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Diastereoselective Total Synthesis of (±)-Toxicodenane A

Toyoharu Kobayashi,[a] Kotono Yamanoue,[a] Hideki Abe,[a] and Hisanaka Ito*[a]

Dedication ((optional))

Abstract: The first total synthesis of tricyclic sesquiterpene (±)-toxicodenane A has been accomplished. This synthetic work was completed in 12 steps from dimedone utilizing diastereoselective reductive desymmetrization of 2,2-disubstituted 5,5-dimethylcyclohexane-1,3-dione, stereocontrolled allylation, ring-closing metathesis of diene compound yielding bicyclic compounds having a 7-membered ring, and construction of the oxygen-bridged moiety via neighboring group assisted ring-opening reaction of epoxide as key steps.

Introduction

In 2013, Cheng and co-workers reported the isolation of a novel sesquiterpenoid, toxicodenane A (**1**), from the dried resin of *Toxicodendron vernicifluum*, which is a traditional Chinese medicine used for the treatment of gastritis, stomach cancer, and atherosclerosis.[1] The structure of **1**, a tricyclic sesquiterpenoid, was established through analysis of 2D NMR spectra including COSY, HMBC, and ROESY experiments and X-ray crystallographic diffraction as depicted in Figure 1. Toxicodenane A (**1**) possesses a unique 12-oxatricyclo[7,2,1,$0^{1,6}$]dodecane skeleton and bears four stereocenters including an all-carbon quaternary center. Related cyclic sesquiterpenoids toxicodenanes B (**2**) and C (**3**), which exhibit anti-diabetic nephropathy activity, were isolated along with toxicodenane A. In addition, toxicodenanes D (**4**) and E (**5**) were isolated from the same plant by the Cheng group in 2015.[2] Although these toxicodenanes have unique structures and biological activities, no total synthesis or synthetic studies have been reported to date. The structural features of **1** attracted our interest, and a synthetic study of toxicodenane A (**1**) was initiated. Herein, we describe the first total synthesis of toxicodenane A (**1**) in 12 steps utilizing the diastereoselective reductive desymmetrization of 2,2-disubstituted 5,5-dimethylcyclohexane-1,3-dione, stereocontrolled allylation, ring-closing metathesis (RCM), and construction of the oxygen-bridged moiety via neighboring group assisted ring-opening reaction of epoxide as key steps.

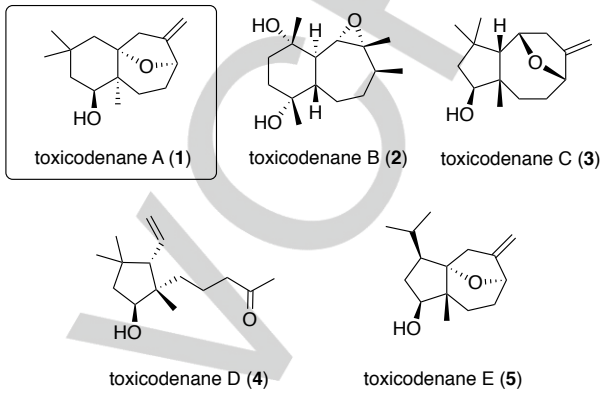

Figure 1. Structure of toxicodenane A and related compounds.

Results and Discussion

The synthetic strategy for toxicodenane A (**1**) is outlined in Figure 2. The target molecule **1** could be synthesized by construction of the *exo*-methylene moiety from compound **6**. The oxygen-bridged compound **6** would be derived from compound **7** via epoxidation followed by ether cyclization. Bicyclic compound **7** would be constructed by RCM of compound **8**, which was derived from ketone **9** via stereocontrolled allylation. Ketone **9** could be synthesized by the diastereoselective reductive desymmetrization of diketone **10**, which was prepared from commercially available dimedone (**11**).

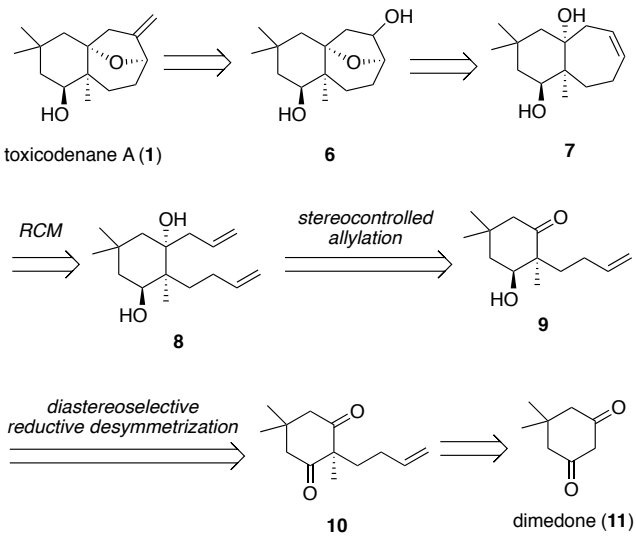

Figure 2. Synthetic strategy toward toxicodenane A.

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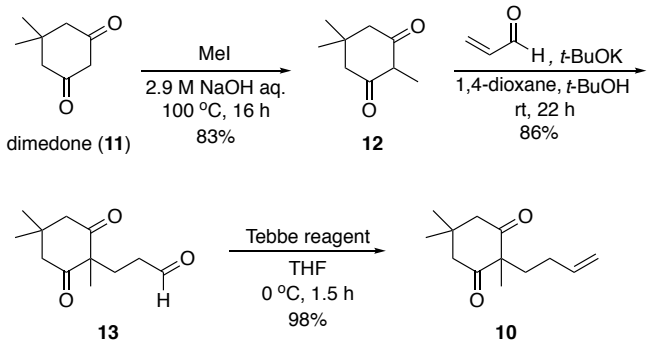
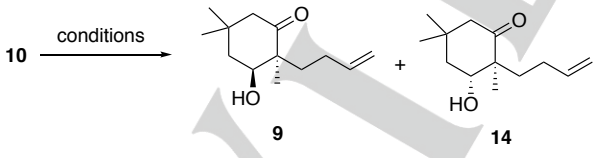
Our synthetic study started by preparing diketone **10** from dimedone (**11**) as shown in Scheme 1. Mono-methylation to the activated methylene moiety of dimedone (**11**) using a modified procedure reported by Franckevicius[3] gave compound **12** in 83% yield. Although the direct introduction of the butenyl group to compound **12** was attempted under several conditions, the desired diketone **10** was obtained in low yield. Therefore, diketone **10** was synthesized via a two-step operation. The Michael addition of compound **12** with acrolein afforded known aldehyde **13**[4] in 86% yield, then a treatment of the resulting aldehyde **13** with Tebbe reagent[5] gave diketone **10** in 98% yield.



Scheme 1. Synthesis of diketone **10**.

Next, the diastereoselective reductive desymmetrization of diketone **10** was attempted. Some examples of the diastereoselective reductive desymmetrization of 2,2-disubstituted cyclohexane-1,3-dione have been reported, [6] but examples for 2,2-disubstituted 5,5-dimethylcyclohexane-1,3-dione are very limited in the literature.[7] Therefore, we investigated the reaction conditions for this reductive desymmetrization of diketone **10** (Table 1). First, treatment of diketone **10** with $NaBH_4$ in MeOH at –78 °C provided the keto alcohols **9** and **14** in 77% yield in a ratio of 2:3 as inseparable mixture by silica-gel column chromatography (entry 1). When using THF as solvent, the keto alcohols **9** and **14** were obtained in 61% yield in a 1:1 ratio (entry 2). The treatment with DIBALH in CH_2Cl_2 at –78 °C provided the mixture of keto alcohols **9** and **14** along with the diol in a ratio of 2:2:5 (entry 3). The undesired diastereomer **14** was obtained preferentially (1:3 ratio) in 58 %

Table 1. Diastereoselective reductive desymmetrization of diketone **10**.

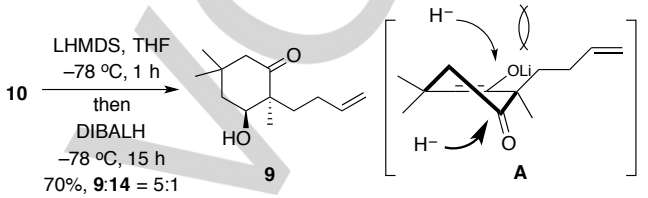


entry	conditions	result[a]
1	$NaBH_4$, MeOH, –78 °C	77% (**9**:**14** = 2:3)
2	$NaBH_4$, THF, 0 °C	61% (**9**:**14** = 1:1)
3	DIBALH, CH_2Cl_2, –78 °C	– (**9**:**14**:diol = 2:2:5)
4	L-Selectride, THF, –78 °C	58% (**9**:**14** = 1:3)

[a] The ratio of compound was determined by ^1H NMR.

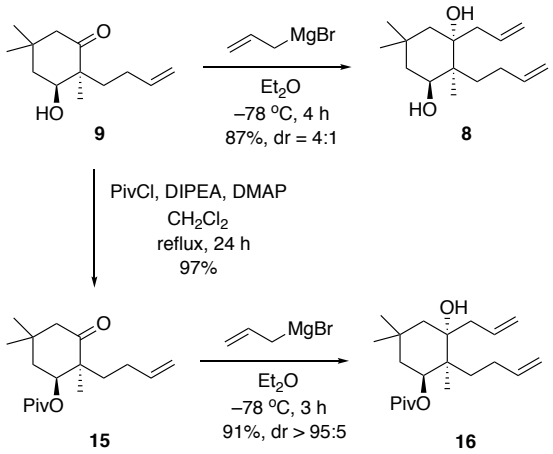
yield by reduction with L-Selectride, which is a bulky reductive reagent, in THF at –78 °C (entry 4).

To invert the diastereoselectivity of the reductive desymmetrization of diketone **10**, the reduction of the enolate form of **10** was attempted according to the modified procedure reported by Simpkins[6e] (Scheme 2). Fortunately, treatment of **10** with LHMDS in THF at –78 °C for 1 h followed by the slow addition of DIBALH at the same temperature provided the desired keto alcohol **9** in 70% yield with 5:1 diastereoselectivity. The stereoselectivity of the reductive desymmetrization via enolate formation of diketone **10** was assumed to be due to the preferentially approach of the hydride to the ketone of enolate **A** from the side opposite the butenyl group.



Scheme 2. The diastereoselective reductive desymmetrization of diketone **10** via enolate formation.

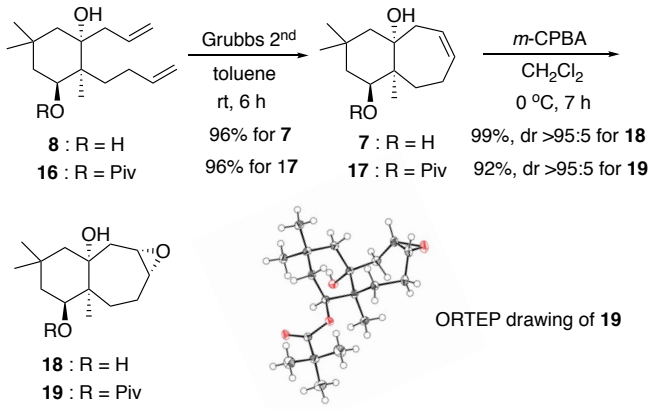
Treatment of **9** with allyl Grignard reagent in Et_2O at –78 °C gave compound **8** in 87% yield with 4:1 diastereoslectivity as separable mixture using silica-gel column chromatography (Scheme 3). To improve the stereoselectivity of the allylation, the solvent, temperature, allylic metal reagents and protecting group for the secondary alcohol were investigated. As a result, we found out that the treatment of pivaloyl protected compound **15**, which was prepared from **9** using pivaloyl chloride, with Grignard reagent in Et_2O at –78 °C afforded the allylated compound **16** in 91% yield as the sole product.



Scheme 3. Stereocontrolled allylation of ketones **9** and **15**.

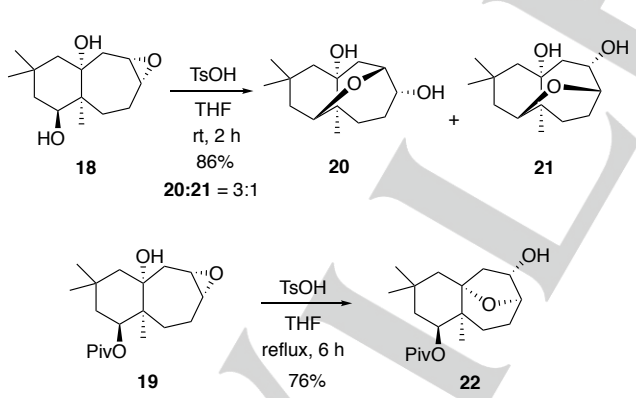
With the successful stereocontrolled synthesis of compounds **8** and **16**, we turned our attention to the construction of the oxygen-bridged moiety. The RCM[8] of diene compounds **8** and **16** using Grubbs second-generation reagent afforded the bicyclic compounds **7** and **17** both in 96% yields. The treatment

of the bicyclic compounds **7** and **17** with *m*-CPBA in CH_2Cl_2 at 0 °C gave the corresponding epoxides **18** and **19** in 99% and 92% yields, respectively, as a sole products. The stereochemistry of compound **19** was confirmed using X-ray crystallographic analysis.[9]



Scheme 4. Synthesis of epoxides **18** and **19**.

To construct the oxygen-bridged moiety, the epoxides **18** and **19** were treated under acidic conditions. Unfortunately, treatment of epoxide **18** with *p*-toluenesulfonic acid in THF at room temperature provided the 3:1 mixture of undesired compounds **20** and **21**, which were bridged from the secondary alcohol to the epoxide moiety, in 86% yield. On the other hand, treatment of epoxide **19**, which has a pivaloyl group, with *p*-toluenesulfonic acid in THF under reflux afforded the desired oxygen-brideged compound **22** in 76% yield.[10]



Scheme 5. Construction of oxygen-bridged moiety.

In the ether cyclization involving acid-mediated epoxide ring-opening, because of the epoxide and tertiary alcohol of compound **19** are present on the same side of the molecule, the backside attack of tertiary alcohol to epoxide is impossible. So, we considered that the pivaloyl group is participated for this reaction. Thus, the carbonyl group of pivaloyl ester attacks to epoxide at C2a to form intermediate **A**, then tertiary alcohol attacks to C2a to afford compound **22**, as described in the possible mechanism in Figure 3.

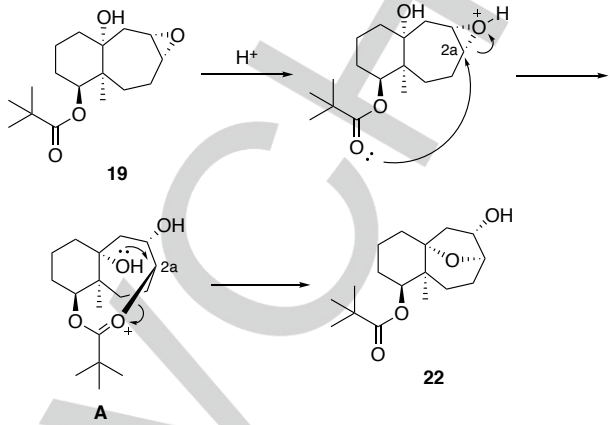
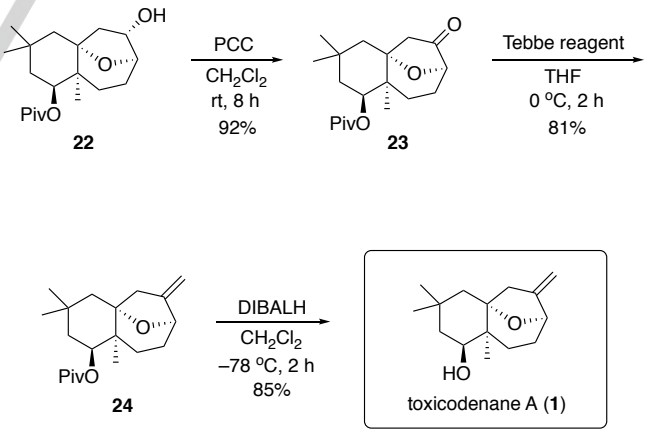


Figure 3. Possible mechanism for ether cyclization involving acid-mediated epoxide ring-opening.

Next, *exo*-methylene construction was achieved from compound **22** via a two-step operation. Thus, the oxidation of compound **22** with PCC gave the corresponding ketone **23** in 92% yield, followed by olefination of the ketone **23** using Tebbe reagent to provide compound **24** in 81% yield. Finally, the reduction of the pivaloyl group of **24** using DIBALH afforded the target molecule **1** in 85% yield. Both the ^1H and ^{13}C NMR spectra of synthetic **1** were identical with those of natural toxicodenane A (**1**).[1]



Scheme 6. Total synthesis of toxicodenane A (**1**).

Conclusions

In conclusion, we have achieved the first total synthesis of tricyclic sesquiterpene toxicodenane A (**1**) in 12 steps from dimedone (**11**). The synthetic method involved the following features: a) diastereoselective reductive desymmetrization of

compound **10**; b) stereocontrolled allylation of the pivaloyl protected compound **15**; c) ring-closing metathesis of diene compounds yielding bicyclic compounds having a 7-membered ring; d) construction of the oxygen-bridged moiety via neighboring group assisted ring-opening reaction of epoxide **19**. It is noteworthy that the pivaloyl group plays important role more than protecting group: improving the diastereoselectivity of the allylation and occurring the epoxide ring-opening reaction. This synthetic strategy will be applicable to the synthesis of toxicodenane A (**1**) in optically active form, which is now in progress in our laboratory.

Experimental Section

All reactions involving air- and moisture-sensitive reagents were carried out using standard syringe-septum cap techniques. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. Routine monitoring of reactions were carried out Merck silica gel 60 F254 TLC plates. Column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 60–230 μm) with the solvents indicated. Melting points were taken on a Yanako MP-S3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Jeol ECZ-400s (400 MHz) or a Burker AV-600 (600 MHz) spectrometer. Chemical shifts were expressed in ppm using $CHCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) in $CDCl_3$ as an internal standard. Infrared spectral measurements were carried out with a JASCO FT/IR-4700 and only noteworthy absorptions were listed. HRMS spectra measured on a Micromass LCT spectrometer.

2,5,5-Trimethylcyclohexane-1,3-dione (12). To a stirred solution of dimedone (**11**) (4.0 g, 28.5 mmol) in 2.9 M NaOH aqueous solution (10 mL) was added methyl iodide (8.1 g, 3.55 mL, 57.1 mmol) at 0 °C, and the mixture was stirred for 16 h at 100 °C. The reaction mixture was cooled to 0 °C, filtered under vacuo. The resulting solid was dissolved in AcOEt and purified by column chromatography (hexane-AcOEt, 1:2) to afford **12** (3.6 g, 83%) as a white solid: The spectral data of **12** was identified with those of the previous report.[3]

3-(1,4,4-Trimethyl-2,6-dioxocyclohexyl)propanal (13). To a stirred solution of **12** (1.0 g, 6.54 mmol) in 1,4-dioxane (3.3 mL) and *t*-BuOH (6.5 mL) was added *t*-BuOK (9.2 mg, 0.082 mmol) in *t*-BuOH (0.3 mL) and acrolein (458 mg, 8.17 mmol) in 1,4-dioxane (3.3 mL) at room temperature. After the mixture was stirred for 22 h at same temperature, the reaction was quenched by adding with acetic acid, and the mixture was concentrated in vacuo. The resulting residue was extracted with AcOEt. The combined organic layers were washed with 0.1 M NaOH aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 4:1) to afforded **13** (1.18 g, 86%) as yellow oil: IR (neat, cm^{-1}); 2955, 1723, 1692, 1458, 1373, 1327, 1192, 1074; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 2.60 (s, 4H), 2.38 (t, *J* = 8.2 Hz, 2H), 2.06 (t, *J* = 8.2 Hz, 2H), 1.28 (s, 3H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (2C), 200.8, 63.4, 51.1 (2C), 39.1, 30.7, 28.7, 28.2, 27.1, 21.0; HRESI calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1154, found 233.1159.

2-(But-3-en-1-yl)-2,5,5-trimethylcyclohexane-1,3-dione (10). To a stirred solution of **13** (53 mg, 0.25 mmol) in THF (5 mL) was added Tebbe reagent (0.5 M in toluene, 0.5 mL, 0.25 mmol) at 0 °C under Ar. After the reaction mixture was stirred for 2 h at same temperature, the reaction was quenched by adding with 30% NaOH aqueous solution. The mixture was filtered under vacuo and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 6:1) to afford **10** (52 mg, 98%) as yellow oil: IR (neat, cm^{-1}) 2961, 1726, 1691, 1460, 1371, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (tdd, *J* = 16.4, 10.0, 5.9 Hz, 1H), 5.03-4.95 (m, 2H), 2.71 (d, *J* = 14.1 Hz, 2H), 2.48 (d, *J* =14.2 Hz, 2H), 1.94-1.88 (m, 2H), 1.84-1.79 (m, 2H), 1.24 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (2C), 137.3, 115.5, 64.6, 51.4 (2C), 36.8, 30.7, 29.4, 28.7, 27.8, 18.2; HRESI calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$ 231.1361, found 231.1367.

(2*S,3*S**)-2-(But-3-en-1-yl)-3-hydroxy-2,5,5-trimethylcyclohexan-1-one (9) and (2*S**,3*R**)-2-(but-3-en-1-yl)-3-hydroxy-2,5,5-trimethylcyclohexan-1-one (14)**. To a stirred solution of **10** (50 mg, 0.24 mmol) in THF (2 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.29 mL, 0.29 mmol) at –78 °C under Ar, and the mixture was stirred for 30 min at room temperature. Then to this solution was added diisobutylaluminium hydride (1.0 M in THF, 0.79 mL, 0.79 mmol) at –78 °C, and the mixture was stirred for 15 h at same temperature. The reaction was quenched by adding with 1 M HCl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 5:1) to give **9** and **14** (35 mg, 70%, 5:1 mixture) as a white solid: Data for **9** (white solid): mp = 84-85 °C; IR (KBr disk, cm^{-1}); 3433, 2955, 1684, 1043, 1006; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.73 (m, 1H), 5.03-5.02 (m, 1H), 4.97-4.93 (m, 1H), 3.73 (dd, *J* = 11.7, 4.8 Hz, 1H), 2.41 (d, *J* = 13.3 Hz, 1H), 2.02 (dd, *J* = 13.7, 2.7 Hz, 1H), 2.02-1.95 (m, 1H), 1.90 (t, *J* = 13.3 Hz, 1H), 1.83-1.58 (m, 4H), 1.15 (s, 3H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 138.2, 114.8, 75.1, 54.1, 50.9, 42.6, 32.03, 31.98, 30.5, 27.8, 26.6, 18.1; HRESI calcd for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1698, found 211.1693.
Data for **14** (colorless oil): IR (neat, cm^{-1}) 3442, 2955, 1697, 1464, 1029, 1000; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (tdd, *J* = 16.9, 10.0, 6.4 Hz, 1H), 5.07-5.01 (m, 1H), 4.97-4.93 (m, 1H), 3.99 (t, *J* = 7.8 Hz, 1H), 2.41 (d, *J* = 14.2 Hz, 1H), 2.09-2.03 (m, 3H), 1.82-1.75 (m, 3H), 1.63-1.55 (m, 2H), 1.11 (s, 3H), 1.07 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 139.1, 114.5, 71.0, 53.4, 50.8, 42.8, 33.7, 32.1, 31.7, 28.7, 27.4, 18.1; HRESI calcd for $C_{13}H_{23}ONa_2$ $[M+Na]^+$ 233.1517, found 233.1510.

(1*S,2*S**,3*S**)-1-Allyl-2-(but-3-en-1-yl)-2,5,5-trimethylcyclohexane-1,3-diol (8)**. To a stirred solution of **9** (66 mg, 0.31 mmol) in Et_2O (3 mL) was added allylmagnesium bromide (1.0 M in Et_2O, 0.75 mL, 0.75 mmol) at –78 °C under Ar. After the reaction mixture was stirred for 4 h at same temperature, the reaction was quenched by adding with NH_4Cl aqueous solution. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 5:1) to afford **8** (55 mg, 70%) as colorless oil and C1- epimer (13 mg, 17%) as colorless oil.
Data for **8**: IR (neat, cm^{-1}); 3456, 2950, 2927, 1638, 1364, 994; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92-5.75 (m, 2H), 5.22-5.19 (m, 1H), 5.14-5.10 (m, 1H), 5.03-4.98 (m, 1H), 4.93-4.91 (m, 1H), 4.08 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.36-2.03 (m, 4H), 1.67 (td, *J* = 14.2, 5.5 Hz), 1.53-1.45 (m, 2H), 1.32-1.17 (m, 3H), 1.09 (s, 6H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 133.9, 120.0, 113.9, 77.7, 72.4, 44.5, 44.4, 42.8, 42.2, 34.2, 31.0, 30.3, 29.8, 29.0, 15.4; HRESI calcd for $C_{16}H_{28}O_2Na$ $[M+Na]^+$ 275.1987, found 275.1979.
Data for C1-epimer: IR (neat, cm^{-1}); 3398, 2950, 1638, 1595, 1246, 994; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96-5.80 (m, 2H), 5.23-5.20 (m, 1H), 5.17-5.10 (m, 1H), 5.05-5.00 (m, 1H), 4.94-4.92 (m, 1H), 4.21 (dd, *J* = 11.9, 4.6 Hz), 2.52-2.42 (m, 1H), 2.37 (dd, *J* = 16.9, 7.8 Hz, 1H), 2.30-1.99 (m, 3H), 1.73-1.40 (m, 5H), 1.29-1.18 (m, 2H), 1.11 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 134.0, 120.1, 113.7, 78.5, 70.2, 46.3, 45.8, 43.8, 42.1, 34.4, 34.3, 31.0, 30.6, 28.7, 15.0; HRESI calcd for $C_{16}H_{28}O_2Na$ $[M+Na]^+$ 275.1987, found 275.1980.

(2*S,3S*)-2-(But-3-en-1-yl)-2,5,5-trimethyl-3-oxocyclohexyl pivalate (15)**. To a stirred solution of **9** (42 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) was added *N*,*N*-diisopropylethylamine (77 mg, 0.10 mL, 0.59 mmol), *N*,*N*-dimethyl-4-aminopyridine (12 mg, 0.10 mmol) and pivaloyl chloride (36 mg, 0.04 mL, 0.30 mmol) at 0 °C under Ar. After the reaction mixture was refluxed for 24 h, to this mixture was added the *N*,*N*-

diisopropylethylamine (77 mg, 0.10 mL, 0.59 mmol), *N*,*N*-dimethyl-4-aminopyridine (12 mg, 0.10 mmol) and pivaloyl chloride (36 mg, 0.04 mL, 0.30 mmol), and the mixture was refluxed for 12 h. To this mixture was added *N*,*N*-diisopropylethylamine (231 mg, 0.30 mL, 1.77 mmol), *N*,*N*-dimethyl-4-aminopyridine (36 mg, 0.30 mmol) and pivaloyl chloride (108 mg, 0.12 mL, 0.90 mmol), and the mixture was refluxed for 3 h. The reaction was quenched by adding with saturated NH_4Cl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 20:1) to give **15** (56 mg, 97%) as a white solid: mp = 70-71 °C; IR (KBr disk, cm^{-1}); 2964, 1730, 1699, 1465, 1366, 1282, 1158; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.73 (m, 1H), 5.03-4.99 (m, 1H), 4.98-4.95 (m, 1H), 4.88 (dd, *J* = 10.6, 5.5 Hz, 1H), 2.38 (d, *J* = 13.7 Hz, 1H), 2.12 (dd, *J* = 13.7, 1H), 2.01-1.76 (m, 4H), 1.71-1.60 (m, 2H), 1.21 (s, 9H), 1.073 (s, 3H), 1.067 (s, 3H), 0.93 (s, 3H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 177.5, 138.0, 114.9, 76.1, 52.5, 51.1, 39.0, 38.9, 32.4, 31.64, 31.59, 27.8, 27.1 (3C), 26.8, 18.4; HRESI calcd for $C_{18}H_{31}O_3$ $[M+H]^+$ 295.2273, found 295.2266.

(1*S,2*S**,3*S**)-3-Allyl-2-(but-3-en-1-yl)-3-hydroxy-2,5,5-trimethylcyclohexyl pivalate (16)**. To a stirred solution of **15** (10.5 mg, 0.036 mmol) in Et_2O (1 mL) was added allylmagnesium bromide (1.0 M in Et_2O, 0.09 mL, 0.09 mmol) at –78 °C under Ar. After the reaction mixture was stirred for 3 h at same temperature, the reaction was quenched by adding with NH_4Cl aqueous solution. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 20:1) to afford **16** (11 mg, 91%) as a white solid: mp = 67-68 °C; IR (KBr disk, cm^{-1}) 3446, 2926, 1704, 1641, 1479, 1363, 1289, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92-5.75 (m, 2H), 5.28 (dd, *J* = 11.4, 4.6 Hz, 1H), 5.20 (dd, *J* = 10.1, 2.3 Hz, 1H), 5.14-5.09 (m, 1H), 5.04-4.99 (m, 1H), 4.95-4.93 (m, 1H), 2.32-2.18 (m, 2H), 2.15-2.05 (m, 1H), 1.70 (td, *J* = 13.7, 5.0 Hz, 1H), 1.55-1.43 (m, 4H), 1.37-1.24 (m, 2H), 1.19 (s, 9H), 1.15 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 139.8, 133.8, 120.0, 114.1, 77.2, 75.1, 44.5, 44.0, 41.7, 39.3, 38.9, 33.7, 31.7, 31.3, 30.9, 30.0, 27.2 (3C), 15.4; HRESI calcd for $C_{21}H_{36}O_3Na$ $[M+Na]^+$ 359.2562, found 359.2564.

(1*S,4a*S**,9a*S**)-3,3,9a-Trimethyl-1,2,3,4,5,8,9,9a-octahydro-4a*H*-benzo[7]annulene-1,4a-diol (7)**. To a stirred solution of **8** (76 mg, 0.30 mmol) in toluene (15 ml) was added Grubbs catalyst second generation (2.6 mg, 3.0 mmol) at room temperature under Ar. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated in vacuo to give the crude products, which were purified by column chromatography on silica gel (hexane/AcOEt, 5:1) to give **7** (65 mg, 96%) as a white solid: mp = 139-140 °C; IR (KBr disk, cm^{-1}) 3418, 2943, 1434, 1342, 1188, 1080, 1036; ^1H NMR (600 MHz, $CDCl_3$) δ 5.87-5.82 (m, 1H), 5.55-5.51 (m, 1H), 4.06 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.74 (d, *J* = 14.8 Hz, 1H), 2.22 (t, *J* = 14.7 Hz, 1H), 2.03-1.97 (m, 1H), 1.94 (d, *J* = 14.7 Hz, 1H), 1.78 (dd, *J* = 13.2, 9.0 Hz, 1H), 1.56-1.43 (m, 4H), 1.20 (s, 3H), 1.14 (s, 3H), 1.04 (d, *J* = 15.1 Hz, 1H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 127.0, 76.8, 72.6, 45.6, 44.7, 42.5, 40.9, 34.4, 31.1, 29.5, 25.7, 22.3, 17.0; HRESI calcd for $C_{14}H_{24}O_2Na$ $[M+Na]^+$ 247.1674, found 247.1683.

(1*S, 4a*S**, 9a*S**)-4a-Hydroxy-3,3,9a-trimethyl-2,3,4,4a,5,8,9,9a-octahadro-1*H*-benzo[7]annulene-1-yl pivalate (17)**. To a stirred solution of **16** (10 mg, 0.03 mmol) in toluene (1.5 ml) was added Grubbs catalyst second generation (0.3 mg, 0.3 mmol) at room temperature under Ar. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated in vacuo to give the crude products, which were purified by column chromatography on silica gel (hexane/AcOEt, 10:1) to give **17** (9.2 mg, 96%) as a white solid: mp = 143-144 °C; IR (KBr disk, cm^{-1}) 3506, 2925, 1707, 1478, 1396, 1364, 1294,1184, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.83 (m, 1H), 5.58-5.52 (m, 1H), 5.26 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.74 (d, *J* = 14.6 Hz, 1H), 2.29-2.22 (m, 1H), 2.04-1.95 (m, 2H), 1.85-1.80 (m, 1H), 1.70-1.44 (m, 5H), 1.21 (s, 3H), 1.19 (s, 9H), 1.11 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 133.7, 127.1, 76.5, 75.3, 45.1, 44.7, 40.7, 39.0, 38.6, 34.2, 31.2, 29.3, 27.4, 27.2 (3C), 22.4, 16.8; HRESI calcd for $C_{19}H_{32}O_3Na$ $[M+Na]^+$ 331.2249, found 331.2248.

(1a*S, 2a*R**, 6*S**, 6a*S**, 8a*R**)-4,4,6a-Trimethyldecahydro-2a*H*-benzo[4,5]cyclohepta[1,2-*b*]oxirene-2a,6-diol (18)**. To a stirred solution of **7** (10 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added 3-chloroperbenzoic acid (12 mg, 0.0 mmol) at 0 °C under Ar. After the reaction mixture was stirred for 7 h at same temperature, the reaction was quenched by adding with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 3:1) to afford **18** (10 mg, 99%) as colorless oil: IR (neat, cm^{-1}); 3456, 2943, 1725, 1472, 1363, 1016, 993; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.07 (td, *J* = 7.3, 4.5 Hz, 1H), 2.85 (td, *J* = 6.8, 4.5 Hz, 1H), 2.18-2.11 (m, 1H), 1.95 (d, *J* = 3.6 Hz, 2H), 1.81 (d, *J* = 14.6 Hz, 1H), 1.58-1.50 (m, 3H), 1.49-1.32 (m, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.7, 72.3, 55.0, 51.0, 45.5, 45.1, 42.4, 41.2, 34.6, 31.2, 29.0, 23.9, 23.8, 17.1; HRESI calcd for $C_{14}H_{24}O_3Na$ $[M+Na]^+$ 263.1623, found 263.1623.

(1a*S, 2a*R**, 6*S**, 6a*S**, 8a*R**)-2a-Hydroxy-4,4,6a-trimethyldecahydro-2*H*-benzo[4,5]cyclopeta[1,2-*b*]oxiren-6-yl pivalate (19)**. To a stirred solution of **17** (114 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) was added 3-chloroperbenzoic acid (96 mg, 0.56 mmol) at 0 °C under Ar. After the reaction mixture was stirred for 7 h at same temperature, the reaction was quenched by adding with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 3:1) to afford **19** (111 mg, 92%) as a white solid: mp = 202-203 °C; IR (KBr disk, cm^{-1}) 3505, 2934, 1707, 1480, 1462, 1294,1185; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (t, 1H, *J* = 8.3 Hz), 3.09 (td, 1H, *J* = 6.9, 4.6 Hz), 2.86 (td, 1H, *J* = 7.3, 4.5 Hz), 2.22-2.11 (m, 1H), 2.02-1.90 (m, 2H), 1.83 (d, 1H, *J* = 14.2 Hz), 1.76-1.70 (m, 1H), 1.62-1.52 (m, 4H), 1.40-1.36 (m, 1H), 1.23 (s, 3H), 1.19 (s, 9H), 0.98 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 77.5, 75.0, 54.9, 50.9, 45.1, 44.9, 41.0, 39.0, 38.6, 34.5, 31.3, 28.7, 27.2 (3C), 25.4, 24.0, 16.8; HRESI calcd for $C_{19}H_{32}O_4Na$ $[M+Na]^+$ 347.2198, found 347.2200.

(1*S, 4a*R**, 6*R**, 7*R**, 9a*S**)-3,3,9a-Trimethyldecahydro-1H-1,6-epoxybenzo[7]annulene-4a,7-diol (20) and (1*S**, 4a*R**, 6*S**, 7*S**, 9a*S**)-3,3,9a-trimethyldecahydro-1H-1,7-epoxybenzo[7]annulene-4a,6-diol (21)**. To a stirred solution of **18** (31 mg, 0.13 mmol) in THF (3 mL) was added *p*-toluenesulfonic acid (12 mg, 0.06 mmol) at room temperature under Ar. After the reaction mixture was stirred for 2 h at same temperature, the reaction was extracted with Et_2O and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 1:2) to afford **20** and **21** (27 mg, 86%, 3:1 mixture) as colorless oil. Data for **20**: IR (neat, cm^{-1}); 3389, 2945, 1469, 1362, 1094, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99-3.96 (m, 1H), 3.90 (ddd, *J* = 8.7, 5.5, 2.7 Hz, 1H), 3.83 (t, *J* = 2.7 Hz, 1H), 2.48 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.14-2.10 (m, 1H), 2.06-1.92 (m, 2H), 1.74-1.65 (m, 2H), 1.55-1.51 (m, 3H), 1.42 (ddd, *J* = 14.6, 11.9, 5.0 Hz, 1H), 1.27 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.7, 74.9, 74.2, 71.2, 52.1, 40.8, 40.2, 36.0, 35.9, 34.3, 31.8, 30.6, 29.3, 22.8; HRESI calcd for $C_{14}H_{24}O_3Na$ $[M+Na]^+$ 263.1623, found 263.1614. Data for **21**: IR (neat, cm^{-1}); 3389, 2930, 2862, 1466, 1086, 1048; ^1H

NMR (400 MHz, $CDCl_3$) δ 4.29 (ddd, *J* = 10.0, 6.8, 3.2 Hz, 1H), 3.85-3.82 (m, 2H), 2.17 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.06-1.90 (m, 3H), 1.83-1.65 (m, 3H), 1.59-1.52 (m, 2H), 1.25-1.19 (m, 1H), 1.23 (s, 3H), 0.97 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8, 74.7, 73.3, 69.5, 51.3, 46.9, 39.1, 38.1, 37.0, 31.8, 30.6, 25.9, 23.7, 18.9; HRESI calcd for $C_{14}H_{24}O_3Na$ $[M+Na]^+$ 263.1623, found 263.1616.

(1*S, 4a*R**, 6*S**, 7*R**, 9a*S**)-6-Hydroxy-3,3,9a-trimethyldecahydro-4a, 7-epoxybenzo[7]annulen-1-yl pivalate (22)**. To a stirred solution of epoxyde **19** (14.2 mg, 0.04 mmol) in THF (2 mL) was added *p*-toluenesulfonic acid (4.2 mg, 0.02 mmol) at room temperature under Ar. After the mixture was refluxed for 6 h, the reaction was quenched by adding with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane-AcOEt, 3:1) to afford **22** (9.9 mg, 76%) as a colorless oil: IR (neat, cm^{-1}) 3424, 2951, 1726, 1477, 1396, 1365, 1283, 1144, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 4.1, 2.3 Hz, 1H), 4.21 (m, 1H), 4.07 (m, 1H), 3.27 (dd, *J* = 14.2, 7.4 Hz, 1H), 2.03-1.94 (m, 2H), 1.86-1.78 (m, 2H), 1.59-1.53 (m, 2H), 1.47-1.36 (m, 2H), 1.24 (s, 9H), 1.16 (s, 3H), 1.08 (s, 3H), 1.06-1.03 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 84.2, 82.9, 77.4, 76.5, 60.3, 47.1, 45.4, 39.3, 37.8, 34.7, 31.4, 29.3, 27.2 (3C), 26.1, 24.3, 20.1; HRESI calcd for $C_{19}H_{32}O_4Na$ $[M+Na]^+$ 347.2198, found 347.2198.

(1*S,4a*R**,7*R**,9a*S**)-3,3,9a-trimethyl-6-oxodecahydro-4a,7-epoxybenzo[7]annulen-1-yl pivalate (23)**. To a stirred solution of alcohol **22** (48 mg, 0.15 mmol) in CH_2Cl_2 (3.7 mL) was added pyridinium chlorochromate (48 mg, 0.22 mmol) at room temperature under Ar. After the mixture was stirred for 8 h at room temperature, the mixture was filtered under vacuo and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 15:1) to afford corresponding ketone (44 mg, 92%) as a white solid. mp = 72-73 °C; IR (KBr disk, cm^{-1}) 2954, 1760, 1725, 1458, 1279, 1137, 1048; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (dd, *J* = 4.1, 2.2 Hz, 1H), 4.03 (d, *J* = 4.1 Hz, 1H), 3.27 (d, *J* = 18.3 Hz, 1H), 2.36 (d, *J* = 17.8 Hz, 1H), 2.12 (tt, *J* = 13.7, 5.5 Hz, 1H), 1.98 (d, *J* = 13.7 Hz, 1H), 1.90 (dd, *J* = 16.0, 4.1 Hz, 1H), 1.73 (td, *J* = 13.7, 5.5 Hz, 1H), 1.62-1.56 (m, 1H), 1.53-1.46 (m, 2H), 1.27 (s, 3H), 1.22 (s, 9H), 1.07 (s, 3H), 1.01 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.3, 177.6, 82.2, 78.2, 77.1, 48.8, 45.7, 39.3, 38.9, 37.9, 34.7, 31.4, 29.6, 27.3 (3C), 26.2, 23.6, 20.5; HRESI calcd for $C_{19}H_{30}O_4Na$ $[M+Na]^+$ 345.2042, found 345.2041.

Pivaloyl protected toxicodenane A (24). To a stirred solution of ketone **23** (7.3 mg, 0.02 mmol) in THF (0.5 mL) was added Tebbe reagent (0.5 M in toluene, 0.025 mmol, 0.05 mL) at 0 °C under Ar. After the reaction mixture was stirred for 2 h at same temperature, the reaction was quenched by adding with 30% NaOH aqueous solution. The mixture was filtered under vacuo and the filtrate was extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 50:1) to give **23** (5.2 mg, 81%) as a white solid. mp = 59-60 °C; IR (KBr disk, cm^{-1}) 2953, 2868, 1726, 1476, 1395, 1366, 1282, 1138, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (br s, 1H), 4.83 (dd, *J* = 4.2, 1.9 Hz, 1H), 4.80 (br s, 1H), 4.49 (br s, 1H), 3.47 (d, *J* = 15.1 Hz, 1H), 2.35 (dt, *J* = 16.5, 2.7 Hz, 1H), 2.12 (tdd, *J* = 12.8, 5.0, 3.2 Hz, 1H), 1.92-1.77 (m, 3H), 1.45 (dt, *J* = 15.6, 1.8 Hz, 1H), 1.40-1.31 (m, 2H), 1.24 (s, 9H), 1.18 (s, 3H), 1.08 (s, 3H), 1.02 (dd, *J* = 13.3, 5.0 Hz, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 152.7, 101.4, 83.0, 79.1, 77.5, 45.1, 43.0, 39.8, 38.9, 38.1, 34.9, 31.4, 29.5, 28.8, 27.3 (3C), 25.8, 21.1; HRESI calcd for $C_{20}H_{32}O_3Na$ $[M+Na]^+$ 343.2249, found 343.2247.

Toxicodenane A (1). To a stirred solution of **24** (8.2 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added diisobutylaluminium hydride (1.0 M in hexane, 0.03 mL, 0.03 mmol) at –78 °C under Ar. After the mixture was stirred for 30 min at –78 °C, the reaction was quenched by adding with 1 M HCl aqueous solution and stirred for 2 h at room temperature. The mixture was extracted with AcOEt and organic layers were combined, washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was dissolved in THF and 1 M HCl aqueous solution was added at 0 °C. After the mixture was stirred for 2 h at room temperature, saturated $NaHCO_3$ aqueous solution was added, and extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (hexane-AcOEt, 15:1) to afforded **1** (6.0 mg, 85%) as a white solid: mp = 151-153 °C; IR (KBr disk, cm^{-1}) 3410 (br), 2955, 2921, 2856, 1668, 1463, 1377, 1173, 1133, 1050, 1034, 1008, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (br s, 1H), 4.79 (br s, 1H), 4.48 (br s, 1H), 3.67 (dd, *J* = 3.6, 2.3 Hz, 1H), 3.62 (d, *J* = 16.9 Hz, 1H), 2.30 (dt, *J* = 16.5, 2.7 Hz, 1H), 2.20-2.08 (m, 2H), 1.89-1.84 (m, 2H), 1.45 (dt, *J* = 15.1, 2.3 Hz, 1H), 1.41-1.37 (m, 1H), 1.30 (d, *J* = 13.3 Hz, 1H), 1.16 (s, 3H), 1.08 (s, 3H), 1.02 (d, *J* = 8.7 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 101.3, 83.4, 79.1, 77.2, 45.4, 43.2, 41.2, 40.1, 35.2, 31.7, 29.9, 28.9, 26.0, 21.1; HRESI calcd for $C_{15}H_{25}O_2$ $[M+H]^+$ 237.1855, found 237.1854.

Supporting Information

(see footnote on the first page of this article): ^{1}H-NMR and ^{13}C-NMR spectra of all compounds are provided in the supporting information.

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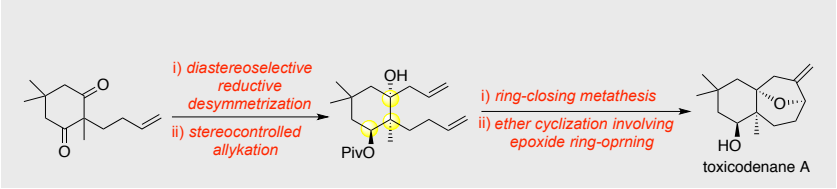

The first total synthesis of toxicodenane A has been accomplished in 12 steps utilizing diastereoselective reductive desymmetrization, stereocontrolled allylation, ring-closing metathesis, and construction of the oxygen-bridged moiety via neighboring group assisted ring-opening reaction of epoxide as key steps.

Total Synthesis

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Diastereoselective Total Synthesis of (±)-Toxicodenane A