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LARGE-SCALE SYNTHESIS OF THE KEY INTERMEDIATES OF TETRAHYDROPYRAN DERIVATIVES UNDER FLOW CONDITIONS

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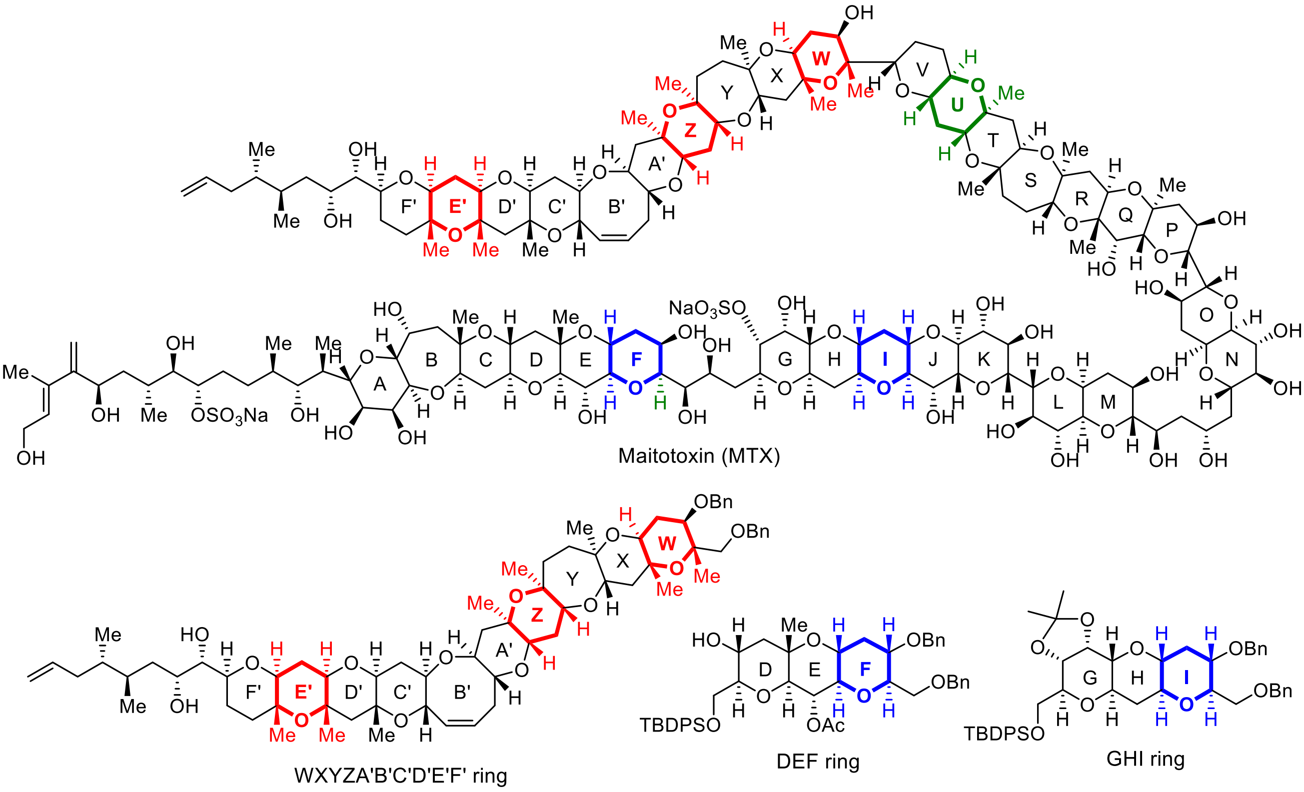
Abstract – An efficient method under continuous flow conditions was developed for successive methylation and DIBALH reduction of a ketoester giving a key intermediate for synthesizing a tetrahydropyran derivative. This method enabled large-scale synthesis of the intermediate at room temperature with safety quenching of the reaction mixture.

Maitotoxin (MTX) is a ladder-shaped polyether isolated from the dinoflagellate *Gambierdiscus toxicus* (Figure 1).[1] MTX is known to induce Ca^{2+} influx at extremely low concentration. Because of its potent biological activity and the complex molecular structure, numerous synthetic studies of MTX have been reported by the Nicolaou, Nakata, Jamison, and our groups.[2–5] As a part of our program on structure–activity relationship study of MTX based on chemical synthesis of partial structures, we reported synthesis of the WXYZA'B'C'D'E'F',[5i] DEF, and GHI rings.[5g]

Tetrahydropyran (THP) derivatives reported by the Nicolaou group[6] and other groups[7] are useful building block for synthesizing ladder-shaped polyethers (Figure 2). For the synthesis of the partial structures of MTX, the derivatives **1a** and **1c** were used as the starting materials for the W-, Z-, and E'-rings, and the F- and I-rings, respectively, while the derivative **1b** can be utilized as a precursor of the U-ring (Figure 1). In order to synthesize the WXYZA'B'C'D'E'F' ring whose molecular weight is 1140, supply of **1a** as the key building blocks in large quantity is important issue due to the multistep synthesis (longest linear sequence is 53 steps with 104 total steps).[5i] The THP derivative **1a**, as well as **1b** and **1c**, was synthesized from 2-deoxy-ᴅ-ribose **2** as outlined in Scheme 1.[6] Modification of the Nicolaou method for diastereoselective methylation of ketone **3** and subsequent reduction of the ester **4a** with DIBALH to one-pot procedure enabled direct synthesis of diol **5a** from **3**.[8] It is also modified that reduction of the ester with DIBALH was carried out without protection of the secondary alcohol of **4b** to furnish **5b**,[8] while protection of the secondary alcohol as TBS ether was required in the case of **4c**.

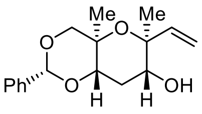

Maitotoxin (MTX)

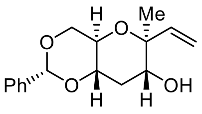
WXYZA'B'C'D'E'F' ring

DEF ring

GHI ring

Figure 1. Structure of maitotoxin (MTX) and synthesized partial structures


1a


1b

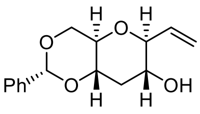
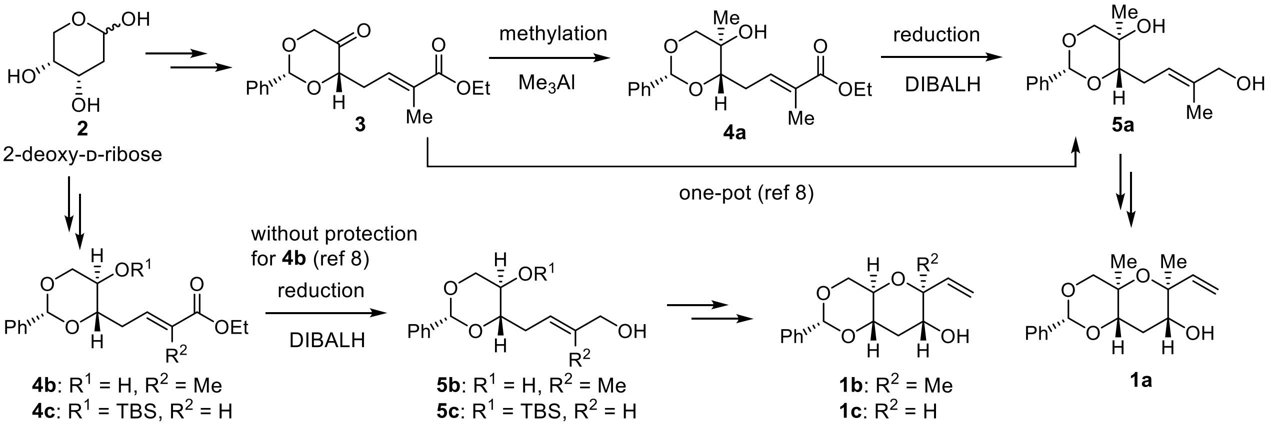

1c

Figure 2. THP derivatives **1a**, **1b**, and **1c**



Scheme 1. Synthetic outlines of THP derivatives **1a**, **1b**, and **1c** and modified steps

However, in the large-scale synthesis of **1a**, one-pot diastereoselective methylation and subsequent DIBALH reduction of the ketoester **3** was problematic. Because of the size limitation of the cooling bath in our laboratory, the maximum size of the available flask is 2 L volume (Figure 3). Therefore, the maximum amount of the substrate **3** is to be ca. 50 g (0.16 mol) considering the concentration of the substrate **3** (0.5 M in CH_2Cl_2, 300 mL) due to the low solubility at low temperature, and the amount of reagents Me_3Al (1.05 M in hexane, 240 mL) and DIBALH (1.0 M in toluene, 370 mL). The maximum total amount of the solution is ca. 1.0 L with keeping the room for safety quenching. In addition, there are drawbacks for large scale synthesis, 1) keeping the reaction solution at low temperature (−20 °C for methylation and −78 °C for reduction), and 2) risk of bumping when quenching.

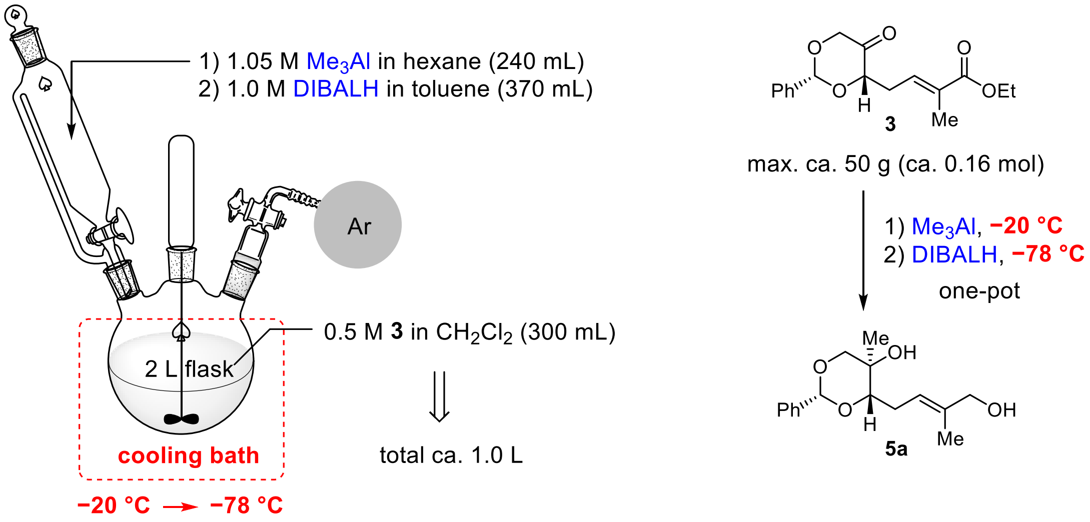
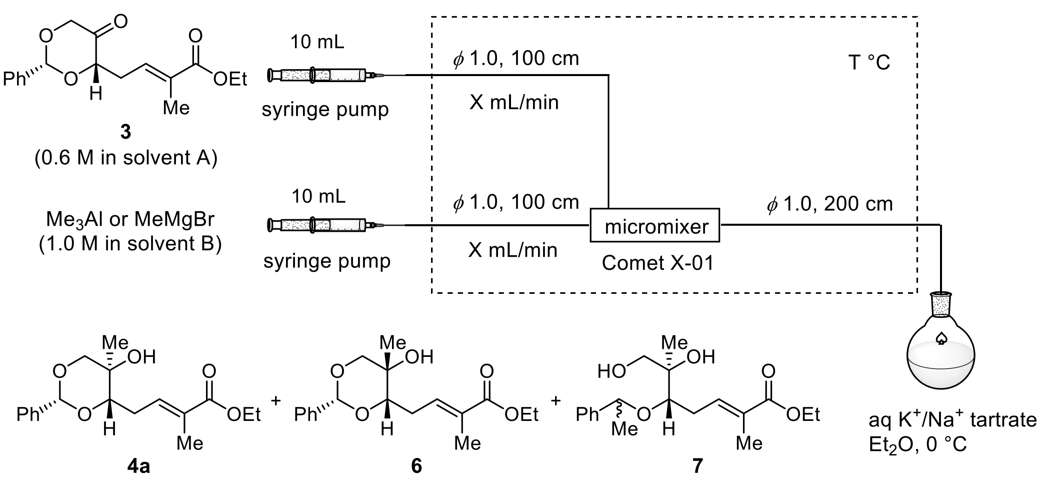


Figure 3. Reaction apparatus for one-pot synthesis of **5a** from **3** under batch conditions

In recent years, the problems have overcome by using microflow reactors.[9] The microflow chemistry is safer than conventional batch reactions due to small reaction volumes in the reactor and precise temperature control due to the efficient thermal diffusion. The greatest advantage is that it is easy to scale up under the identical reaction conditions, and it is possible to carry out reactions on a large scale of several hundred grams even in the laboratory. Actually, we succeeded in large-scale synthesis of sequential half reduction of an ester with DIBALH under microfluidic conditions followed by Grignard reaction of the resulting aldehyde under batch conditions.[10] Herein, we report an application of the microflow chemistry to the large-scale synthesis of the intermediates of THP derivatives.

First, we optimized reaction conditions for methylation of **3** under flow conditions (Scheme 2). A 0.6 M solution of **3** in solvent A and a 1.0 M solution of reagent (Me_3Al or MeMgBr) in solvent B were transferred to the micromixer Comet X-01[11] by using syringes (10 mL) and syringe pumps at a rate of X mL/min at T °C. After passing through the Teflon tube, the reaction mixture was poured into a mixture of saturated aqueous potassium sodium tartrate (Rochelle salt) and Et_2O at 0 °C for quenching.



Scheme 2. Methylation of ketone **3** under flow conditions

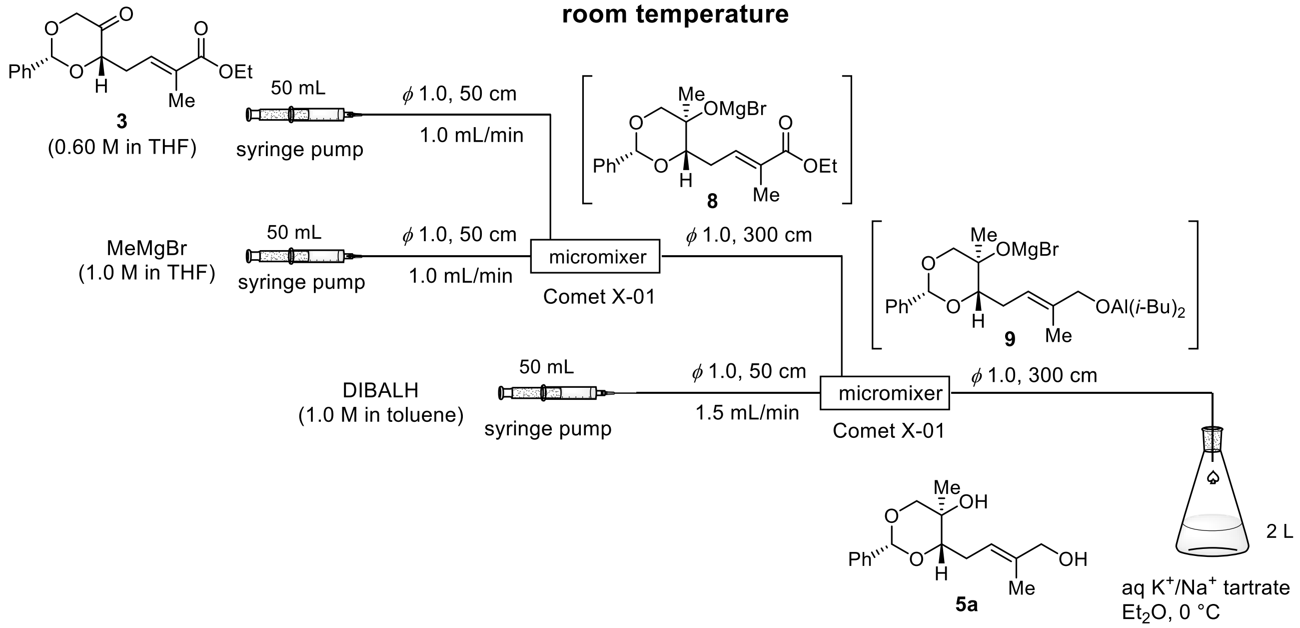
As shown in Table 1, mixing a solution of **3** in CH_2Cl_2 with a solution of Me_3Al in hexane at a rate of 5.0 mL/min at 0 °C resulted in the formation of **4a** with recovery of **3** in a 55% and 45% ratio as determined by 600 MHz ^{1}H NMR analysis (entry 1). Decreasing the flow rate to 2.5 mL/min did not increase the ratio of **4a** (entry 2). In order to increase the reaction rate, the temperature was raised from 0 °C to room temperature (entry 3). Although the ratio of **4a** was improved to 77%, its diastereomer **6** was obtained in 3% with concomitant formation of byproduct **7** in 6% and recovery of **3** (15%). Decreasing the flow rate to 1.0 mL/min increased the ratio of **4a** to 82% (entry 4), while the starting material **3** remained in 10% with **6** (3%) and **7** (6%). Then, the reagent was changed from Me_3Al to MeMgBr (entry 5). As a result, the ratio of **4a** was improved to 85% but the diastereomer **6** was obtained in 12% with recovery of **3** (3%), while no byproduct **7** was obtained. Therefore, conditions in entry 5 were used for the next transformation.

Table 1. Methylation of ketone **3** under flow conditions

entry	solvent A	reagent/solvent B	T (°C)	flow rate (mL/min)	ratio (%)[a]			
					4a	**6**	**7**	**3**
1	CH_2Cl_2	Me_3Al/hexane	0	5.0	55	0	0	45
2	CH_2Cl_2	Me_3Al/hexane	0	2.5	55	0	0	45
3	CH_2Cl_2	Me_3Al/hexane	rt	2.5	77	3	6	15
4	CH_2Cl_2	Me_3Al/hexane	rt	1.0	82	3	6	10
5	THF	MeMgBr/THF	rt	1.0	85	12	0	3

[a]The ratio was determined by ^{1}H NMR analysis.

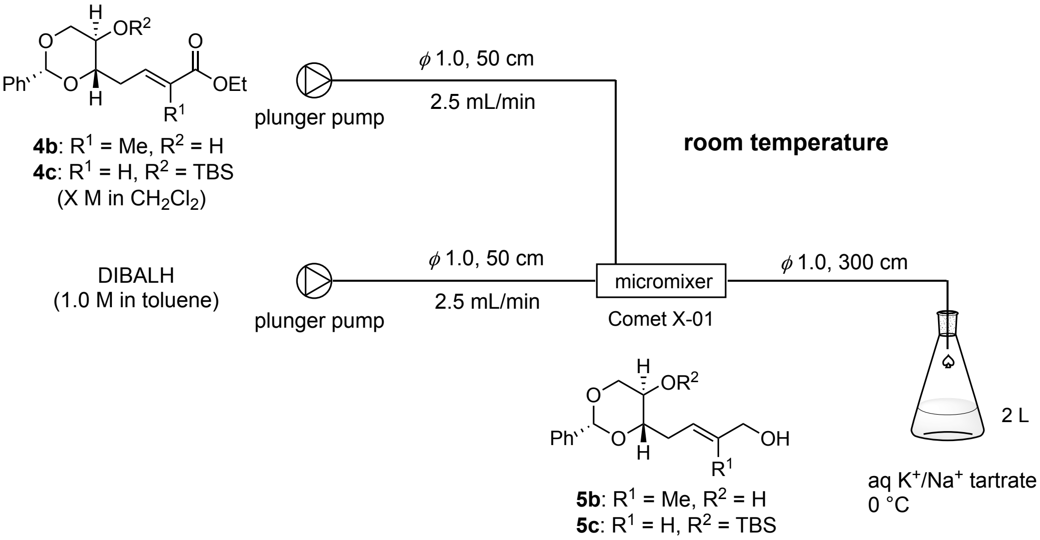
Having optimized the reaction conditions in methylation of ketone **3** under flow conditions (Table 1, entry 5), continuous methylation of the ketone and reduction of the ester giving alcohol **5a** was examined as shown in Scheme 3. A 0.60 M solution of **3** in THF and a 1.0 M solution of MeMgBr in THF were transmitted to the first Comet X-01 by using syringes (50 mL volume) and syringe pumps at a rate of 1.0 mL/min, respectively, at room temperature. Then, the eluent containing the intermediate **8** was transmitted to the second Comet X-01, which was mixed with a 1.0 M solution of DIBALH in toluene at a rate of 1.5 mL/min at **room temperature**. After passing through the Teflon tube, the eluent containing the intermediate **9** was quenched by pouring into a mixture of saturate aqueous Rochelle salt and Et_2O at 0 °C to afford **5a** in 83% yield. Since the reaction mixture was poured dropwise, quenching was carried out safely without bumping. As a result, from 84.7 g of **3** (0.276 mol), 63.7 g of **5a** (0.229 mol) was obtained successfully, with concomitant formation of its diastereomer (6%).



Scheme 3. Methylation and DIBALH reduction of ketoester **3** under continuous flow conditions

Having succeeded in the large-scale synthesis of **5a**, the method for ester reduction with DIBALH under flow conditions was applied to synthesize **5b** and **5c**, intermediates for synthesizing THP derivatives **1b** and **1c**, respectively (Scheme 4 and Table 2). A 0.30 M solution (1.00 L) of ester **4b** (88.9 g, 0.290 mol) in CH_2Cl_2 and a 1.0 M solution (1.00 L) of DIBALH in toluene and were transferred to the Comet X-01 by using plunger pumps at a rate of 2.5 mL/min at room temperature (entry 1). After passing through the Teflon tube, the reaction mixture was poured into saturated aqueous Rochelle salt at 0 °C for quenching. As a result, 74.5 g of **5b** was obtained in 97% yield. In an analogous manner, mixing a 0.40 M solution

(1.38 L) of **4c** (223 g) in CH_2Cl_2 with a 1.0 M solution (1.38 L) of DIBALH in toluene resulted in the formation of 183 g of **5c** in 91% yield (entry 2).



Scheme 4. DIBALH reduction of esters **4b** and **4c** under flow conditions

Table 2. Results of reduction of esters **4b** and **4c** with DIBALH under flow conditions

entry	substrate	weight (g)	mole (mol)	conc (M)	product	weight (g)	yield (%)
1	**4b**	88.9	0.290	0.30	**5b**	74.5	97
2	**4c**	223	0.549	0.40	**5c**	183	91

In conclusion, the kotoester **3** was converted to the intermediate **5a** for synthesizing the THP derivative **1a** under continuous flow conditions by successive methylation of the ketone with MeMgBr and reduction of the ester with DIBALH. Although these reactions are to be carried out at low temperature (−20 °C for methylation and −78 °C for reduction) under batch conditions, the application of flow chemistry allowed these reactions to perform at room temperature due to the efficient thermal diffusion of the micromixer. It is also beneficial that quenching was carried out safely without bumping since the reaction mixture was poured dropwise. In addition, reduction of the esters **4b** and **4c** with DIBALH under flow conditions was also successful in large-scale synthesis to afford **5b** and **5c**, respectively, which are precursors for synthesizing the THP derivative **1b** and **1c**.

EXPERIMENTAL

All reactions sensitive to air or moisture were performed under argon atmosphere with dry glassware unless otherwise noted in particular. The dehydrated solvents, CH_2Cl_2 and THF were purchased from local venders and were used without further dehydrations. All other chemicals were obtained from local venders and used as supplied unless otherwise stated. TLC of E. Merck silica gel 60 F_{254} pre-coated plates (0.25-mm thickness) was used for the reaction analyses. For column chromatography, Kanto silica gel 60N (spherical, neutral, 100–210 μm) was used. ^1H NMR spectra were recorded on a JEOL JNM-ECA600 spectrometer. Micromixers (Comet X-01, Teflon) were purchased from Techno Applications Co., Inc. Micromixers were connected with Teflon tubes (ϕ1.0 mm). Solutions were introduced to the microflow system using syringe pumps, Harvard Model 11 Plus, equipped with gastight syringes or using plunger pumps, FLOM Intelligent Pump UI-22-410D.

Alcohol 4a. <flow conditions, Table 1, entry 5> A 0.60 M solution of ketoester **3** was prepared from 2.45 g (7.93 mmol) of the substrate by dissolving in THF (11.3 mL). A 0.60 M solution of **3** in THF (10.0 mL) and a 1.0 M solution of MeMgBr in THF (10.0 mL) were introduced to micromixer (Comet X-01) by using gastight syringes (10 mL volume, respectively) and syringe pumps at a flow rate of 1.0 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 1.0 m), respectively. After passing through a Teflon tube (ϕ1.0 mm × 2.0 m), the reaction mixture was poured into a mixture of Et_2O (10 mL) and saturated aqueous potassium sodium tartrate (10 mL) in a flask (30 mL volume) at 0 °C with stirring. The reaction mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue as a mixture of alcohol **4a**, alcohol **6**, and ketone **3** in a **4a**:**6**:**3** = 85:12:3 ratio as determined by 600 MHz ^1H NMR.

Alcohol 5a. <flow conditions> A 0.60 M solution of ketoester **3** (453 mL) in THF was prepared from 84.7 g (0.276 mol) of the substrate. A 0.60 M solution of **3** in THF (50 mL ×2) and a 1.0 M solution of MeMgBr in THF (50 mL ×2) were introduced to the first micromixer (Comet X-01) by using gastight syringes (50 mL volume, respectively) and syringe pumps at a flow rate of 1.0 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 0.5 m), respectively. After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture was introduced to the second micromixer (Comet X-01) and mixed with a 1.0 M solution of DIBALH in toluene (50 mL ×3) by using a gastight syringe (50 mL volume) and a syringe pump at a flow rate of 1.5 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 0.5 m). After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture was poured into a mixture of Et_2O (250 mL) and saturated aqueous potassium sodium tartrate (250 mL) in a Erlenmeyer flask (PP, 2 L) at 0 °C with stirring. After stirring for 16 h, the combined reaction mixtures were extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated. This procedure was repeated with the remaining solution of **3**. The combined residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to give alcohol **5a** (63.7 g, 0.229 mol, 83%) as a colorless sticky oil, and its diastereomer (4.30 g, 15.6 mmol, 6%).

Alcohol 5b. <flow conditions, Table 2, entry 1> A 0.30 M (1.00 L) solution of ester **4b** (88.9 g, 0.290 mol) in CH_2Cl_2 and a 1.0 M (1.00 L) solution of DIBALH in toluene were introduced to micromixer (Comet X-01) by using plunger pumps at a flow rate of 2.5 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 50 cm), respectively. After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture was poured into saturated aqueous potassium sodium tartrate (400 mL) in a Erlenmeyer flask (PP, 2 L ×5) at 0 °C with vigorous stirring. The reaction mixture was diluted with EtOAc (200 mL) and saturated aqueous potassium sodium tartrate (150 mL), and stirred for additional 16 h. The combined reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) to give alcohol **5b** (74.5 g, 0.282 mol, 97%) as a colorless sticky oil.

Alcohol 5c. <flow conditions, Table 2, entry 2> A 0.40 M of ester **4c** (223 g, 0.549 mol) in CH_2Cl_2 (1.38 L) and a 1.0 M solution of DIBALH in toluene (1.38 L) were introduced to micromixer (Comet X-01) by using plunger pumps at a flow rate of 2.5 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 50 cm), respectively. After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture was poured into saturated aqueous potassium sodium tartrate (400 mL) in a Erlenmeyer flask (PP, 2 L ×5) at 0 °C with vigorous stirring. The reaction mixture was diluted with EtOAc (200 mL) and saturated aqueous potassium sodium tartrate (150 mL), and stirred for additional 16 h. The combined reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 50/1 to 5/1) to give alcohol **5c** (183 g, 0.502 mol, 91%) as a colorless sticky oil.

ACKNOWLEDGEMENTS

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