aS*)- and (3*aS*,6*S*,7*aS*)-6-hydroxy-3,3*a*,5,6,7,7*a*-hexahydrobenzo[*b*]furan-2,4-dione (8*a*) (298 mg, 38%) as a mixture (ca. 1: 1) of C-6 epimers: IR (neat)  $3550, 1760, \text{ and } 1715 \text{ cm}^{-1}$ . HRMS Calcd for  $\text{C}_8\text{H}_{10}\text{O}_4$ : ( $\text{M}^+$ ), 170.0579. Found:  $m/z$  170.0589. This compound was used in the next reaction without further purification. To a solution of compound 8*a* (298 mg, 1.75 mmol) in pyridine (6 ml) at  $0^\circ\text{C}$  was

added methanesulfonyl chloride (0.196 ml, 2.53 mmol), and the mixture was stirred at room temperature for 4.5 h. The reaction mixture was diluted with water at 0 °C and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (x4). The organic layer was dried and then concentrated to give a residue, which was chromatographed on a column of silica gel (25 g), with EtOAc–toluene (1:2) as eluent, to afford compound 9 (202 mg, 29% from 7) as a crystalline residue: M.p. 51–54 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 15 (c 1.5, CHCl<sub>3</sub>); IR (neat) 1780 and 1660 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 2.80 (m, 1 H), 2.84 (dd, 1 H, J = 9.2, 18.0 Hz), 2.95 (m, 1 H), 3.05 (dd, 1 H, J = 2.2, 18.0 Hz), 3.16 (ddd, 1 H, J = 2.2, 5.5, 9.2 Hz), 5.06 (dddd, 1 H, J = 1.5, 2.6, 5.5, 5.5 Hz), 6.22 (ddd, 1 H, J = 2.6, 2.9, 10.4 Hz), 6.92 (dddd, 1 H, J = 1.5, 2.9, 4.8, 10.4 Hz); <sup>13</sup>C NMR (67 MHz in CDCl<sub>3</sub>)  $\delta$  = 27.2, 33.2, 44.6, 76.9, 129.2, 145.6, 174.5, 194.9. HRMS Calcd for C<sub>8</sub>H<sub>8</sub>O<sub>3</sub>: (M<sup>+</sup>), 152.0474. Found: *m/z* 152.0470.

**(3a*S*,7a*S*)-6-Methyl-3,3a,7,7a-tetrahydrobenzo[*b*]furan-2,4-dione (11).** To a suspension of CuI (351 mg, 1.84 mmol) in THF (2 ml) under Ar at –78 °C was added methylmagnesium bromide in diethyl ether (0.82 mol dm<sup>-3</sup> solution, 2.24 ml, 1.84 mmol), and the mixture was stirred at –78 °C for 1 h. To this solution at –78 °C was added a solution of compound 9 (187 mg, 1.23 mmol) in THF (3 ml). After being stirred at –78 °C for 1 h, a mixture of trimethylsilyl chloride (1.6 ml) and triethylamine (1.6 ml) was added, and the resultant mixture was further stirred at –78 °C for 10 min, and then at 0 °C for 2 h. The reaction was quenched with a buffer solution (pH = 8, prepared from saturated aqueous solution of NH<sub>4</sub>Cl and aqueous ammonia), and the products were extracted with EtOAc (x4). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub> (1 : 1 w/w), and then concentrated to give crude silyl enol ether 10 (236 mg, 80% crude yield), which was used in the next reaction without isolation. A mixture of crude 10 (236 mg, 0.982 mmol) and Pd(OAc)<sub>2</sub> (441 mg, 1.96 mmol) in acetonitrile (6 ml) under Ar was stirred at room temperature for 72 h. The mixture was diluted with EtOAc and the insoluble material was removed by filtration through Celite and the filtrate was washed successively with 20% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, aqueous saturated NaHCO<sub>3</sub> solution, and brine, and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (6 g), with EtOAc–toluene (1:3) as eluent, to afford compound 11 (119 mg, 58% from 9) as crystalline residue: M.p. 82–85 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 19 (c 1.1, CHCl<sub>3</sub>); IR (KBr) 1770 and 1660 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 2.03 (s, 3H), 2.77 (m, 2 H), 2.83 (dd, 1 H, J = 9.2, 18.0 Hz), 3.03 (dd, 1 H, J = 2.2, 18.0 Hz), 3.05 (ddd, 1 H, J = 2.2, 5.2, 9.2 Hz), 5.04 (ddd, 1 H, J = 2.9, 5.2, 5.2 Hz), 6.06 (m, 1 H); <sup>13</sup>C NMR (67 MHz in CDCl<sub>3</sub>)  $\delta$  = 24.5, 32.1, 33.5, 43.4, 77.0, 126.0, 158.0, 174.6, 194.9. HRMS Calcd for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>: (M<sup>+</sup>), 166.0630. Found: *m/z* 166.0625.

**Reduction of compound 11.** To a solution of compound 11 (29.0 mg, 0.175 mmol) and CeCl<sub>3</sub>·7H<sub>2</sub>O (97.5 mg, 0.262 mmol) in methanol (6 ml) at 0 °C was slowly added NaBH<sub>4</sub> (7.3 mg, 0.192 mmol) over 5 min. After being stirred at 0 °C for 1 h, additional NaBH<sub>4</sub> (2.9 mg, 0.077 mmol) was added and the mixture was further stirred at 0 °C for 30 min. The reaction mixture was diluted with water and the product was extracted twice with EtOAc. The combined organic layer was dried and then concentrated to give a residue, which was chromatographed on a column of silica gel (2 g), with EtOAc–toluene (2:3) as eluent, to afford an inseparable mixture of (3a*R*,4*R*,7a*S*)-4-hydroxy-6-methyl-3a,4,7,7a-tetrahydrobenzo[*b*]furan-2(3*H*)-one (12), its isomer (13), and saturated derivative (14) (4:1:1, 26.3 mg, 90%) as a syrup: <sup>1</sup>H NMR (270 MHz, for the major product 12)  $\delta$  = 1.77 (d, 3 H, J = 1.0 Hz), 2.25–2.50 (m, 2 H), 2.58 (dd, 1 H, J = 8.8, 17.6 Hz), 2.75 (dd, 1 H, J = 3.4, 17.6 Hz), 2.82 (m, 1 H), 4.28 (m, 1 H), 4.87 (ddd, 1 H, J = 2.9, 6.6, 6.6 Hz), 5.68 (bs, 1 H). This mixture was used in the next reaction without further purification.

**(1a*R*,2a*S*,5a*S*,6*S*,6a*S*)-2,2a,5,5a,6,6a-Hexahydro-1a-methyl-6-[(triethylsilyl)oxy]oxireno[*f*]benzofuran-4(1a*H*)-one (3).** To a solution of a mixture of compounds 12, 13 and 14 (4:1:1, 26.3 mg) in CH<sub>2</sub>Cl<sub>2</sub> (1.6 ml) were added at 0 °C NaHCO<sub>3</sub> (20.2 mg, 0.24 mmol) and mCPBA (38.0 mg, 0.22 mmol), and the mixture was stirred at 0 °C for 3.5 h, and then at 5 °C for 12 h. The insoluble material was removed by filtration and filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (2 g), with EtOAc–Et<sub>2</sub>O (4:1) as eluent, to afford compound 15 (12.2 mg, 38% from 11) as a syrup, and a mixture of its stereoisomers and compound 14. To a solution of triethylchlorosilane (67  $\mu$ l, 0.40 mmol), triethylamine (56  $\mu$ l, 0.40 mmol), and 4-dimethylaminopyridine (1.9 mg, 0.02 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) at room temperature under Ar was added a solution of compound 15 (12.2 mg, 0.066 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml). After being stirred at room temperature for 3.5 h, the reaction mixture was diluted with EtOAc and successively with saturated aqueous NH<sub>4</sub>Cl solution, saturated aqueous NaHCO<sub>3</sub> solution, and brine, and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (2 g), with Et<sub>2</sub>O–



hexanes (2:3) as eluent, to afford compound **3** (14.9 mg, 75% from **15**, 29% from **11**) as a syrup:  $[\alpha]_D^{24} + 1$  (*c* 0.5, CHCl<sub>3</sub>); IR (neat) 1770 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 0.62 (q, 6 H, *J* = 7.6 Hz), 0.97 (t, 9 H, *J* = 7.6 Hz), 1.35 (s, 3H), 1.95 (dd, 1 H, *J* = 5.4, 16.1 Hz), 2.32 (dd, 1 H, *J* = 1.5, 16.1 Hz), 2.41 (dd, 1 H, *J* = 11.2, 18.6 Hz), 2.91 (m, 1 H), 3.02 (s, 1 H), 3.09 (dd, 1 H, *J* = 5.9, 18.6 Hz), 4.19 (d, 1 H, *J* = 6.8 Hz), 4.69 (ddd, 1 H, *J* = 1.5, 5.4, 10.3 Hz). HRMS Calcd for C<sub>15</sub>H<sub>27</sub>O<sub>4</sub>Si: (*M*<sup>+</sup>+H), 299.1679. Found: *m/z* 299.1665.

**(1aS,2aS,5S,5aS,6S,6aS)-2,2a,5,5a,6,6a-Hexahydro-1a-methyl-5-(4-methyl-3-pentenyl)-6-[(triethylsilyl)oxy]oxireno[*f*]benzofuran-4(1aH)-one (2).** To a solution of compound **3** (48.1 mg, 0.161 mmol) in THF (1 ml) under Ar at -78 °C was added 1.0 mol dm<sup>-3</sup> solution of lithium bis(trimethylsilyl)amide in THF (0.210 ml, 0.210 mmol). After being stirred at -78 °C for 20 min, and then at -40 °C for 1 h, the reaction mixture was cooled to -78 °C. To the reaction mixture was added 5-iodo-2-methyl-2-pentene (70.0 mg, 0.331 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 20 min, and then at 5 °C for 15 h. The mixture was diluted at 0 °C with saturated aqueous NH<sub>4</sub>Cl solution and the product was extracted three times with EtOAc. The combined organic layer was dried and concentrated to give a residue, which was chromatographed on a column of silica gel (3 g), with Et<sub>2</sub>O–hexanes (1:4) as eluent, to afford first, compound **2** (14.4 mg, 24%) as a syrup:  $[\alpha]_D^{23} - 39$  (*c* 1.1, CHCl<sub>3</sub>) {lit.<sup>11</sup>  $[\alpha]_D^{26} - 39.77$  (*c* 1.115, CHCl<sub>3</sub>)}; IR (neat) 1760 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 0.65 (q, 6 H, *J* = 7.8 Hz), 0.99 (t, 9 H, *J* = 7.8 Hz), 1.34 (s, 3H), 1.58–1.69 (m, 2 H), 1.60 and 1.67 (2s, each 3 H), 1.95 (dd, 1 H, *J* = 5.1, 15.7 Hz), 2.00–2.18 (m, 2 H), 2.29 (dd, 1 H, *J* = 1.6, 15.7 Hz), 2.57 (ddd, 1 H, *J* = 6.2, 6.9, 10.1 Hz), 2.98 (s, 1 H), 3.13 (dt, 1 H, *J* = 6.2, 6.9 Hz), 4.25 (d, 1 H, *J* = 6.9 Hz), 4.59 (ddd, 1 H, *J* = 1.6, 5.1, 10.1 Hz), 5.09 (t, 1 H, *J* = 6.9 Hz); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 4.9, 6.8, 17.7, 22.0, 24.7, 25.7, 31.8, 34.0, 42.0, 42.9, 56.8, 62.3, 67.9, 73.4, 123.5, 132.2, 179.1. HRMS Calcd for C<sub>21</sub>H<sub>36</sub>O<sub>4</sub>Si: (*M*<sup>+</sup>), 380.2383. Found: *m/z* 380.2389. Found: C, 66.19; H, 9.83%. Calcd for C<sub>21</sub>H<sub>36</sub>O<sub>4</sub>Si: C, 66.33; H, 9.54%. The <sup>1</sup>H and <sup>13</sup>C NMR data were fully identical to those reported by Smith,<sup>6</sup> and Narasaka.<sup>11</sup> Further elution gave starting material (**3**) (11.4 mg, 24%).

**Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-(4-methoxybenzyl)- $\alpha$ -D-arabinopyranoside (17).** A mixture of methyl 4,6-*O*-benzylidene-3-deoxy- $\alpha$ -D-arabinopyranoside (**16**, 511 mg, 1.92 mmol) and NaH (60% in oil, 115 mg, 2.88 mmol) in DMF (20 ml) was stirred at 0 °C for 30 min. To this mixture at 0 °C was added 4-methoxybenzyl chloride (0.390 ml, 2.88 mmol). After being stirred at 0 °C for 3 h, the reaction mixture was poured into cold saturated aqueous NaHCO<sub>3</sub> solution, and the mixture was further stirred at 0 °C for 30 min. The products were extracted twice with EtOAc and the combined organic layer was washed with brine, and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (30 g), with EtOAc–toluene (1:25) as eluent, to afford compound **17** (729 mg, 98%) as crystals: M.p. 59–63 °C (from EtOH);  $[\alpha]_D^{22} + 44$  (*c* 0.4, CHCl<sub>3</sub>); IR (KBr) 1610 and 1515 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.95 (ddd, 1 H, *J* = 2.9, 11.7, 12.8 Hz), 2.20 (ddd, 1 H, *J* = 3.3, 3.3, 12.8 Hz), 3.38 (s, 3 H), 3.64–3.68 (m, 1 H), 3.80 (s, 3 H), 3.76–3.87 (m, 2 H), 3.95–4.04 (m, 1 H), 4.23 (m, 1 H), 4.51 and 4.58 (2d, each 1 H, *J* = 11.7 Hz), 4.62 (br s, 1 H), 5.57 (s, 1 H), 6.85–6.92 (m, 2 H), 7.25–7.50 (m, 7 H); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 29.2, 54.7, 55.3, 65.0, 69.3, 70.9, 74.1, 74.5, 98.9, 102.0, 113.9, 126.1, 128.3, 129.0, 129.3, 129.9, 137.6, 159.3. Found: C, 68.33; H, 6.85%. Calcd for C<sub>22</sub>H<sub>26</sub>O<sub>6</sub>: C, 68.38; H, 6.78%.

**Methyl 3-Deoxy-2-*O*-(4-methoxybenzyl)- $\alpha$ -D-arabinopyranoside (18).** A mixture of compound **17** (5.23 g, 13.5 mmol) in acetic acid (80 ml) and water (20 ml) was heated at 70 °C for 1.5 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (200 g), with acetone–toluene (1:2) as eluent, to afford compound **18** (3.59 g, 89%) as a colorless syrup:  $[\alpha]_D^{28} + 66$  (*c* 1.1, CHCl<sub>3</sub>); IR (neat) 3400, 1610 and 1515 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.74 (ddd, 1 H, *J* = 2.9, 11.4, 13.2 Hz), 2.15 (ddd, 1 H, *J* = 3.7, 4.8, 13.2 Hz), 2.67 (br s, 2 H), 3.35 (s, 3 H), 3.49–3.57 (m, 2 H), 3.79 (s, 3 H), 3.80–3.83 (m, 2 H), 3.95 (ddd, 1 H, *J* = 4.8, 9.5, 11.4 Hz), 4.47 and 4.53 (2d, each 1 H, *J* = 11.7 Hz), 4.58 (br s, 1 H), 6.87 and 7.25 (2d, each 2 H, *J* = 9.2 Hz); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 32.0, 54.7, 55.3, 63.0, 63.3, 70.6, 72.9, 74.3, 98.2, 113.8, 129.3, 130.0, 159.3. Found: C, 59.83; H, 7.62%. Calcd for C<sub>15</sub>H<sub>22</sub>O<sub>6</sub>·1/4H<sub>2</sub>O: C, 59.49; H, 7.49%.

**Methyl 3,6-Dideoxy-6-iodo-2-*O*-(4-methoxybenzyl)-4-*O*-methoxymethyl- $\alpha$ -D-arabinopyranoside (19).** To a solution of compound **18** (1.06 g, 3.55 mmol) in toluene (20 ml) at room temperature were added triphenylphosphine (1.49 g, 5.68 mmol), imidazole (773 mg, 11.4 mmol), and iodine (1.352 g,

5.33 mmol). After being stirred at room temperature for 24 h, the mixture was diluted with EtOAc and washed successively with 20% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (55 g), with EtOAc–toluene (1:7) as eluent, to afford primary iodide (1.27 g), which was used in the next reaction without further purification. To a solution of the primary iodide (1.27 g, 3.11 mmol) and diisopropylethylamine (8.66 ml, 49.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (26 ml) at room temperature was added chloromethyl methyl ether (1.89 ml, 24.9 mmol), and the mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with EtOAc and washed successively with 1 mol  $\text{dm}^{-3}$  aqueous HCl solution, saturated aqueous  $\text{NaHCO}_3$  solution and brine, and dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (60 g), with EtOAc–toluene (1:15) as eluent, to afford **19** (1.31 g, 82%) as a colorless syrup:  $[\alpha]_D^{22} + 63$  (c 1.8,  $\text{CHCl}_3$ ); IR (neat) 1610 and 1515  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.75 (ddd, 1 H,  $J$  = 2.9, 10.7, 13.2 Hz), 2.22 (ddd, 1 H,  $J$  = 3.9, 3.9, 13.2 Hz), 3.27 (dd, 1 H,  $J$  = 8.8, 10.7 Hz), 3.37 and 3.45 (2s, each 3 H), 3.53–3.62 (m, 3 H), 3.68 (ddd, 1 H,  $J$  = 4.4, 10.7, 10.7 Hz), 3.80 (s, 3 H), 4.51 (s, 2 H), 4.62 (d, 1 H,  $J$  = 6.8 Hz), 4.64 (br s, 1 H), 4.68 (d, 1 H,  $J$  = 6.8 Hz), 6.87 and 7.27 (2d, each 2 H,  $J$  = 8.5 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 7.1, 30.2, 55.0, 55.2, 55.7, 70.7, 71.5, 72.8, 74.2, 95.5, 98.4, 113.8, 129.2, 130.1, 159.2. Found: C, 45.12; H, 5.74%. Calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_6$ : C, 45.15; H, 5.57%.

**Methyl 3,6-Dideoxy-2-O-(4-methoxybenzyl)-4-O-methoxymethyl- $\alpha$ -D-threo-hex-5-enopyranoside (20).** To a solution of compound **19** (98.2 mg, 0.217 mmol) in THF (50 ml) at room temperature was added potassium *t*-butoxide (73.1 mg, 0.651 mmol). After being stirred at room temperature for 3.5 h, the mixture was diluted with EtOAc and washed with 1 mol  $\text{dm}^{-3}$  aqueous HCl solution, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (2.8 g), with EtOAc–toluene (1:15) containing 1 vol%  $\text{Et}_3\text{N}$  as eluent, to afford **20** (60.1 mg, 85%) as a colorless syrup:  $[\alpha]_D^{25} + 1$  (c 2.2,  $\text{CHCl}_3$ ); IR (neat) 1660, 1610, 1510 and 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.95–2.10 (m, 2 H), 3.38 and 3.48 (2s, each 3 H), 3.64–3.70 (m, 1 H), 3.80 (s, 3 H), 4.35 (dd, 1 H,  $J$  = 5.0, 9.0 Hz), 4.56–4.73 (m, 7 H), 6.88 and 7.27 (2d, each 2 H,  $J$  = 8.3 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 14.3, 32.3, 55.5, 55.7, 69.1, 71.6, 74.0, 95.2, 95.6, 102.2, 114.0, 129.5, 130.4, 156.1, 159.5. Found: C, 62.73; H, 7.73%. Calcd for  $\text{C}_{17}\text{H}_{24}\text{O}_6$ : C, 62.95; H, 7.46%.

**(4S,6S)-4-[(4-Methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-2-cyclohexene-1-one (21).** To a solution of compound **20** (723 mg, 2.33 mmol) in  $\text{H}_2\text{O}$  (5 ml) and acetone (10 ml) at room temperature was added mercury(II) trifluoroacetate (47.6 mg, 0.112 mmol). After being stirred at room temperature for 24 h, the mixture was diluted with EtOAc and washed with 10% aqueous KI solution, 20% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution, and then dried. Removal of the solvent gave a residue, which was dissolved in  $\text{CH}_2\text{Cl}_2$  (15 ml). To this solution at 0 °C were added triethylamine (1.87 ml, 13.4 mmol) and  $\text{MsCl}$  (0.52 ml, 6.7 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc and washed successively with 0.5 mol  $\text{dm}^{-3}$  aqueous  $\text{H}_2\text{SO}_4$  solution, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (30 g), with EtOAc–toluene (1:6) as eluent, to afford **21** (438 mg, 67%) as a colorless syrup:  $[\alpha]_D^{23} - 187$  (c 1.78,  $\text{CHCl}_3$ ); IR (neat) 1690, 1610, 1515 and 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 2.26–2.42 (m, 2 H), 3.39 and 3.81 (2s, each 3 H), 4.37 (m, 1 H), 4.39 (dd, 1 H,  $J$  = 5.1, 7.3 Hz), 4.56 and 4.62 (2d, each 1 H,  $J$  = 11.4 Hz), 4.71 and 4.79 (2d, each 1 H,  $J$  = 7.0 Hz), 5.97 (d, 1 H,  $J$  = 10.6 Hz), 6.90 (d, 2 H,  $J$  = 8.8 Hz), 6.87–6.93 (m, 1 H), 7.29 (d, 2 H,  $J$  = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 35.3, 55.3, 55.7, 70.1, 71.3, 73.7, 95.9, 113.9, 128.4, 129.4, 129.8, 147.9, 159.5, 196.8. MS  $m/z$  293 ( $\text{M}^+ + \text{H}$ , 11%), 292 (58), 261 (7), 230 (13), 202 (11), 166 (100). Found: C, 65.52; H, 7.12%. Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_5$ : C, 65.74; H, 6.90%.

**(4S,6R)-4-[(4-Methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-2-cyclohexene-1-one (22).** To a solution of compound **21** (1.24 g, 4.24 mmol) in toluene (25 ml) at room temperature was added DBU (0.190 ml, 1.27 mmol). After being stirred at room temperature for 24 h, the mixture was diluted with EtOAc and washed with 1 mol  $\text{dm}^{-3}$  aqueous HCl solution, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (150 g), with EtOAc–toluene (1:15) as eluent, to afford first, compounds **21** (620 mg, 50%). Further elution gave **22** (522 mg, 42%) as a colorless syrup. Compound **21** (620 mg) was subjected to the same reaction conditions to give **21** (284 mg, 23%) and **22** (242 mg, 20%). **22**:  $[\alpha]_D^{24} + 15$  (c 1.04,  $\text{CHCl}_3$ ); IR (neat) 1695, 1610, 1515 and

1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 2.07 (ddd, 1 H,  $J$  = 10.3, 11.7, 13.6 Hz), 2.71 (dddd, 1 H,  $J$  = 2.2, 4.8, 4.8, 11.7 Hz), 3.44 and 3.82 (2s, each 3 H), 4.14 (dd, 1 H,  $J$  = 4.8, 13.6 Hz), 4.37–4.43 (m, 1 H), 4.59 and 4.63 (2d, each 1 H,  $J$  = 11.6 Hz), 4.79 and 4.87 (2d, each 1 H,  $J$  = 6.8 Hz), 6.03 (dd, 1 H,  $J$  = 2.2, 10.4 Hz), 6.91 (d, 2 H,  $J$  = 8.8 Hz), 6.90–6.96 (m, 1 H), 7.29 (d, 2 H,  $J$  = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 37.4, 55.3, 55.8, 70.7, 72.7, 74.3, 96.0, 114.0, 128.0, 128.6, 129.4, 150.9, 159.5, 197.1. Found: C, 65.51; H, 7.12%. Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_5$ : C, 65.74; H, 6.90%.

**(3*S*,4*R*,6*S*)-3-Hydroxy-6-[(4-methoxybenzyl)oxy]-4-[(methoxymethyl)oxy]-cyclohexene (23) and its (3*R*,4*R*,6*S*)-isomer (24).** To a mixture of compound 22 (227 mg, 0.777 mmol) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (434 mg, 1.16 mmol) in methanol (8 ml) at  $-78^\circ\text{C}$  was added  $\text{NaBH}_4$  (30.9 mg, 0.817 mmol). After being stirred at  $-78^\circ\text{C}$  for 20 min, the mixture was diluted with water and the product was extracted four times with EtOAc. The combined organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (15 g), with EtOAc-toluene (1:8) as eluent, to afford first, compound 23 (196 mg, 86%) as a colorless syrup:  $[\alpha]_{\text{D}}^{24} - 110$  (c 0.75,  $\text{CHCl}_3$ ); IR (neat) 3440, 1615, 1505 and 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.69 (ddd, 1 H,  $J$  = 9.9, 12.5, 12.5 Hz), 2.39 (ddd, 1 H,  $J$  = 3.7, 5.1, 12.5 Hz), 3.40 (ddd, 1 H,  $J$  = 3.7, 7.3, 12.5 Hz), 3.46 and 3.80 (2s, each 3 H), 4.13–4.23 (m, 2 H), 4.48 and 4.54 (2d, each 1 H,  $J$  = 10.8 Hz), 4.74 and 4.75 (2d, each 1 H), 5.68 and 5.82 (2bd, each 1 H,  $J$  = 10.3 Hz), 6.88 and 7.27 (2d, each 2 H,  $J$  = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 34.8, 55.3, 55.7, 69.9, 71.8, 73.4, 82.1, 97.1, 113.8, 129.3, 129.7, 129.8, 130.3, 159.2. Found: C, 65.29; H, 7.83%. Calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_5$ : C, 65.29; H, 7.53%. Further elution gave compound 24 (14.6 mg, 6%) as a colorless syrup:  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.74 (bs, 1 H), 1.97 (ddd, 1 H,  $J$  = 9.2, 11.9, 11.9 Hz), 2.08–2.18 (m, 1 H), 3.42 (s, 3 H), 3.66 (ddd, 1 H,  $J$  = 3.6, 3.6, 11.9 Hz), 3.80 (s, 3 H), 4.00–4.08 (m, 1 H), 4.20 (dd, 1 H,  $J$  = 3.6, 4.2 Hz), 4.50 and 4.56 (2d, each 1 H,  $J$  = 11.7 Hz), 4.73 and 4.78 (2d, each 1 H,  $J$  = 7.0 Hz), 5.89 (ddd, 1 H,  $J$  = 1.5, 4.4, 9.9 Hz), 5.98 (bd, 1 H,  $J$  = 9.9 Hz), 6.88 and 7.27 (2d, each 2 H,  $J$  = 8.8 Hz). HRMS Calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_5$ : ( $\text{M}^+$ ), 294.1467. Found:  $m/z$  294.1469.

**(1*R*,2*R*,4*R*)-1-Acetoxy-4-hydroxy-2-[(methoxymethyl)oxy]-cyclohexane (25).** A solution of compound 23 (83 mg, 0.28 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in pyridine (1 ml) and acetic anhydride (0.5 ml) was stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc and washed successively with 1 mol  $\text{dm}^{-3}$  aqueous HCl solution, saturated aqueous  $\text{NaHCO}_3$  solution and brine, and dried. Removal of the solvent left a crude acetate (96 mg) as a syrup, which was dissolved in ethanol (2 ml). To this solution was added 10% Pd on carbon (50 mg), and the mixture was stirred under 1 atm of  $\text{H}_2$  at room temperature for 15 h. The catalyst was removed by filtration, and filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (2 g), with EtOAc-toluene (1:3) as eluent, to afford compound 25 (55 mg, 89%) as a colorless syrup:  $[\alpha]_{\text{D}}^{20} - 33$  (c 1.0,  $\text{CHCl}_3$ ); IR (neat) 3440 and 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz)  $\delta$  = 1.29–1.61 (m, 3 H), 1.82–1.92 (m, 1 H), 1.98–2.08 (m, 1 H), 2.03 (s, 3 H), 2.17–2.30 (m, 2 H), 3.35 (s, 3 H), 3.63 (ddd, 1 H,  $J$  = 4.4, 7.7, 9.3 Hz), 3.70–3.80 (m, 1 H), 4.64 (s, 2 H), 4.76 (ddd, 1 H,  $J$  = 4.0, 7.7, 9.2 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 21.3, 24.6, 31.3, 37.9, 55.5, 67.6, 73.6, 74.6, 95.7, 170.5; MS  $m/z$  219 ( $\text{M}^+ + \text{H}$ , 2%), 201 (1), 187 (29), 173 (31), 158 (100). HRMS Calcd for  $\text{C}_{10}\text{H}_{19}\text{O}_5$ : ( $\text{M}^+ + \text{H}$ ), 219.1232. Found:  $m/z$  219.1232.

**(3*S*,4*S*,6*R*)-3-[(*N,N*-Dimethylaminocarbonyl)methyl]-4-[(4-methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-cyclohexene (26).** A suspension of 23 (391 mg, 1.33 mmol), molecular sieves powder (3A, 4.0 g), and *N,N*-dimethylacetamide dimethyl acetal (1.94 ml, 13.3 mmol) in *o*-xylene (8 ml) under Ar was stirred at  $140^\circ\text{C}$  for 24 h. After cooling, the mixture was filtered to remove the molecular sieves and the filtrate was concentrated to give a syrup, which was chromatographed on a column of silica gel (20 g), with acetone-toluene (1:4) as eluent, to afford compound 26 (429 mg, 89%) as a colorless syrup:  $[\alpha]_{\text{D}}^{25} + 41$  (c 1.2,  $\text{CHCl}_3$ ); IR (neat) 1645, 1510, 1245 and 1030  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.63 (ddd, 1 H,  $J$  = 10.3, 11.7, 11.7 Hz), 2.03 (dd, 1 H,  $J$  = 10.8, 16.1 Hz), 2.52–2.61 (m, 1 H), 2.64–2.78 (m, 1 H), 2.72 (dd, 1 H,  $J$  = 3.9, 16.1 Hz), 2.90 and 2.93 (2s, each 3 H), 3.34 (ddd, 1 H,  $J$  = 2.9, 8.8, 11.7 Hz), 3.39 and 3.80 (2s, each 3 H), 4.23–4.33 (m, 1 H), 4.33 and 4.64 (2d, each 1 H,  $J$  = 11.4 Hz), 4.71 and 4.75 (2d, each 1 H,  $J$  = 7.0 Hz), 5.62–5.74 (m, 2 H), 6.87 and 7.26 (2d, each 2 H,  $J$  = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 32.3, 34.9, 35.7, 38.1, 39.0, 41.7, 55.3, 56.1, 70.5, 70.7, 74.3, 75.6, 95.0, 113.8, 129.3, 130.4, 159.2, 173.3. Found: C, 65.82; H, 8.35; N, 3.84%. Calcd for  $\text{C}_{20}\text{H}_{29}\text{O}_5\text{N}$ : C, 66.09; H, 8.04; N, 3.85%.

**(3aR,4S,6R,7S,7aR)-7-Iodo-4-[(methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (27).** A solution of compound **26** (118 mg, 0.324 mmol) and iodine (434 mg, 1.16 mmol) in THF (1.2 ml) and H<sub>2</sub>O (1.2 ml) was stirred at 0 °C for 6 h. The mixture was diluted with 20% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, and the products were extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (4 g), with EtOAc-toluene (1:8) as eluent, to afford **27** (141 mg, 94%) as a colorless syrup:  $[\alpha]_D^{21} + 62$  (c 0.3, CHCl<sub>3</sub>); IR (neat) 1780, 1610, 1515 and 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.86 (ddd, 1 H, J = 11.7, 11.7, 11.7 Hz), 2.23 (dddd, 1 H, J = 1.0, 3.3, 4.4, 11.7 Hz), 2.57–2.64 (m, 2 H), 2.72–2.80 (m, 1 H), 2.95 (ddd, 1 H, J = 3.3, 3.3, 11.7 Hz), 3.26 (ddd, 1 H, J = 4.4, 9.9, 11.7 Hz), 3.43 and 3.81 (2s, each 3 H), 4.33 and 4.62 (2d, each 1 H, J = 10.8 Hz), 4.69 and 4.74 (2d, each 1 H, J = 7.0 Hz), 4.86–4.88 (m, 1 H), 4.91 (dd, 1 H, J = 4.8, 4.8 Hz), 6.89 and 7.24 (2d, each 2 H, J = 8.8 Hz); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 33.1, 33.7, 36.1, 38.7, 55.3, 56.4, 70.6, 71.1, 76.1, 84.4, 95.3, 114.1, 129.4, 129.5, 159.6, 175.3. MS *m/z* 463 (M<sup>+</sup>+H, 7%), 462 (33), 430 (6), 417 (100). Found: C, 47.16; H, 5.32%. Calcd for C<sub>18</sub>H<sub>23</sub>O<sub>6</sub>I: C, 46.77; H, 5.01%.

**(3aR,4S,6R,7aS)-4-[(4-Methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (28).** A mixture of compound **27** (418 mg, 0.904 mmol), azobisisobutyronitrile (74.3 mg, 0.452 mmol), and tributyltin hydride (0.292 ml, 1.09 mmol) in toluene (8.5 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (20 g), with EtOAc-toluene (1:4) as eluent, to afford **28** (302 mg, 99%) as a colorless syrup:  $[\alpha]_D^{22} + 32$  (c 0.8, CHCl<sub>3</sub>); IR (neat) 1770, 1610, 1515 and 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.31 (ddd, 1 H, J = 11.7, 11.7, 11.7 Hz), 1.61 (ddd, 1 H, J = 4.0, 11.4, 15.0 Hz), 2.27 (ddd, 1 H, J = 5.1, 6.4, 9.9 Hz), 2.50–2.60 (m, 3 H), 2.66 (dd, 1 H, J = 6.4, 17.2 Hz), 3.21 (ddd, 1 H, J = 3.9, 9.9, 11.7 Hz), 3.38 (s, 3 H), 3.69–3.83 (m, 1 H), 3.80 (s, 3 H), 4.33 and 4.62 (2d, each 1 H, J = 10.8 Hz), 4.64–4.73 (m, 1 H), 4.66 and 4.71 (2d, each 1 H, J = 7.0 Hz), 6.88 and 7.23 (2d, each 2 H, J = 8.8 Hz); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 34.1, 35.68, 35.71, 41.8, 55.3, 55.4, 69.7, 71.0, 75.9, 95.1, 114.0, 129.5, 129.7, 159.5, 176.2. Found: C, 64.00; H, 7.37%. Calcd for C<sub>18</sub>H<sub>24</sub>O<sub>6</sub>: C, 64.27; H, 7.19%.

**(3S,3aR,4S,6R,7aS)-4-[(4-Methoxybenzyl)oxy]-6-[(methoxymethyl)oxy]-3-(4-methyl-3-pentenyl)-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (29).** To a solution of compound **28** (13.1 g, 38.9 mmol) in THF (250 ml) under Ar at –20 °C was added 1.0 mol dm<sup>-3</sup> solution of lithium bis(trimethylsilyl)amide in THF (40.9 ml, 40.9 mmol), and the mixture was stirred at –20 °C for 15 min. To the reaction mixture was added 5-iodo-2-methyl-2-pentene (18.0 g, 85.5 mmol) at –20 °C. The reaction mixture was stirred at –20 °C for 30 min, and then at 5 °C for 2 h. The mixture was diluted with saturated aqueous NH<sub>4</sub>Cl solution and the product was extracted with EtOAc. The organic layer was dried and concentrated to give a residue, which was chromatographed on a column of silica gel (300 g), with EtOAc-toluene (1:15) as eluent, to afford **29** (11.5 g, 71%) as a colorless syrup:  $[\alpha]_D^{25} - 12$  (c 1.5, CHCl<sub>3</sub>); IR (neat) 1770, 1610, 1515 and 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.31 (ddd, 1 H, J = 11.4, 11.7, 11.7 Hz, 1 H), 1.54–1.76 (m, 3 H), 1.59 and 1.68 (2s, each 3 H), 2.03 (dd, 1 H, J = 4.7, 9.5 Hz), 2.12 (td, 2 H, J = 7.3, 7.3 Hz), 2.48–2.58 (m, 3 H), 3.20 (ddd, 1 H, J = 3.9, 9.5, 11.0 Hz), 3.37 (s, 3 H), 3.74 (dddd, 1 H, J = 4.0, 4.0, 11.0, 11.0 Hz), 3.82 (s, 3 H), 4.33 and 4.61 (2d, each 1 H, J = 11.0 Hz), 4.66 and 4.70 (2d, each 1 H, J = 7.0 Hz), 4.77 (ddd, 1 H, J = 2.6, 4.4, 4.7 Hz), 5.09 (bt, 1 H, J = 7.2 Hz), 6.88 and 7.23 (2d, each 2 H, J = 8.8 Hz); <sup>13</sup>C NMR (75 MHz in CDCl<sub>3</sub>)  $\delta$  = 17.7, 25.7, 25.9, 29.1, 34.1, 35.7, 46.5, 46.9, 55.3, 55.4, 69.6, 70.9, 76.0, 77.3, 95.1, 113.9, 122.7, 129.3, 129.9, 133.1, 159.4, 178.8. Found: C, 69.23; H, 8.46%. Calcd for C<sub>24</sub>H<sub>34</sub>O<sub>6</sub>: C, 68.87; H, 8.19%.

**(3S,3aR,4S,6R,7aS)-6-Hydroxy-4-[(4-methoxybenzyl)oxy]-3-(4-methyl-3-pentenyl)-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (30).** To a solution of compound **29** (11.5 g, 27.5 mmol) in MeOH (472 ml) at 0 °C was added acetyl chloride (0.728 ml, 10.2 mmol). After being stirred at 0 °C for 4 days, to the reaction mixture was neutralized with triethylamine. The mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (300 g), with acetone-hexanes (1:3) as eluent, to afford **30** (9.58 g, 93%) as a colorless syrup:  $[\alpha]_D^{25} + 25$  (c 1.0, CHCl<sub>3</sub>); IR (neat) 3400, 1770, 1610, 1510 and 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz)  $\delta$  = 1.50–1.89 (m, 4 H), 1.60 and 1.69 (2s, each 3 H), 2.06–2.26 (m, 6 H), 2.47 (ddd, 1 H, J = 4.3, 6.8, 7.6 Hz), 3.42 (ddd, 1 H, J = 3.8, 7.6, 8.9 Hz), 3.81 (s, 3 H), 3.94 (m, 1 H), 4.39 and 4.59 (2d, each 1 H, J = 11.4 Hz), 4.80 (ddd, 1 H, J = 4.7, 5.1, 5.1 Hz), 5.07 (bt, 1

H, J = 7.3 Hz), 6.88 and 7.23 (2d, each 2 H, J = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 17.7, 25.6, 25.7, 29.1, 35.7, 36.2, 44.8, 45.7, 55.3, 64.8, 70.9, 75.6, 76.2, 114.0, 122.7, 129.4, 129.5, 133.2, 159.5, 178.6. Found: C, 70.18; H, 8.38%. Calcd for  $\text{C}_{22}\text{H}_{30}\text{O}_5$ : C, 70.56; H, 8.08%.

**(3S,3aR,4S,6R,7aS)-6-[(Methanesulfonyl)oxy]-4-[(4-methoxybenzyl)oxy]-3-(4-methyl-3-pentenyl)-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (31).** To a solution of compound **30** (55.4 mg, 0.148 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) at 0 °C were added triethylamine (0.165 ml, 1.18 mmol) and methanesulfonyl chloride (0.0458 ml, 0.592 mmol). After being stirred at 0 °C for 30 min the reaction mixture was diluted with  $\text{CHCl}_3$ , and washed successively with 1 mol  $\text{dm}^{-3}$  aqueous HCl solution, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-toluene (1:5) as eluent, to afford **31** (67.0 mg, 100%) as a colorless syrup:  $[\alpha]_{\text{D}}^{26} - 2$  (c 0.6,  $\text{CHCl}_3$ ); IR (neat) 1770, 1610, 1510 and 1255  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.53–1.78 (m, 3 H), 1.59 and 1.68 (2s, each 3 H), 1.87 (ddd, 1 H, J = 4.2, 11.0, 15.1 Hz), 2.04–2.20 (m, 3 H), 2.53 (dd, 1 H, J = 6.8, 8.8 Hz), 2.63 (m, 2 H), 3.03 (s, 3 H), 3.26 (ddd, 1 H, J = 3.9, 9.5, 11.2 Hz), 3.81 (s, 3 H), 4.34 and 4.61 (2d, each 1 H, J = 11.0 Hz), 4.71–4.81 (m, 2 H), 5.09 (bt, 1 H, J = 5.6 Hz), 6.88 and 7.22 (2d, each 2 H, J = 8.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 18.0, 25.9, 26.0, 29.3, 33.9, 35.9, 38.8, 46.3, 46.6, 55.5, 71.4, 74.4, 75.2, 76.3, 114.2, 122.7, 129.6, 129.7, 133.6, 159.8, 178.2. MS  $m/z$  453 ( $\text{M}^+$ +H, 21%), 452 (74), 357 (9), 356 (21), 331 (30), 316 (23), 274 (42), 235 (100). HRMS Calcd for  $\text{C}_{23}\text{H}_{32}\text{O}_7\text{S}$ : ( $\text{M}^+$ ), 452.1868. Found:  $m/z$  452.4873. Found: C, 60.94; H, 7.43%. Calcd for  $\text{C}_{23}\text{H}_{32}\text{O}_7\text{S}$ : C, 61.04; H, 7.13%.

**(3S,3aR,4S,6R,7aS)-4-Hydroxy-6-[(methanesulfonyl)oxy]-3-(4-methyl-3-pentenyl)-3a,4,5,6,7,7a-hexahydrobenzo[b]furan-2(3H)-one (32).** A mixture of compound **31** (9.58 g, 21.2 mmol), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (14.1 g, 62.1 mmol) in  $\text{H}_2\text{O}$  (10 ml) and  $\text{CH}_2\text{Cl}_2$  (200 ml) was stirred at room temperature for 2 h. The mixture was diluted with saturated aqueous  $\text{NaHCO}_3$  solution and the product was extracted with  $\text{CHCl}_3$ . The organic layer was washed with brine, and dried. Removal of the solvent gave a residue, which was chromatographed on a column of silica gel (300 g), with EtOAc-toluene (1:15) as eluent, to afford **32** (4.40 g, 63%) as a colorless syrup:  $[\alpha]_{\text{D}}^{24} - 34$  (c 1.2,  $\text{CHCl}_3$ ); IR (neat) 3500 and 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.56–1.80 (m, 3 H), 1.62 (s, 3 H), 1.70 (s, 3 H), 1.88 (ddd, 1 H, J = 4.4, 11.0, 14.9 Hz), 2.02 (dd, 1 H, J = 4.9, 8.3 Hz), 2.16 (m, 2 H), 2.41–2.48 (m, 2 H), 2.57–2.66 (m, 1 H), 2.69 (t, 1 H, J = 7.6 Hz), 3.05 (s, 3 H), 3.53–3.64 (m, 1 H), 4.75–4.85 (m, 2 H), 5.10 (bt, 1 H, J = 7.1 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 17.8, 25.7, 25.9, 29.0, 33.5, 38.5, 39.6, 46.3, 47.5, 68.3, 74.3, 76.4, 122.5, 133.4, 178.3. Found: C, 54.10; H, 7.67%. Calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_6\text{S}$ : C, 54.20; H, 7.28%.

**(3S,3aR,7aS)-3-(4-Methyl-3-pentenyl)-3a,7,7a-trihydrobenzo[b]furan-2(3H)-dione (33).** A suspension of compound **32** (89.6 mg, 0.270 mmol), pyridinium chlorochromate (98.2 mg, 0.456 mmol) and molecular sieves powder (4A, 0.3 g) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was stirred for at 0 °C 4.5 h, and then at room temperature for 5 h. The mixture was diluted with  $\text{Et}_2\text{O}$  and filtered through a pad of silica gel. The filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (4 g), with EtOAc-toluene (1:4) as eluent, to afford **33** (63.1 mg, 100%) as a colorless syrup:  $[\alpha]_{\text{D}}^{24} + 17$  (c 1.6,  $\text{CHCl}_3$ ); IR (neat) 1770 and 1675  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.53–1.83 (m, 2 H), 1.56, 1.63 (2s, each 3 H), 2.09–2.18 (m, 2 H), 2.72–2.76 (m, 2 H), 2.82–2.89 (m, 2 H), 4.96–5.07 (m, 2 H), 6.11 (ddd, 1 H, J = 1.9, 1.9, 10.3 Hz), 6.82 (ddd, 1 H, J = 3.7, 3.7, 10.3 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 17.7, 25.3, 25.7, 27.7, 29.5, 43.7, 49.8, 74.7, 122.4, 129.3, 133.4, 145.2, 176.9, 195.0. Found: C, 71.55; H, 8.02%. Calcd for  $\text{C}_{14}\text{H}_{18}\text{O}_3$ : C, 71.80; H, 7.75%.

**(3S,3aS,7aS)-6-Methyl-3-(4-methyl-3-pentenyl)-3a,7,7a-trihydrobenzo[b]furan-2,4-dione (34).** To a suspension of  $\text{CuI}$  (76.1 mg, 0.40 mmol) in diethyl ether (0.5 ml) under Ar at 0 °C was added methylolithium in diethyl ether (1.06 mol  $\text{dm}^{-3}$  solution, 0.75 ml, 0.80 mmol), and the mixture was stirred at 0 °C for 10 min. To this solution at 0 °C was added a solution of compound **33** (31.2 mg, 0.133 mmol) in diethyl ether (1 ml) and the mixture was stirred at 0 °C for 20 min. A mixture of trimethylsilyl chloride (0.17 ml) and triethylamine (0.17 ml) was added to the reaction mixture at 0 °C, and the resultant mixture was further stirred at 0 °C for 1.5 h. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  solution, and the products were extracted with EtOAc. The organic layer was washed with brine, and then dried over  $\text{Na}_2\text{CO}_3$ . Removal of the solvent gave a crude silyl enol ether, which was used in the next reaction without isolation. A mixture of the crude silyl enol ether and  $\text{Pd}(\text{OAc})_2$  (44.8 mg, 0.200 mmol) in acetonitrile (0.8 ml) under Ar was stirred at

room temperature for 16 h. The mixture was diluted with EtOAc and the insoluble material was removed by filtration through Celite, and the filtrate was washed with 20% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-toluene (1:10) as eluent, to afford compound **34** (22.1 mg, 67%) as crystalline residue: M.p. 67.5–68.5 °C;  $[\alpha]_{\text{D}}^{24} - 14$  (c 0.96,  $\text{CHCl}_3$ ); IR (KBr) 1770 and 1670  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta = 1.63, 1.70$  (2s, each 3 H), 1.65–1.90 (m, 2 H), 2.03 (s, 3 H), 2.16–2.25 (m, 2 H), 2.73 (bd, 2 H,  $J = 4.9$  Hz), 2.82 (dd, 1 H,  $J = 4.4, 6.1$  Hz), 2.92 (ddd, 1 H,  $J = 4.4, 6.6, 7.8$  Hz), 5.04 (ddd, 1 H,  $J = 4.9, 4.9, 6.1$  Hz), 5.11 (bt, 1 H,  $J = 7.1$  Hz), 6.04 (bs, 1 H);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta = 17.8, 24.5, 25.5, 25.7, 29.8, 32.7, 44.2, 48.6, 75.0, 122.5, 126.1, 133.4, 157.5, 177.1, 195.0$ . Found: C, 72.40; H, 8.19%. Calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_3$ : C, 72.55; H, 8.12%.

**(3S,3aS,4S,7aS)-4-Hydroxy-6-methyl-3-(4-methyl-3-pentenyl)-3a,4,7,7a-**

**tetrahydrobenzo[*b*]furan-4(3*H*)-one (35).** To a solution of compound **34** (9.2 mg, 0.037 mmol) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (13.8 mg, 0.037 mmol) in methanol (0.5 ml) at 0 °C was slowly added  $\text{NaBH}_4$  (7.3 mg, 0.19 mmol). After being stirred at 0 °C for 30 min, the reaction mixture was diluted with water and the product was extracted with EtOAc. The organic layer was dried and then concentrated to give a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-toluene (1:20) as eluent, to afford **35** (6.4 mg, 64%) as a colorless syrup:  $[\alpha]_{\text{D}}^{20} - 50$  (c 0.4,  $\text{CHCl}_3$ ); IR (neat) 3450 and 1750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta = 1.62, 1.70$  (2s, each 3 H), 1.65–1.87 (m, 3 H), 1.77 (s, 3 H), 2.11–2.20 (m, 2 H), 2.26 (dd, 1 H,  $J = 7.8, 17.3$  Hz), 2.45 (dd, 1 H,  $J = 2.9, 17.3$  Hz), 2.55 (ddd, 1 H,  $J = 4.4, 5.9, 7.8$  Hz), 2.80 (ddd, 1 H,  $J = 4.4, 6.1, 7.6$  Hz), 4.28 (bs, 1 H), 4.84 (ddd, 1 H,  $J = 2.9, 5.9, 7.8$  Hz), 5.12 (bt, 1 H,  $J = 7.1$  Hz), 5.67 (bs, 1 H);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta = 17.8, 23.1, 25.4, 25.7, 31.3, 33.1, 41.5, 44.2, 66.1, 75.8, 123.2, 125.1, 132.9, 135.6, 179.5$ . MS  $m/z$  251 ( $\text{M}^+ + \text{H}$ , 10%), 250 (32), 232 (96), 217 (46), 204 (18), 187 (89), 131 (100). HRMS Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_3$ : ( $\text{M}^+$ ), 250.1569. Found:  $m/z$  250.1569. Found: C, 71.70; H, 9.16%. Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_3$ : C, 71.97; H, 8.86%.

**(1aR,2aS,5S,5aS,6S,6aS)-2,2a,5,5a,6,6a-Hexahydro-6-hydroxy-1a-methyl-5-(4-methyl-3-pentenyl)-oxireno[*f*]benzofuran-4(1a*H*)-one (36).** To a solution of compound **35** (13.8 mg, 0.055 mmol) and  $\text{VO}(\text{acac})_2$  (0.3 mg, 0.001 mmol) in toluene (0.5 ml) at –20 °C under Ar was added *t*-BuOOH in decane (5–6 mol  $\text{dm}^{-3}$  solution, 0.030 ml, 0.15–0.18 mmol). After being stirred at –20 °C for 27 h, the reaction mixture was quenched by addition of excess  $\text{Me}_2\text{S}$ . The mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-toluene (1:20 → 1:2) as eluent, to afford first, compound **34** (2.1 mg, 15%). Further elution gave **36** (10.5 mg, 78%) as crystalline residue: M.p. 153–155 °C;  $[\alpha]_{\text{D}}^{26} - 47$  (c 0.9,  $\text{CHCl}_3$ ); IR (KBr) 3404 and 1758  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta = 1.35$  (s, 3 H), 1.56–1.80 (m, 2 H), 1.61, 1.68 (2s, each 3 H), 1.96 (dd, 1 H,  $J = 5.1, 16.1$  Hz), 2.07–2.15 (m, 2 H), 2.29 (dd, 1 H,  $J = 1.7, 16.1$  Hz), 2.60 (bs, 1 H), 2.70 (ddd, 1 H,  $J = 5.6, 6.8, 10.3$  Hz), 3.02 (ddd, 1 H,  $J = 5.6, 5.6, 7.1$  Hz), 3.14 (s, 1 H), 4.31 (d, 1 H,  $J = 6.8$  Hz), 4.65 (ddd, 1 H,  $J = 1.7, 5.1, 10.3$  Hz), 5.10 (bt, 1 H,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta = 17.7, 21.9, 24.8, 25.6, 31.8, 33.6, 42.0, 42.1, 57.0, 61.8, 67.1, 73.7, 123.3, 132.7, 179.4$ . MS  $m/z$  267 ( $\text{M}^+ + \text{H}$ , 14%), 266 (55), 248 (5), 230 (5), 215 (7), 184 (100). HRMS Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_3$ : ( $\text{M}^+$ ), 266.1519. Found:  $m/z$  266.1518. Found: C, 67.38; H, 8.61%. Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_4$ : C, 67.64; H, 8.33%.

**Preparation of 2 from 36.** To a solution of compound **36** (17.8 mg, 0.067 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml) under Ar at room temperature were added 2,6-lutidine (61  $\mu\text{l}$ , 0.53 mmol) and triethylsilyl trifluoromethanesulfonate (60  $\mu\text{l}$ , 0.525 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with  $\text{CHCl}_3$  and washed with saturated aqueous  $\text{NaHCO}_3$  solution, and brine, and then dried. Removal of the solvent left a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-toluene (1:20) as eluent, to afford compound **2** (24.1 mg, 95%) as a colorless syrup, whose physical and spectral data were identical with those of the sample prepared from compound **3** (vide supra).

**(1aR,2aS,5S,5aS,6S,6aS)-2,2a,5,5a,6,6a-Hexahydro-1a-methyl-5-(4-methyl-3-pentenyl)-5-phenylseleno-6-[(triethylsilyloxy)oxireno[*f*]benzofuran-4(1a*H*)-one (37).** To a solution of potassium bis(trimethylsilyl)amide (0.238 ml, 0.5 mol  $\text{dm}^{-3}$  solution in THF, 0.119 mmol) in THF (0.2 ml) under Ar at 0 °C was added dropwise a solution of compound **2** (15.1 mg, 0.0397 mmol) in THF (0.3 ml) and the mixture was stirred at 0 °C for 5 min and then cooled to –78 °C. To the reaction mixture at –78 °C was added dropwise a solution of diphenyl diselenide (61.9 mg, 0.198 mmol) and HMPA (0.030 ml) in THF (0.15

ml) via cannula. The mixture was stirred at  $-78^{\circ}\text{C}$  for 30 min and then oxygen was bubbled into the mixture at  $-78^{\circ}\text{C}$  for 1 h. The reaction was quenched with a buffer solution (pH = 7, prepared from 0.2 mol  $\text{dm}^{-3}$  aqueous  $\text{NaH}_2\text{PO}_4$  solution and 0.2 mol  $\text{dm}^{-3}$  aqueous  $\text{NaOH}$  solution), and products were extracted twice with EtOAc. The combined organic layer was washed with brine, and then dried. Removal of solvent gave a residue, which was chromatographed on a column of silica gel (2 g), with EtOAc-hexanes (1:9) as eluent, to afford **37** (12.4 mg, 58 %) as a colorless syrup:  $[\alpha]_{\text{D}}^{24} - 24$  (c 0.62,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $1755\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 0.62 (q,  $J$  = 8.0 Hz, 6 H), 0.94 (t,  $J$  = 8.0 Hz, 9 H), 1.36 (s, 3 H), 1.67, 1.70 (2s, each 3 H), 1.90–2.08 (m, 3 H), 2.11–2.30 (m, 2 H), 2.44 (dd,  $J$  = 3.2, 7.5 Hz, 1 H), 2.63–2.77 (m, 1 H), 2.97 (d,  $J$  = 3.2 Hz, 1 H), 4.40 (dd,  $J$  = 3.2, 3.2 Hz, 1 H), 4.99 (ddd,  $J$  = 7.5, 7.5, 14.6 Hz, 1 H), 5.11 (dd,  $J$  = 6.6, 6.6 Hz, 1 H), 7.26–7.44 (m, 3 H), 7.61–7.66 (m, 2 H);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 4.8, 6.8, 17.9, 22.4, 25.1, 25.7, 30.9, 32.8, 48.6, 54.2, 54.8, 59.7, 66.4, 72.6, 123.7, 126.1, 129.0, 129.8, 132.0, 137.8, 175.5. MS  $m/z$  536 ( $\text{M}^+$ , 8%), 379 (60), 351 (21), 281 (21), 185 (66), 115 (49), 87 (59), 69 (100). HRMS Calcd for  $\text{C}_{27}\text{H}_{40}\text{O}_4\text{SeSi}$ : ( $\text{M}^+$ ), 536.1861. Found:  $m/z$  536.1871.

(+)-**Paniculide A (1)**. To a solution of compound **37** (9.9 mg, 0.0185 mmol) and pyridine (6.7  $\mu\text{l}$ , 0.083 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) at  $0^{\circ}\text{C}$  was added  $\text{H}_2\text{O}_2$  (3.5  $\mu\text{l}$ , 35% solution in  $\text{H}_2\text{O}$ , 0.371 mmol). After being stirred at room temperature for 40 min, the reaction mixture was diluted with Et<sub>2</sub>O and washed with brine, and then dried. Removal of the solvent gave a residue, which was dissolved in a mixture of AcOH-THF- $\text{H}_2\text{O}$  (3:2:2, v/v/v, 1 ml), and the mixture was stirred at  $0^{\circ}\text{C}$  for 6 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc-hexanes (2:3) as eluent, to afford (+)-paniculide **A 1** (4.6 mg, 94 %) as a crystalline residue: M.p.  $116\text{--}117^{\circ}\text{C}$  [lit.  $120\text{--}121^{\circ}\text{C}$ ,<sup>5a</sup>  $118.8\text{--}121.1^{\circ}\text{C}$ ];  $[\alpha]_{\text{D}}^{20} + 14.5$  (c 0.17, MeOH), [lit.<sup>11</sup>  $+14.98$  (c 0.747, MeOH)]; IR (KBr) 3440 and  $1750\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (270 MHz)  $\delta$  = 1.45, 1.57, and 1.77 (3s, each 3 H), 1.85 (ddd, 1 H,  $J$  = 1.0, 10.3, 14.4 Hz), 2.16–2.27 (m, 2 H), 2.48–2.66 (m, 4 H), 3.26 (d, 1 H,  $J$  = 2.7 Hz), 4.71 (dd, 1 H,  $J$  = 10.3, 10.3 Hz), 4.94 (bd, 1 H,  $J$  = 11.2 Hz), 5.20 (bt, 1 H,  $J$  = 7.8 Hz);  $^{13}\text{C}$  NMR (75 MHz in  $\text{CDCl}_3$ )  $\delta$  = 17.9, 23.5, 23.6, 25.6, 26.0, 36.4, 58.5, 64.5, 68.4, 75.2, 122.8, 129.1, 135.5, 158.3, 173.4. MS  $m/z$  265 ( $\text{M}^+\text{+H}$ , 16%), 264 (44), 218 (12), 196 (73), 178 (100). HRMS Calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4$ : ( $\text{M}^+$ ), 264.1361. Found:  $m/z$  264.1362. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were fully identical to those of the authentic sample reported in the literature.<sup>6,11</sup>

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