Synthetic Studies on Aromadendrane-Type Compounds. II.[1] Stereoselective Synthesis of (+)-1,2-Didehydroaromadendrane

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The reactivity of the tricyclic enone, (+)-(1*S*,2*R*,4*R*,7*R*)-3,3,7-trimethyltricyclo[6.3.0.0^{2,4}]undec-8-en-10-one (1), obtained previously as the key intermediate for the synthesis of compounds bearing the aromadendrane nucleus was investigated, and a natural aromadendrane-type sesquiterpene, (+)-1,2-didehydroaromadendrane (2), was synthesized *via* regio- and stereo-specific introduction of a methyl group at the C-11 position of 1 followed by reductive deoxygenation.

Keywords aromadendrane; (+)-1,2-didehydroaromadendrane; stereoselective synthesis; stereospecific methylation; tricyclo[6.3.0.0^{2,4}]undecane; reductive deoxygenation

In the previous report we described the stereoselective synthesis of a tricyclic enone, (+)-(1*S*,2*R*,4*R*,7*R*)-3,3,7-trimethyltricyclo[6.3.0.0^{2,4}]undec-8-en-10-one (**1**), and its conversion into B/C-*trans* and *cis* compounds corresponding to the aromadendrane and alloaromadendrane nuclei, respectively.[1] As compound **1** already has 14 carbon atoms, one carbon atom is required at the C-11 position for the synthesis of aromadendrane-type sesquiterpenes. In this paper, we report the reactivity of the enolate anion derived from the enone system of **1** and the first total synthesis of the natural product (+)-1,2-didehydroaromadendrane (**2**).[2]

As C-11 of **1** is the α′-position of the enone system, it should be easy to introduce a C-1 unit at this position *via* a kinetic enolate (**A**). The enone **1** was treated with lithium diisopropylamide (LDA) at −78 °C, followed by addition of hexamethylphosphoric triamide (HMPA) and methyl iodide to give the β-methyl compound (**3**) as a sole product in 94% yield. The configuration of the newly introduced methyl group was confirmed by analysis of the 500 MHz ^{1}H-NMR spectrum, including nuclear Overhauser effect (NOE) measurement. The C-1 H signal appeared at 2.15 ppm as a doublet (J=9.8 Hz) coupled only with the C-2 cyclopropyl proton. This shows that the dihedral angle between C-1H and C-11H is 90°. Furthermore, an NOE was observed between C-11H and C-2H. These observations clearly show that the methyl group was introduced stereospecifically from the β-side of the kinetic dienolate (**A**). (Chart 1)

Most natural products with the aromadendrane skeleton have an α-methyl group at C-11.[3] Accordingly, isomerization of the C-11 methyl group of **3** is required for the synthesis of natural products. Treatment of **3** with LDA at −78 °C and addition of 1 eq of *n*-butyllithium (*n*-BuLi),[4] followed by quenching with D_2O gave no deuterated compound, whereas treatment with LDA at −20 °C for 3 h followed by a similar procedure afforded a deuterated compound (**4**: 92% yield), in which the C-11 methyl group was located at the α-position. Namely, the deuterium was introduced exclusively from the β-side of the dienolate (**B**). This result indicates that the isomerization of C-11 β-methyl to α is possible. On the other hand, treatment of **3** with LDA at 0 °C for 5 h followed by similar procedure gave a C-7 deuterated compound (**5**: 88% yield), in which the deuterium is located at the β-position and the C-11 methyl group is α-oriented. This result shows that a kinetic cross-dienolate (**B**) is isomerized to a thermodynamic linear-dienolate (**C**) at 0 °C. At this time, we examined functionalization of the enone **3**. Treatment of the kinetic enolate (**B**) with phenylselenenyl bromide afforded a C-11 β-phenylseleno compound (**6**: 69% yield), while the thermodynamic enolate (**C**) afforded the C-7 β-phenylthio compound (**7**: 71% yield) by reaction with diphenyl disulfide. These

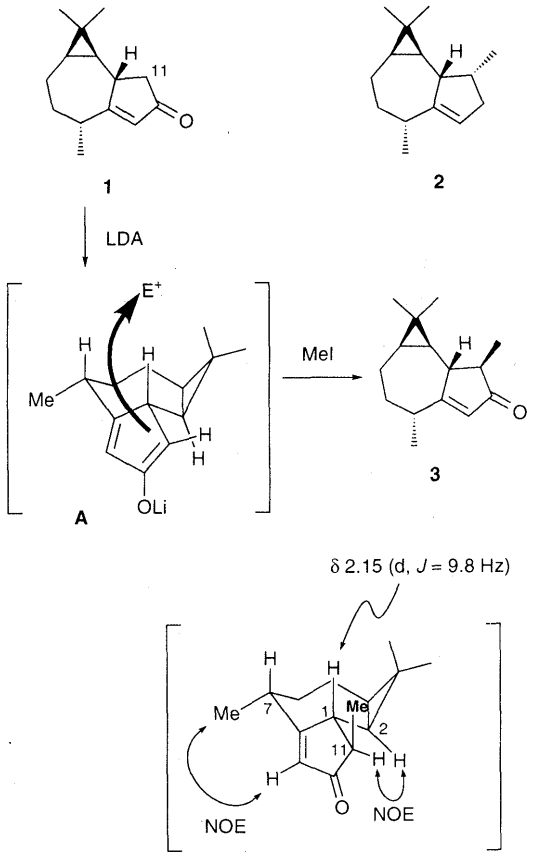

Chart 1

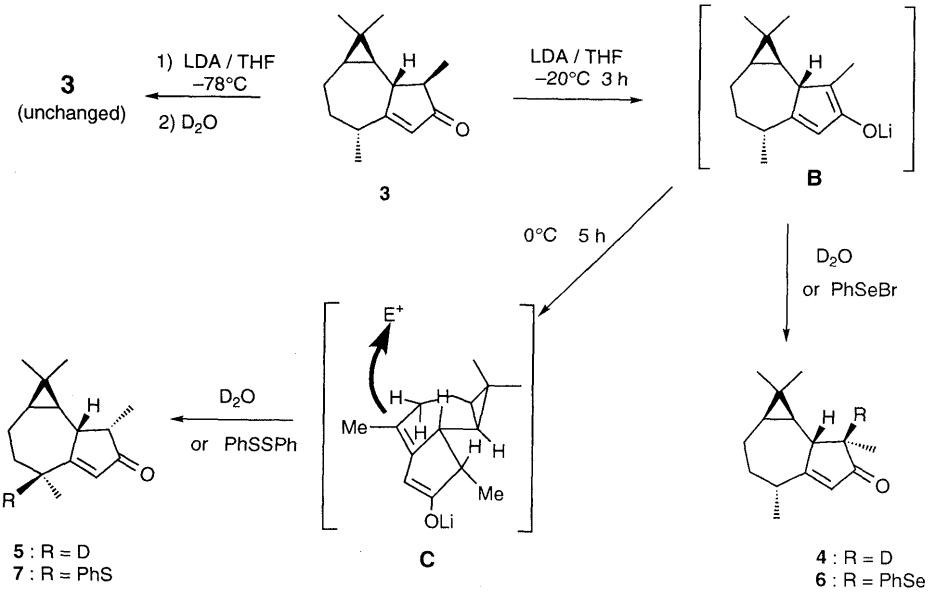

Chart 2

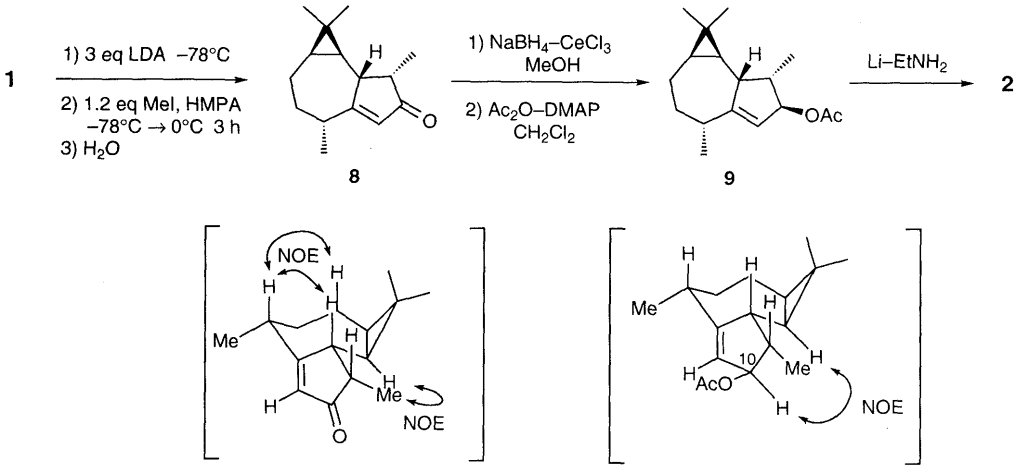

Chart 3 DMAP = 4-dimethylaminopyridine

findings would be useful for the synthetic elaboration of compounds bearing the aromadendrane skeleton.

We next tried one-pot introduction of a methyl group at the C-11 α-position. The enone **1** was treated with 3 eq of LDA at −78 °C followed by the addition of HMPA and MeI at that temperature, then the mixture was warmed to 0 °C and the temperature was maintained at 0 °C for 3 h. Quenching of the mixture with water afforded a C-11 α-methyl compound (**8**) in 78% yield. Reductive deoxygenation of the C-10 carbonyl group of **8** would lead to the natural product, (+)-1,2-didehydroaromadendrane (**2**), isolated by Friedel and Matusch.[2] The enone **8** was converted to an allylic acetate **9** by the reduction with the sodium borohydride–cerium trichloride system[5] followed by acetylation in 96% yield. Reductive deoxygenation[6] of **9** with lithium in ethylamine at 0 °C afforded (+)-1,2-didehydroaromadendrane (**2**: 96% yield), the spectral data and $[\alpha]_D$ value of which were identical with the reported data.

As described above, enolate anion formation from the tricyclic enone (**1** or **3**) could be controlled by varying the reaction temperature, and the first total synthesis of (+)-1,2-didehydroaromadendrane (**2**) was accomplished by a four-step sequence from **1**.

Experimental

Optical rotations were recorded with a JASCO DIP-360 polarimeter. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-GX-500 (500 MHz) instrument. The chemical shifts are given as δ (ppm) values with tetramethylsilane (TMS) or chloroform in deuteriochloroform as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a Shimadzu QP-1000 or a JEOL JMS D-300 mass spectrometer. For column chromatography, Kieselgel 60 (E. Merck) was used. All organic extracts were dried over anhydrous $MgSO_4$ before evaporation.

(+)-(1*R*,2*R*,4*R*,7*R*,11*R*)-3,3,7,11-Tetramethyltricyclo[6.3.0.0^{2,4}]-undec-8-en-10-one (3) A solution of the enone **1** (97.3 mg, 0.477 mmol) in tetrahydrofuran (THF) (0.5 ml) was added at −78 °C to an LDA solution [prepared from iso-Pr_2NH (0.08 ml, 0.572 mmol) in THF (2 ml) and *n*-BuLi (1.6 M in hexane, 0.34 ml, 0.572 mmol) at −20 °C], and the mixture was stirred for 30 min. Then HMPA (0.2 ml) was added, and stirring was continued for 15 min. After the addition of MeI (0.034 ml, 0.572 mmol) at −78 °C, the resulting mixture was allowed to warm to room temperature. Saturated NH_4Cl solution was added, and the whole

was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **3** (97.7 mg, 94%) as a colorless oil, $[\alpha]_D^{23}$ +84.8° (*c* = 0.40, $CHCl_3$). IR ($CHCl_3$): 1698, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.26 (1H, dd, *J* = 9.1, 9.8 Hz, C-2H), 0.68 (1H, ddd, *J* = 6.1, 9.1, 11.6 Hz, C-4H), 1.00—1.31 (1H, m, C-5βH), 1.05, 1.11 (each 3H, s, C-3Me), 1.14 (3H, d, *J* = 7.3 Hz, C-11Me), 1.25 (3H, d, *J* = 6.7 Hz, C-7Me), 1.37 (1H, m, C-6αH), 1.96 (1H, m, C-6βH), 2.03 (1H, m, C-5αH), 2.15 (1H, d, *J* = 9.8 Hz, C-1H), 2.19—2.33 (1H, m, C-7H), 2.24 (1H, m, C-11H), 5.77 (1H, s, C-9H). MS *m/z*: 218 (M^+, 100). HRMS Calcd for $C_{15}H_{22}O$: 218.1672. Found: 218.1675.

(+)-(1*R*,2*R*,4*R*,7*R*,11*S*)-11-Deuterio-3,3,7,11-tetramethyltricyclo-[6.3.0.0^{2,4}]undec-8-en-10-one (4) A solution of **3** (26.6 mg, 0.122 mmol) in THF (0.5 ml) was added at −78 °C to an LDA solution [prepared from iso-Pr_2NH (0.018 ml, 0.134 mmol) in THF (1 ml) and *n*-BuLi (1.6 M in hexane, 0.084 ml, 0.134 mmol) at −20 °C], and the mixture was warmed to −20 °C. The temperature was maintained at this temperature for 3 h, then *n*-BuLi (0.08 ml, 0.122 mmol) was added and the resulting mixture was stirred for 20 min. To this mixture was added D_2O (1 ml) at −20 °C and the whole was warmed to room temperature, then extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **4** (24.5 mg, 92%) as a colorless oil. IR ($CHCl_3$): 1695, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (1H, dd, *J* = 9.2, 10.6 Hz, C-2H), 0.67 (1H, ddd, *J* = 6.1, 9.2, 11.7 Hz, C-4H), 1.03, 1.07 (each 3H, s, C-3Me), 1.11 (3H, s, C-11Me), 1.22 (3H, d, *J* = 6.7 Hz, C-7Me), 2.32 (1H, m, C-7H), 2.58 (1H, d, *J* = 10.2 Hz, C-1H), 5.79 (1H, s, C-9H). MS *m/z*: 219 (M^+, 12), 176 (100). HRMS Calcd for $C_{15}H_{21}DO$: 219.1734. Found: 219.1717.

(+)-(1*R*,2*R*,4*R*,7*R*,11*S*)-7-Deuterio-3,3,7,11-tetramethyltricyclo-[6.3.0.0^{2,4}]undec-8-en-10-one (5) A solution of **3** (34.7 mg, 0.170 mmol) in THF (0.5 ml) was added at −78 °C to an LDA solution [prepared from iso-Pr_2NH (0.026 ml, 0.204 mmol) in THF (1 ml) and *n*-BuLi (1.6 M in hexane, 0.128 ml, 0.204 mmol) at −20 °C], and the mixture was warmed to 0 °C. The temperature was maintained at this value for 5 h, then *n*-BuLi (0.11 ml, 0.170 mmol) was added to the mixture and the whole was stirred for 20 min. Then D_2O (1 ml) was added at 0 °C and the reaction mixture was warmed to room temperature and extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **5** (31.3 mg, 88%) as a colorless oil. IR ($CHCl_3$): 1695, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (1H, dd, *J* = 9.2, 10.6 Hz, C-2H), 0.67 (1H, ddd, *J* = 6.1, 9.2, 11.7 Hz, C-4H), 1.04, 1.08 (each 3H, s, C-3Me), 1.12 (3H, s, C-7Me), 1.23 (3H, d, *J* = 6.7 Hz, C-11Me), 5.80 (1H, s, C-9H). MS *m/z*: 219 (M^+, 41), 176 (100).

(+)-(1*S*,2*R*,4*R*,7*S*,11*R*)-11-Phenylseleno-3,3,7,11-tetramethyltricyclo-[6.3.0.0^{2,4}]undec-8-en-10-one (6) A solution of **3** (253 mg, 1.16 mmol) in THF (1.5 ml) was added at −78 °C to an LDA solution [prepared from iso-Pr_2NH (0.25 ml, 1.74 mmol) in THF (6 ml) and *n*-BuLi (1.6 M in hexane, 1.09 ml, 1.74 mmol) at −20 °C], and the mixture was stirred for 3 h at −20 °C and then cooled to −78 °C. Phenylselenenyl bromide (274 mg, 1.16 mmol) in THF (1.5 ml) was added all at once, and the reaction mixture was stirred for 5 min, then warmed to room temperature. Saturated NH_4Cl solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 15 : 1) to give **6** (299 mg, 69%) as a colorless oil, $[\alpha]_D^{23}$ +86.6° (*c* = 1.90, $CHCl_3$). IR ($CHCl_3$): 1680, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (1H, dd, *J* = 9.2, 9.2 Hz, C-2H), 0.65 (1H, ddd, *J* = 6.0, 9.2, 11.6 Hz, C-4H), 0.99 (3H, d, *J* = 6.7 Hz, C-7Me), 1.02, 1.03 (each 3H, s, C-3Me), 1.51 (3H, s, C-11Me), 2.52 (1H, d, *J* = 9.8 Hz, C-1H), 5.64 (1H, s, C-9H), 7.25—7.53 (5H, m, Ph). MS *m/z*: 374 (M^+, 10), 218 (100). HRMS Calcd for $C_{21}H_{26}OSe$: 374.1150. Found: 374.1128.

(−)-(1*R*,2*R*,4*R*,7*S*,11*S*)-7-Phenylthio-3,3,7,11-tetramethyltricyclo-[6.3.0.0^{2,4}]undec-8-en-10-one (7) A solution of **3** (536 mg, 2.46 mmol) in THF (3 ml) was added at −20 °C to an LDA solution [prepared from iso-Pr_2NH (0.52 ml, 3.69 mmol) in THF (20 ml) and *n*-BuLi (1.6 M in hexane, 2.30 ml, 3.69 mmol) at −20 °C], and the mixture was stirred for 5 h at 0 °C. Then diphenyl disulfide (536 mg, 2.46 mmol) in THF (3 ml) was added, and the mixture was stirred for 3 h at room temperature. Saturated NH_4Cl solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 15 : 1) to give **7** (569 mg, 71%) as a colorless oil, $[\alpha]_D^{26}$ −79.7° (*c* = 1.19, $CHCl_3$). IR ($CHCl_3$): 1685, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (1H, dd, *J* = 9.2, 10.4 Hz, C-2H), 0.71 (1H, ddd, *J* = 6.0, 9.2, 11.3 Hz, C-4H), 1.05, 1.18 (each 3H, s, C-3Me), 1.14 (3H, d, *J* = 7.3 Hz, C-11Me), 1.46 (3H, s, C-7Me), 2.56 (1H, m, C-11H), 3.30 (1H, dd, *J* = 6.7, 10.4 Hz, C-1H), 5.39 (1H, s, C-9H), 7.24—7.34 (5H, m, Ph). MS *m/z*: 326 (M^+, 10), 217 (100). HRMS Calcd for $C_{21}H_{26}OS$: 326.1706 Found: 326.1696.

(+)-(1*R*,2*R*,4*R*,7*R*,11*S*)-3,3,7,11-Tetramethyltricyclo[6.3.0.0^{2,4}]-undec-8-en-10-one (8) A solution of **1** (29.4 mg, 0.144 mmol) in THF (0.5 ml) was added at −78 °C to an LDA solution [prepared from iso-Pr_2NH (0.060 ml, 0.432 mmol) in THF (1 ml) and *n*-BuLi (1.6 M in hexane, 0.27 ml, 0.432 mmol) at −20 °C], and the mixture was stirred for 30 min at −78 °C. After the addition of MeI (0.011 ml, 0.173 mmol), the mixture was gradually warmed up to 0 °C, and stirring was continued for 3 h at that temperature. Saturated NH_4Cl solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **8** (24.5 mg, 78%) as a colorless oil, $[\alpha]_D^{24}$ +73.8° (*c* = 0.55, $CHCl_3$). IR ($CHCl_3$): 1695 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (1H, dd, *J* = 9.2, 10.6 Hz, C-2H), 0.67 (1H, ddd, *J* = 6.1, 9.2, 11.7 Hz, C-4H), 1.04, 1.08 (each 3H, s, C-3Me), 1.12 (3H, d, *J* = 6.7 Hz, C-11Me), 1.23 (3H, d, *J* = 6.7 Hz, C-7Me), 2.32 (1H, m, C-7 H), 2.52—2.67 (2H, m, C-1H and C-11H), 5.80 (1H, s, C-9H). MS *m/z*: 218 (M^+, 11), 175 (100). HRMS Calcd for $C_{15}H_{22}O$: 218.1672. Found: 218.1661.

(+)-(1*R*,2*R*,4*R*,7*R*,10*R*,11*S*)-10-Acetoxy-3,3,7,11-tetramethyltricyclo-[6.3.0.0^{2,4}]undec-8-ene (9) Sodium borohydride (5.9 mg, 0.156 mmol) was added at 0 °C to a solution of **8** (34 mg, 0.156 mmol) and $CeCl_3 \cdot 7H_2O$ (58.1 mg, 0.156 mmol) in MeOH (2 ml), and the mixture was stirred for 30 min. Saturated $NaHCO_3$ solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give an allylic alcohol, (+)-(1*R*,2*R*,4*R*,7*R*,10*R*,11*S*)-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]-undec-8-en-10-ol, (33.6 mg, 98%) as a colorless oil, $[\alpha]_D^{24}$ +81.6° (*c* = 0.26, $CHCl_3$). IR ($CHCl_3$): 3560, 3275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.25 (1H, dd, *J* = 9.7, 9.8 Hz, C-2H), 0.55 (1H, m, C-4H), 1.03 (6H, s, C-3Me × 2), 1.13 (3H, d, *J* = 6.7 Hz, C-7Me), 1.15 (3H, d, *J* = 6.7 Hz, C-11Me), 2.00—2.14 (1H, m, C-7H), 2.23 (1H, dd, *J* = 7.4, 9.8 Hz, C-1H), 4.52 (1H, d, *J* = 7.3 Hz, C-10H), 5.32 (1H, s, C-9H). MS *m/z*: 220 (M^+, 15), 58 (100). HRMS Calcd for $C_{15}H_{24}O$: 220.1828. Found: 220.1825. Acetic anhydride (0.0086 ml, 0.091 mmol) was added at 0 °C to a solution of the allylic alcohol (10 mg, 0.046 mmol) and dimethylaminopyridine (11.1 mg, 0.091 mmol) in CH_2Cl_2 (1 ml), and the mixture was stirred for 2 h. Water (1 ml) was added and the whole was extracted with $CHCl_3$. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **9** (11.8 mg, 98%) as a colorless oil, $[\alpha]_D^{25}$ +150.8° (*c* = 0.43, $CHCl_3$). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.27 (1H, dd, *J* = 7.3, 10.4 Hz, C-2H), 0.54 (1H, m, C-4H), 1.02 (6H, s, C-3Me × 2), 1.09 (3H, d, *J* = 6.7 Hz, C-11Me), 1.11 (3H, d, *J* = 6.7 Hz, C-7Me), 1.86 (1H, m, C-6βH), 1.91 (1H, m, C-5αH), 2.07 (3H, s, CH_3CO), 2.24 (1H, dd, *J* = 7.3, 10.4 Hz, C-1H), 2.31 (1H, m, C-11H), 5.30 (1H, s, C-9H), 5.50 (1H, d, *J* = 7.9 Hz, C-10H). MS *m/z*: 262 (M^+, 5), 159 (100). HRMS Calcd for $C_{17}H_{26}O_2$: 262.1934. Found: 262.1936.

(+)-(1*R*,2*R*,4*R*,7*R*,11*R*)-3,3,7,11-Tetramethyltricyclo[6.3.0.0^{2,4}]-undec-8-ene [(+)-1,2-Didehydroaromadendrane] (2) Li (1.0 mg, 0.143 mg-atom) was added to $EtNH_2$ (20 ml) at 0 °C, and the mixture was stirred for 5 min. To the resulting mixture was added **9** (5.2 mg, 0.0198 mmol) in THF (0.1 ml), and the reaction mixture was refluxed for 30 min. The $EtNH_2$ was allowed to evaporate off at room temperature, then water (2 ml) was added to the residue, and the whole was extracted with hexane. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-pentane) to give **2** (3.9 mg, 96%) as a colorless oil, $[\alpha]_D^{21}$ +41.0° (*c* = 0.23, pentane) [lit.[2] +42.0° (*c* = 0.2)]. IR ($CHCl_3$): 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.45 (1H, dd, *J* = 9.2, 9.8 Hz, C-2H), 0.52 (1H, ddd, *J* = 5.5, 9.2, 11.3 Hz, C-4H), 1.01, 1.02 (each 3H, s, C-3Me), 1.09 (3H, d, *J* = 7.3 Hz, C-11Me), 1.16 (3H, d, *J* = 6.7 Hz, C-7Me), 1.70 (1H, m, C-6βH), 1.87 (1H, m, C-5αH), 2.27 (1H, m, C-10βH), 2.42 (1H, m, C-11H), 5.34 (1H, d, *J* = 1.2 Hz, C-9H). MS *m/z*: 204 (M^+, 57), 161 (100). HRMS Calcd for $C_{15}H_{24}$: 204.1879. Found: 204.1865.

References

1) Part I: T. Tanaka, Y. Funakoshi, K. Uenaka, K. Maeda, H. Mikamiyama, Y. Takemoto, N. Maezaki, C. Iwata, *Chem. Pharm. Bull.*, **42**, 300 (1994).
2) H. D. Friedel, R. Matusch, *Helv. Chim. Acta*, **70**, 1753 (1987).
3) For example, see: L. Dolejš, O. Motl, M. Šoucek, V. Herout, F. Šorm, *Collect. Czech. Chem. Commun.*, **25**, 1483 (1960); H. Becker, J. Reichling, W. C. Hsieh, *J. Chromatogr.*, **237**, 307 (1982); E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, D. Sica, *Tetrahedron*, **30**, 3911 (1974); *idem*, *ibid.*, **31**, 269 (1975); P. Ciminiello, E. Fattorusso, S. Magno, L. Mayol, *Can. J. Chem.*, **65**, 518 (1987); L. Dolejš, V. Herout, F. Šorm, *Collect. Czech. Chem. Commun.*, **26**, 811 (1961); C. Pizza, N. De Tommasi, *Phytochemistry*, **27**, 2205 (1988).
4) T. Laube, J. D. Dunitz, D. Seebach, *Helv. Chim. Acta*, **68**, 1373 (1985).
5) J.-L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978); J.-L. Luche, L. Rodriquez-Hahn, P. Crabbe, *J. Chem. Soc., Chem. Commun.*, **1978**, 601.
6) A. S. Hallsworth, H. B. Henbest, T. I. Wrigley, *J. Chem. Soc.*, **1957**, 1969.