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Practical Diastereoselective Synthesis and Scale-up Study of (+)-2-((1*R*,2*R*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)ethanol: A Key Intermediate of the Novel Prostaglandin D_2 Receptor Antagonist S-5751

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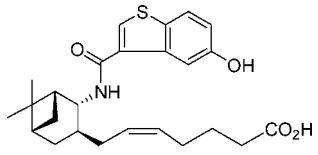
Abstract:

A new synthetic process was developed for (+)-2-((1*R*,2*R*,3*R*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)ethanol, a key intermediate of S-5751. Diastereoselective alkylation of (+)-nopinone with ethyl bromoacetate, formation of *O*-methyl oxime, and diastereoselective reduction with $NaBH_4-AlCl_3$ could be safely carried out. Stereochemistry of the (1*R*,2*R*,3*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane ring was discussed to achieve high diastereoselectivity on these reactions. For the scale-up, detailed consideration was given to the safety of the $NaBH_4-AlCl_3$ reduction.

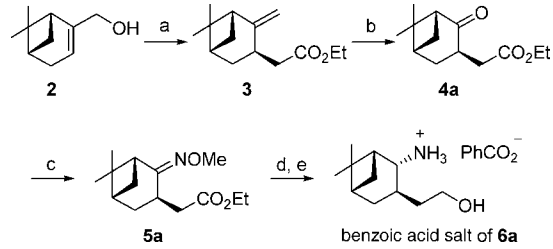
Introduction

(*Z*)-7-[(1*R*,2*R*,3*S*,5*S*)-2-(5-Hydroxybenzo[*b*]thiophen-3-yl-carbonylamino)-10-norpinan-3-yl]-hept-5-enoic (S-5751 **1**), which was discovered in Shionogi Research Laboratories,[1,2] is a novel prostaglandin D_2 (PGD_2) receptor antagonist that is a promising alternative antiallergic drug candidate. The most important step in its synthesis is the preparation of a (1*R*,2*R*,3*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane ring skeleton having an amide moiety and alkyl moiety with high diastereoselectivity, because its diastereoisomers did not show strong activity in PGD_2 receptor binding and cAMP formation assays in the in vivo assay.[2]



S-5751 **1**

Scheme 1. **Discovery route of 6a from (−)-myrtenol 2**[a]



[a] Reagents: (a) Triethyl orthoacetate, hydroquinone (165−195 °C). (b) (1) O_3 (−78 °C), (2) Me_2S (−10 °C) in methanol. (c) $MeONH_2$·HCl, pyridine in ethanol (reflux). (d) Sodium metal in *n*-propanol (90 °C). (e) Benzoic acid in diethylether and recrystallization from acetone.

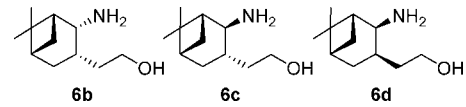
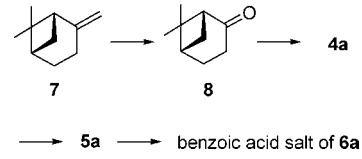


Figure 1. **Diastereoisomers of 6a generated at Bouveault−Blanc reduction.**

Scheme 2. **New synthetic route of 6a from *β*-pinene 7**



In our synthetic strategy, the benzoic acid salt of (+)-2-((1*R*,2*R*,3*R*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl) ethanol **6a** is a key intermediate of **1**, and its preparation with high diastereoselectivity is indispensable for large-scale manufacturing. In a discovery route using (−)-myrtenol **2** as a starting material, **6a** was obtained by ozonolysis of **3**, formation of *O*-methyl oxime **5a**, and Bouveault−Blanc reductions of both *O*-methyl oxime and ester in **5a** (Scheme 1).[3] However, there were two serious problems for industrial manufacturing: **2** was not available commercially, and reduction of **5a** gave the three isomers shown in Figure 1. The overall yield of **6a** from **2** was only 23%. Using *β*-pinene **7**, a commercially available material, we tried to establish a new synthetic route, which is described in Scheme 2. There are two key steps to controlling the diastereoselectivity: one is alkylation of (+)-nopinone **8**, and

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|| Nichia Pharmaceutical Industry.

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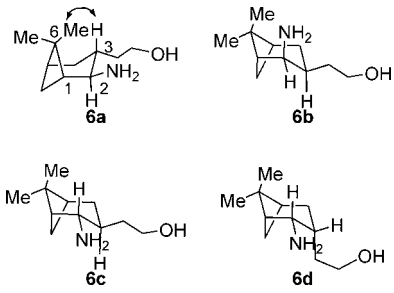


Figure 2. **Steric conformation of 6a−d.**

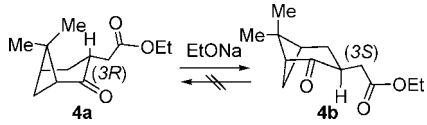


Figure 3. **Epimerization of 4a.**

the other is reduction of **5a**. We investigated the stereochemistry of the 6,6-dimethylbicyclo[3.1.1]heptane ring to achieve high diastereoselectivity and also evaluated the safety of the reduction.

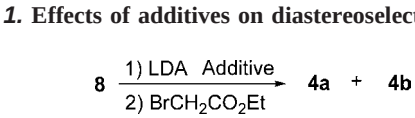
Results and Discussion

Determination of Steric Conformation. We focused on the stereochemistry of the (1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1] heptane ring. Steric hindrance of the 6,6-dimethyl group seemed to be the key to controlling the diastereoselectivity. We first determined the steric conformation of each isomer by NMR. The NOE of the methyl group at the 6-C position and a proton at the 3-C position was observed. We found the cyclohexane ring including the 6,6-dimethyl group of **6a** to be of the boat conformation, while one of the other isomers has the chair conformation (Figure 2). This shows that retaining the boat conformation is one of the key points for preparing **6a** from **7**.

To obtain **6a**, epimerization of the alkyl group at the 3-C position in **4a** or **5a** should not proceed. However, **4a** can be very easily epimerized to **4b** by a base (Figure 3); in other words, **4b** is more thermodynamically stable than **4a**. Next, we investigated the diastereoselective alkylation of (+)-nopinone **8**.

Diastereoselective Alkylation of (+)-Nopinone. (+)-Nopinone **8** was obtained by ozonolysis of **7**. Alkylation of **8** by lithium diisopropylamide (LDA) was investigated (Table 1). Without additive, the yield and diastereoselectivity was not enough to give the desired result (entry 1). The lithium enolate anion aggregates in THF solvent[4] and the reactivity seemed to decrease.[5] Next, we screened additives for the deaggregation. Addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) did not improve dramatically the reactivity (entry 2). TMEDA can form a dimeric aggregate of lithium enolate,[4] and the reactivity did not seem to improve. Hexamethylphosphoric triamide (HMPA) causes deaggregation,[6] and the reactivity and diastereoslectivity were improved (entry 3). However, HMPA has a negative health impact,[7] and its use should be avoided for large-scale manufacturing. The alkylation of **8** using 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidione (DMPU) has been reported.[8] We also investigated the effect of addition of a urea compound and found that 1,3-dimethyl-2-imidazolidinone (DMI) gave better diastereoselectivity than DMPU (entries 4 and 5) and thus chose it as the additive for alkylation. Next, we optimized the reaction conditions (Table 2). LDA and ethyl bromacetate were sufficient at 1.05 equiv, and the yield and diastereoselectivity relied solely on the alkylation temperature, irrespective of the lithiation temperature. This diastereoselectivity is kinetically controlled, and the generation of **4b** seems to rely on a thermodynamically favored conformation of enolate anion (Figure 4).

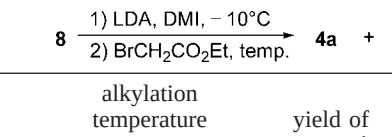
Table 1. **Effects of additives on diastereoselective alkylation[a]**



entry	additive (equiv)	yield of **4a** + **4b**[b] (%)	ratio of **4a**:**4b**[b]
1	none	82	76:24
2	TMEDA (1)	85	89:11
3	HMPA (1)	89	98:2
4	DMPU (1)	95	97:3
5	DMI (1)	90	99:1

[a] All reactions were carried out in THF using 1.2 equiv of LDA and 3.0 equiv of ethyl bromoacetate at −60 °C. After dropwise addition of ethyl bromoacetate, the mixture was heated to 0 °C. [b] Determined by HPLC.

Table 2. **Effects of temperature on diastereoselective alkylation[a]**



entry	alkylation temperature (°C)	yield of **4a** (%)[b]	ratio of **4a**:**4b**[b]
1	−15	66	86:14
2	−40	76	97:3
3	−45	86	98:2
4	−50	92	99:1

[a] All lithiations were carried out in THF using 1.05 equiv of LDA and 1.0 equiv of DMI at −10 °C, and then 1.05 equiv of ethyl bromoacetate was added under several temperatures followed by stirring for 2 h. [b] Yield and diastereoselectivity were determined by HPLC.

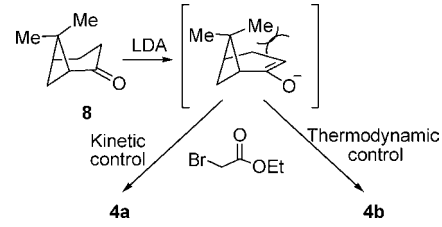


Figure 4. **Mechanism of kinetically or thermodynamically controlled alkylation.**

Diastereoselective Reduction of 5a. We considered the reasons for the low diastereoselectivity in the Bouveault−Blanc reductions of the discovery route to be as follows: one-electron reduction could not control the stereoselective reduction of

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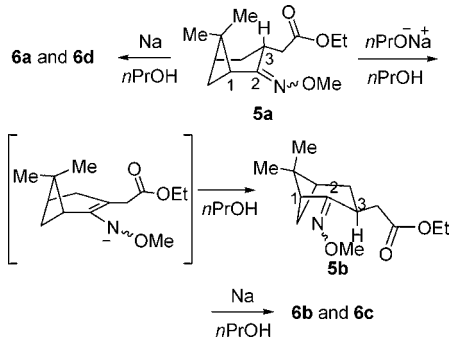
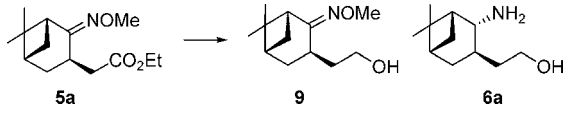


Figure 5. **Epimerization mechanism on Bouveault−Blanc type reduction of 5a.**

Table 3. **Screening of reagents on reduction of 5a**



5a 9 6a

entry	reagent (equiv)	additive (equiv)	solvent	reaction temp	yield of **6a** (%)[a]
1	Vitride (2.5)	none	toluene	reflux	0[b]
2	BH_3 (5.0)	none	THF	reflux	43
3	$LiAlH_4$ (4.0)	H_2SO_4 (2.0)	THF	reflux	78
4	$NaBH_4$ (5.0)	BF_3-Et_2O (0.5)	DME	reflux	24
5	$NaBH_4$ (5.0)	$TiCl_4$ (0.6)	DME	70 °C	74
6	$NaBH_4$ (7.0)	$AlCl_3$ (0.9)	DME	70 °C	82

[a] Isolated yield of benzoic acid salt of **6a** based on charged **5a**. [b] Only ester was reduced to alcohol, which gave **9**.

O-methyl oxime; sodium propoxide which seemed to be generated in the course of the reaction caused α-proton abstraction of *O*-methyl oxime, and epimerization of alkyl group at the 3-C position proceeded (Figure 5).

We investigated some hydride reductions which do not cause α-proton abstraction (Table 3). Vitride (70% sodium bis(2-methoxyethoxy)aluminum hydride toluene solution) could reduce the ester but could not reduce *O*-methyl oxime (entry 1). Reduction of *O*-methyl oxime required a much stronger reducing reagent. Although borane gave **6a** in 43% yield (entry 2), it was not enough to improve the process. Lithium aluminum hydride ($LiAlH_4$) with sulfuric acid gave **6a** in good yield (entry 3);[9] however $LiAlH_4$ is difficult to handle in large-scale manufacturing. We investigated a method using sodium borohydride ($NaBH_4$) and several Lewis acids (entries 4−6).[10−12] The best yield of **6a** with excellent diastereoselectivity was obtained with a combination of aluminum trichloride ($AlCl_3$) and $NaBH_4$ (entry 6). No isomers **6b−d** were detected. From these results, we decided to develop a process using $NaBH_4-AlCl_3$.

This excellent diastereoselective reduction seems to rely on steric hindrance of the 6,6-dimethyl group. α-Proton abstraction of *O*-methyl oxime did not proceed, and the conformation of the 6,6-dimethyl cyclohexane ring could retain the boat form and the hydride could not attack from the *β*-face of *O*-methyl oxime because of steric hindrance of the 6,6-dimethyl group (Figure 6). In fact, reduction of the chair form **5b**, in which

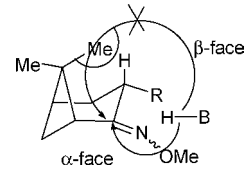
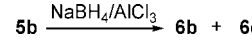


Figure 6. **Stereoselective reduction of *O*-methyl oxime.**

Scheme 3. **Reduction of 5b with $NaBH_4-AlCl_3$**



steric hindrance of the 6,6-dimethyl group is not large, gave **6b** and **6c** without diastereoselectivity (Scheme 3).

Safety Evaluation for Reduction of 5a. We developed the new synthetic route of **6a** from *β*-pinene as previously mentioned. However, some safety concerns must be overcome for scale-up of this method. In particular, the $NaBH_4-AlCl_3$ reduction required attention to safety issues. The total heat of reaction value on reduction of the ester and *O*-methyl oxime is very large. In addition, a case of severe explosion has been reported in the past.[13] According to the reference, hydrogen ignition, generated by contact with the powder containing both $NaBH_4$ and $AlCl_3$, caused the explosion.[13] This means that complete dissolution of both $NaBH_4$ and $AlCl_3$ is one of the most important points. As the reaction solvent, we chose diglyme, in which both $NaBH_4$ and $AlCl_3$ are soluble. Due to this choice, the $NaBH_4$ can be added dropwise. Next, we optimized the amount of $NaBH_4$ and $AlCl_3$ (Table 4). The amount of $NaBH_4$ was minimized to reduce the hydrogen gas generated by the workup. Based on this optimization, $NaBH_4$ and $AlCl_3$ were sufficient at 1.5 and 0.6 equiv, respectively. (entry 3). With such a small amount of $NaBH_4$, the reduction of *O*-methyl oxime did not proceed completely and the yield of **6a** was low as shown in entry 4.

Table 4. **Optimization of amount of $NaBH_4$ and $AlCl_3$**

entry	$NaBH_4$ (equiv)	$AlCl_3$ (equiv)	yield of **6a** (%)[a]
1	2.5	1.0	77
2	1.6	0.6	75
3	1.5	0.6	75
4	1.2	0.8	51[b]

[a] Isolated yield of benzoic acid salt of **6a** from **8**. [b] The reduction of *O*-methyl oxime did not proceed completely.

Careful monitoring of the process showed that the required reduction temperature of *O*-methyl oxime and that of the ester differ. Reduction of *O*-methyl oxime required heating, while that of the ester can proceed at room temperature. This meant that the reduction process could be carried out in a stepwise manner. RC1e data are summarized in Figure 7 and Table 5. Into a diglyme solution of **5a** and $AlCl_3$, 5.3% (w/w) of $NaBH_4$/diglyme solution was added dropwise. The heat of reduction of the ester could be completely controlled by dropwise addition of $NaBH_4$/diglyme solution at 35 °C. The reduction of *O*-methyl oxime proceeded mildly at 65 °C. Although the total heat of reaction was 437.3 kJ/mol, it could be controlled and the potential risk of a runaway reaction was decreased.

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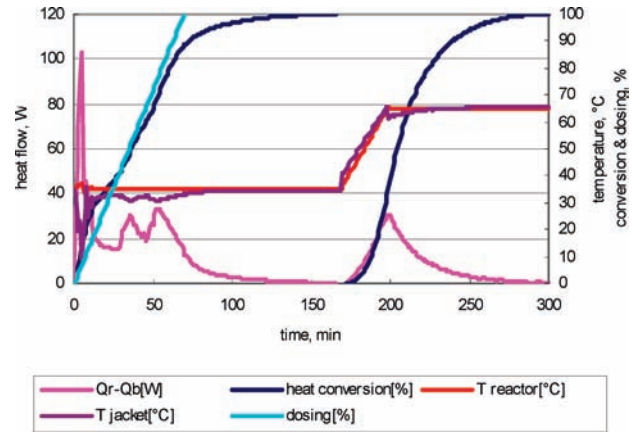

Figure 7. **Experimental heat flow of reduction of 5a from RC1e.**

Table 5. **Result of RC1e experiment**

operation	process temperature (°C)	ΔH_{reac} (kJ/mol)	specific heat of reaction mass (J/(g·K))	ΔT_{ad} (K)	ratio of **5a**:**9**:**6a**[a]
dosing[b]	35	262.1	1.955	136.2	21:66:14
stirring 1 h	35	35.1		18.2	6:62:24
heating	35→65	140.1	1.940	32.6	0:3:97
stirring 2 h	65				0:0:100

[a] Determined by GC. [b] Dropwise addition of 5.3% (w/w) $NaBH_4$/diglyme solution for 1 h.

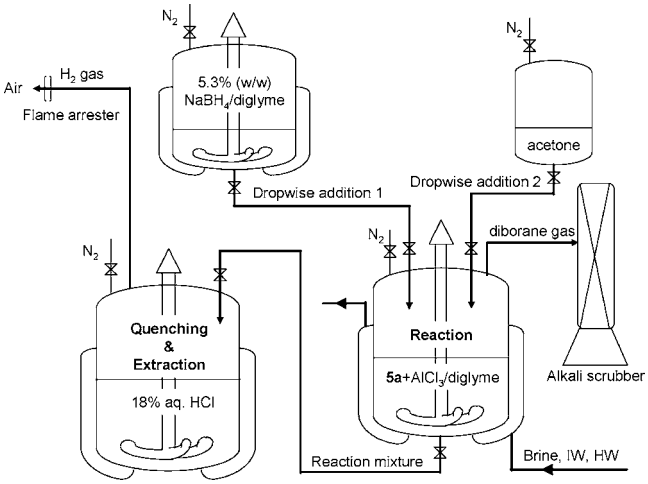

Figure 8. **Pilot plant sketch.**

Application in a Manufacturing Facility. This process was applied to pilot manufacturing. Treatment of diborane gas generated in the course of the reaction was also a serious problem for scale-up manufacturing. Diborane gas, which is deadly and pyrophoric in dry air, was detected at >2 ppm in the vapor phase.[14] The facility design is shown in Figure 8. Water vapor decreases the rate of flame propagation due to hydrolysis of diborane.[15] Therefore, leakage of diborane gas from the reactor to the air had to be prevented, and the hydrolysis was carried out in an alkali scrubber. Until the reaction mixture was quenched in aqueous 18% HCl, opening of the reactor was forbidden. Excess borohydride in the reaction mixture was deactivated by dropwise addition of acetone after the reaction, and then the mixture was added dropwise into aqueous 18% HCl. Hydrogen gas generated at quenching was sent out from a flame arrester.

Reaction Species. H. C. Brown estimated that the reactive species in this reduction is $Al(BH_4)_3$ (eq 1).[10]

$$3NaBH_4 + AlCl_3 \rightarrow Al(BH_4)_3 + 3NaCl \qquad (1)$$

A diglyme solution of both $NaBH_4$ and $AlCl_3$ was mixed to measure the heat of formation of $Al(BH_4)_3$; however no heat was detected and NaCl was not generated. We checked the vapor phase with ICP-MS but did not detect the Al^{3+} ion. Therefore, we concluded that $Al(BH_4)_3$ was not generated in this reduction. $AlCl_3$ seemed to only be chelated to ester, and NaCl generated on reduction of ester.

Conclusion

The steric effect of the 6,6-dimethyl group in the (1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane ring was clarified, and a new synthetic process was developed for the key intermediate **6a** of S-5751 **1**. Kinetically controlled diastereoslective alkylation of (+)-nopinone **8** and diastereoselective reduction of both the ester and *O*-methyl oxime with $NaBH_4-AlCl_3$ were achieved. Overall yield increased from 23% for the discovery route to 59% for the new route. The safety of the diastereoselective reduction using $NaBH_4-AlCl_3$ was studied in detail. The key points for ensuring safety are complete dissolution of both $NaBH_4$ and $AlCl_3$, separation of the heat of reduction of the ester and *O*-methyl oxime with temperature control, and containment of diborane gas from the reactor to air. The process was safely applied to pilot manufacturing of **6a** on a 160 kg/lot basis.

Experimental Section

NMR spectra were measured on a Varian[Unity] Inova-500 or Inova-600. Gas chromatographic (GC) analysis was carried out using HP 6780. High performance liquid chromatographic (HPLC) analysis was carried out using a Shimadzu LC-2010HT. β-Pinene, trimethyl phosphite, diisopropylamine, ethyl bromoacetate, pyridine, $NaBH_4$, $AlCl_3$, and benzoic acid were obtained from Wako Pure Chemical Industry. A 24% *n*-butyl lithium/hexane solution was obtained from Aldrich.

Preparation of (+)-Nopinone 8. In a four-neck 3 L flask, β-pinene (150 g, 1.10 mol) was mixed with methanol (1.5 L), and the mixture was cooled to −50 °C and stirred with a stream of ozonized oxygen gas for 4 h. The reaction termination was checked by TLC, and then the mixture was heated to −25 °C. Trimethyl phosphite (278.6 g, 2.25 mol) was added dropwise under the same conditions for over 2 h. The reaction mixture was heated to 0 °C, and aqueous 10% H_2SO_4 (440.4 g) was added. After stirring at 25 °C for 4 h, toluene (810 mL) and water (3 L) were added and stirred. The organic layer was separated and washed with aqueous 5% $NaHCO_3$ (750 g), followed by aqueous 10% Na_2SO_3 (750 g). After the removal of

(14) Diborane in the vapor phase was detected by gas detector tube (GASTEC CORPORATION). Threshold Limit Values-Time Weighted Average of diborane gas is 0.1 ppm.
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toluene, the residue was distilled under 20 mmHg at 100 °C and gave (+)-nopinone **8**[16] (123.8 g, 81.4%).

Procedure for Manufacturing 6a. *Preparation of Ethyl 2-((1R,3R,5S)-6,6-Dimethyl-2-oxobicyclo[3.1.1]heptan-3-yl)-acetate **4a** by Diastereoselective Alkylation of (+)-Nopinone **8**.* In a four-neck 1 L flask, a mixture of diisopropylamine (48.3 g, 0.48 mol) and THF (360 mL) was cooled to −15 °C, and then a 24% hexane solution of *n*-butyl lithium (127.4 g, 0.48 mol) was added dropwise under the same temperature. Next, (+)-nopinone **8** (60.0 g, 0.43 mol) was added dropwise at −15 °C followed by dropwise addition of DMI (46.9 mL). This mixture was cooled to −50 °C, and ethyl bromoacetate (76.1 g, 0.46 mol) was added dropwise over 30 min under the same temperature followed by stirring for 2 h. The reaction termination was checked by HPLC analysis, and water (180 mL) was added dropwise from −50 to 0 °C. After adjustment of the pH to 7.0 with aqueous 20% HCl below 25 °C, the organic layer was separated and washed with water (90 mL). The organic layer was evaporated, and the obtained residue (121.5 g) of **4a** was used for the next step.

*Preparation of Ethyl 2-((1R,3R,5S)-2-(Methoxyimino)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)acetate **5** from **4a**.* To the evaporated residue of **4a**, toluene (193 mL), *O*-methylhydroxylamine hydrochloride (47.2 g, 0.57 mol), pyridine (44.7 g, 0.57 mol), and methanol (97 mL) were added, and the mixture was heated under reflux for 2 h. After the termination of the reaction was confirmed by HPLC analysis, the reaction mixture was cooled to 25 °C. Water (90 mL) and aqueous 35% HCl (31.7 g, 0.30 mol) were added and stirred. The organic layer was separated and washed with water (90 mL), followed by aqueous 1% $NaHCO_3$ (90 g). The organic layer was evaporated, and the obtained residue (127.6 g) of **5a** was used for the next step.

*Preparation of Benzoic Acid Salt of 2-((1R,2R,3R,5S)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol **6a** from **5a** with Diastereoselective Reduction.* To the evaporated residue of **5a**, $AlCl_3$ (34.7 g, 0.26 mol) dissolved in diglyme (264 mL) was added (*Caution! exothermic dissolution*), and the mixture was stirred at 35 °C. A solution of $NaBH_4$ (26.3 g, 0.69 mol) in diglyme (468 mL) was added dropwise to the mixture at 35 °C. The reaction mixture was stirred for 1 h under the same conditions and then heated to 65 °C followed by stirring for 2 h. After the termination of the reaction was confirmed by GC analysis, the reaction mixture was cooled to 10 °C. Acetone (39.0 g) was added dropwise to the mixture at the same temperature, and then the mixture was added dropwise to aqueous 18% HCl (271 g, 1.34 mol) at 10−30 °C. Into this mixture, aqueous 34% NaOH (291.6 g, 2.48 mol) was added dropwise and toluene (840 mL) was also added. The organic layer was separated and washed with aqueous 10% NaCl (240 g × 2). It was evaporated azeotropically. Into the obtained residue (702 g), a solution of benzoic acid (47.7 g, 0.39 mol) in acetone (175 mL) was added dropwise at 30 °C to obtain white crystals and cooled to 5 °C. These crystals were filtrated, washed with cold acetone (300 mL), and dried in vacuo. By this procedure, 94.23 g (0.31 mol) of benzoic acid salt of **6a**[3] was obtained (isolated yield: 72.1%).

Preparation of 2-((1*R*,2*R*,3*S*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol 6b and 2-((1*R*,2*S*,3*S*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol 6c. *Epimerization of **4a** (Preparation of **4b**).* In a four-neck 1 L flask, **4a** (47.0 g, 0.21 mol), 236 mL of toluene, and 20% sodium ethylated ethanol solution (146.0 g, 0.42 mol) were mixed, and then the mixture was heated to 90 °C. After 170 mL of ethanol and toluene were distilled, the reaction mixture was cooled to room temperature and poured into 465 g of 4% HCl. The organic layer was separated and washed with aqueous 0.5% $NaHCO_3$ (400 g). The aqueous layer was extracted with 200 mL of toluene, and then the toluene layers were combined. The combined organic layer was evaporated, and the obtained residue (38.07 g) of **4b** was used for the next step to prepare **6b** and **6c**.

*Preparation of **6b** and **6c**.* To a four-neck 500 mL flask, the residue of **4b** 30.6 g (0.14 mmol), *O*-methyl hydoroxylamine hydrochloride (14.8 g, 0.18 mol), pyridine (14.0 g, 0.18 mol), and ethanol (123 mL) were added and heated under reflux for 4 h. After the termination of the reaction was confirmed by TLC analysis, the reaction mixture was cooled to 25 °C and evaporated. Toluene (200 mL) and aqueous 1 N HCl (160 mL) were added and stirred. The organic layer was separated and washed with water (200 mL), followed by aqueous 1% $NaHCO_3$ (90 g). The organic layer was evaporated, and the obtained residue (34.2 g) of **5b** was purified by silica gel chromatography (250 g of SiO_2; 70−230 mesh ASTM (Merck), hexane/acetone = 100/1−25/1 as an eluent). Purified **5b** (22.5 g, 0.09 mol) and $AlCl_3$ (11.8 g, 0.09 mol) were dissolved in diglyme (170 mL) (*Caution! exothermic dissolution*) and stirred at 35 °C. $NaBH_4$ powder (8.4 g, 0.22 mol) was added over 30 min at 35 °C. The reaction mixture was stirred for 1 h under the same conditions and then heated to 65 °C followed by stirring for 3 h. After the reaction termination was checked by TLC, the reaction mixture was cooled to 10 °C. Acetone (32.0 g) was added dropwise to the mixture at the same temperature, and then the mixture was added dropwise to aqueous 11% HCl (220 g, 0.67 mol) at 10−30 °C. Into this mixture, aqueous 48% NaOH (107 g, 1.28 mol) was added dropwise and toluene was also added (200 mL). The organic layer was separated and washed with aqueous 10% NaCl (50 g × 2). It was evaporated azeotropically. The residue included diglyme, and the extraction was carried out again. Toluene (200 mL) and aqueous 2 N HCl (210 mL) were added to the obtained residue, and the aqueous layer was separated. The pH of the aqueous layer was adjusted to over 12.3 with aqueous 48% NaOH, and then the mixture of **6b** and **6c** was extracted with toluene (200 mL × 3). The separated organic layer was washed with 10% NaCl (100 g × 2) and evaporated to obtain the residue (15.0 g). Isomer **6b** (2.25 g) and **6c** (1.26 g) were isolated by silica gel chromatography of this residue. Compound **6b**: mp 110−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 5 °C) 1.01 (s, 3H), 1.21 (s, 3H), 1.33 (d, J = 10.0 Hz, 1H), 1.55 (dd, J = 13.6, 9.4 Hz, 1H), 1.63 (brdt, J = 14.8, ∼3 Hz, 1H), 1.93 (q-like, J = ∼5 Hz, 1H), 1.97 (m, 1H), 2.02 (m, 1H), 2.05 (m, 1H), 2.18 (dt, J = 10.0, 5.7 Hz, 1H), 2.49 (m, 1H), 3.50 (dd, J = 10.0, 3.9 Hz, 1H), 3.62 (brt, J = 10.6 Hz, 1H), 3.85 (ddd, J = 10.6, 4.3, 2.9 Hz, 1H). Compound **6c**: mp 58−60 °C. ^{1}H NMR (600 MHz,

$CDCl_3$, 10 °C) 0.83 (s, 3H), 1.26 (s, 3H), 1.46 (ddt, J = 13.3, 9.3, 1.0 Hz, 1H), 1.49 (d, J = 10.5 Hz, 1H), 1.54 (m, 1H), 1.70−1.77 (m, 2H), 1.83 (td, J = 5.5, 1.0 Hz, 1H), 1.96 (q, J = 5.5 Hz, 1H), 2.00 (m, 1H), 2.09 (dtt, J = 10.5, 5.5, 1.0 Hz, 1H), 2.99 (dt, J = 7.9, 1.0 Hz, 1H), 3.65−3.69 (m, 1H), 3.80 (ddd, J = 12.1, 4.8, 3.6 Hz, 1H).

Preparation of 2-((1*R*,2*S*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol 6d. The reduction of **5a** (15.0 g, 66.9 mmol) was carried out as follows based on a literature method.[3] The reaction mixture was extracted with toluene. The ratio of **6a**−**d** in the extracted solution was 78:14:5:3, which was determined by GC analysis. Isomer **6d** was isolated by silica gel chromatography of this residue from this mixture. ^{1}H NMR (500 MHz, $CDCl_3$, −10 °C) 0.97 (s, 3H), 1.00 (d, J = 10.3 Hz, 1H), 1.23 (s, 3H), 1.43 (m, 1H), 1.54 (brd, J = 14.5 Hz, 1H), 1.94 (m, 2H), 1.98 (m, 1H), 2.14 (m, 1H), 2.22 (m, 1H), 2.46 (m, 1H), 3.53 (brd, J = 10.1 Hz, 1H), 3.56 (brt, J = 10.6 Hz, 1H), 3.83 (dt, J = 10.6, 3.5 Hz, 1H).

Preparation of 2-((1*R*,3*R*,5*S*)-2-(Methoxyimino)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol 9. To a mixture of **5a** (23.8 g, 94.0 mmol) and toluene (111 mL), Vitride (70% sodium bis(2-methoxyethoxy)aluminum hydride toluene solution) was added dropwise at 25 °C and then the reaction mixture was heated to reflux. After the reaction, the mixture was cooled to 25 °C and acetone (7 g, 120.7 mmol) was added dropwise. Next, 30% aqueous NaOH (70.0 g, 525.0 mmol) was added, and the organic layer was separated. The aqueous layer was extracted with toluene. The combined organic layer was washed with water (30 mL × 3) and evaporated. The residue was purified by silica gel chromatography, and **9** was obtained.[17]

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Supporting Information Available

Copies of 2D ^{1}H NMR spectra of stereo isomers **6a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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