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Asymmetric synthesis of abietane diterpenoids via *B*-alkyl Suzuki–Miyaura coupling. Formal total asymmetric synthesis of 12-deoxyroyleanone and cryptoquinone

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Abstract—A convergent synthetic strategy for abietane diterpenoids via *B*-alkyl Suzuki–Miyaura coupling and Lewis acid-mediated cyclization reactions is established. Asymmetric total synthesis of 12-deoxyroyleanone, an antileishmanial diterpene, is described.

1. Introduction

Abietane diterpenoids are widely distributed in nature, and many of them are found as biologically active natural products. Due to their interesting biological activities and relatively simple structures, abietane diterpenoids are good synthetic targets and many synthetic studies have been reported.[1] One classical methodology for the construction of the tricyclic skeleton is an acid-promoted B-ring closure by intramolecular Friedel–Crafts alkylation between C-9 and C-10 (Fig. 1). Since the applied acids were such strong acids as H_2SO_4,[2] P_2O_5,[3] or $AlCl_3$,[4] which often cause drastic rearrangement of the resulting carbocation intermediate, the yield of the B-ring closure was relatively low. Furthermore, since the rearrangement of the carbocation from C-10 to C-5 destroys the asymmetric center, this strategy has been avoided for enantioselective synthesis. In 2001, Yamamoto and co-workers reported Lewis acid-assisted chiral Brønsted acid-catalyzed enantioselective biomimetic cyclization of homo(polyprenyl)arenes (Fig. 1).[5] The products, obtained in good yields and moderate enantiomeric purities, are useful intermediates for various diterpenoid synthesis. But the main product was partially cyclized, a bicyclic compound with about 10% of the target tricyclic compound. They also reported Lewis acid-promoted B-ring closure of the bicyclic product without loss of the enantiomeric purity by using $BF_3 \cdot OEt_2$ in $MeNO_2$. Originally, the effectiveness of gaseous BF_3 in $MeNO_2$ to promote cationic cyclization reaction was reported by Harring and Livinghouse in 1994.[6] They also reported that $BF_3 \cdot OEt_2$ in $MeNO_2$ is equally effective in the total synthesis of (±)-taxodione via the biomimetic cationic cyclization. Although the reason for the effectiveness is not clear, the combination of BF_3 with $MeNO_2$ as the solvent is advantageous in terms of yield and seems to avoid a rearrangement of the carbocation intermediate than any other Lewis acids.

Recently we reported the synthesis of antifungal meroterpenoids, cordiaquinones J[7,8] and K,[8] via *B*-alkyl Suzuki–Miyaura coupling[9] as a key step. This synthetic methodology requires an easily available chiral homocyclogeranyl

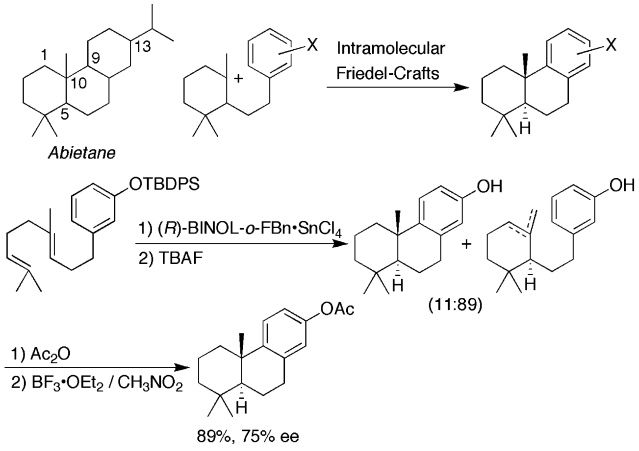

Figure 1. General synthetic method for abietane diterpenes and the Lewis acid-assisted chiral Brønsted acid-catalyzed enantioselective biomimetic cyclization of homo(polyprenyl)arenes reported by Yamamoto.

Keywords: Abietane diterpenes; *B*-Alkyl Suzuki–Miyaura coupling reaction; 12-Deoxyroyleanone; Cryptoquinone.
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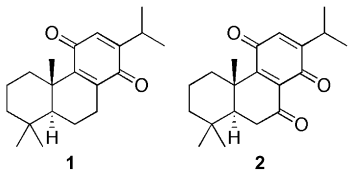
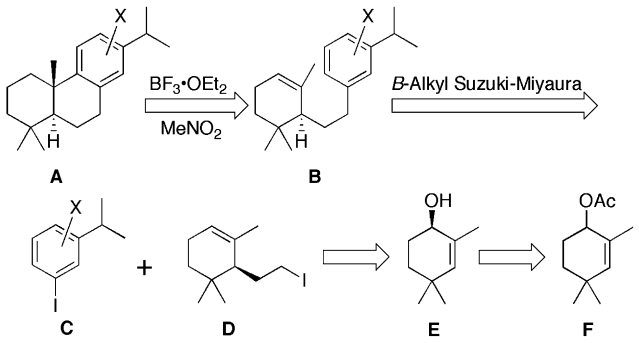


Figure 2. Structures of 12-deoxyroyleanone and cryptoquinone.

fragment and an aryl fragment, and it is possible to provide various synthetic intermediates of biologically active terpenoids by a slight modification of either/both of the fragment(s). So we became interested in applying the methodology to the synthesis of tricyclic terpenoids. To demonstrate the versatility of the methodology, the biologically active abietane diterpenoids, 12-deoxyroyleanone (**1**) and cryptoquinone (**2**), were selected as the synthetic targets. 12-Deoxyroyleanone (**1**) with antileishmanial activity was isolated from the root extracts of the Lamiaceae plant, *Salvia cilicica* Boiss and Kotschy, by Kolodziej et al.,[10] and cryptoquinone (**2**) with antifungal and cytotoxic activities was isolated from the bark of the Sugi plant, *Cryptomeria japonica* D. Don, by Kofujita et al.[11] (Fig. 2). Although synthetic studies toward these two biologically active diterpenes have been reported by Alvarez-Manzaneda[12] and Matsushita,[13] respectively, their methods were partial syntheses starting from naturally occurring abietic acid or dehydroabietic acid. This paper describes asymmetric formal total synthesis of 12-deoxyroyleanone and cryptoquinone via *B*-alkyl Suzuki–Miyaura coupling followed by $BF_3 \cdot OEt_2$ in $MeNO_2$-promoted cationic B-ring formation. The ^{13}C NMR assignments of a synthetic intermediate of **1** are also discussed.

2. Results and discussion

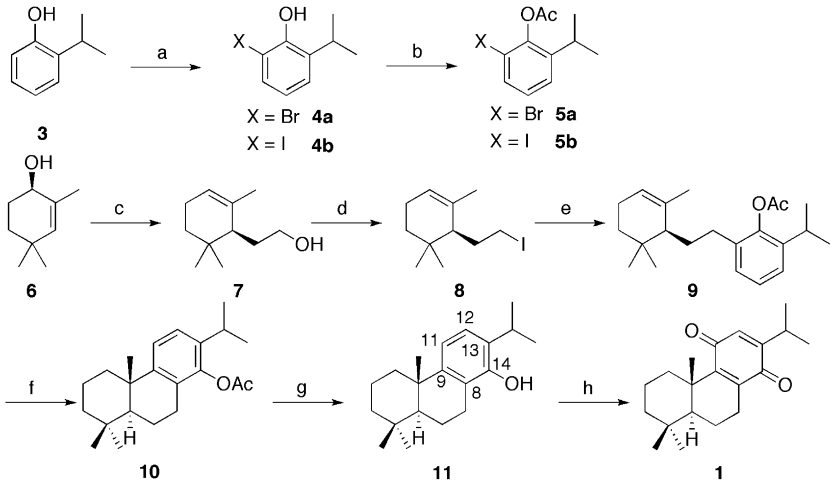
Our synthetic strategy for the synthesis of abietane diterpenes is shown in Scheme 1. $BF_3 \cdot OEt_2$ in $MeNO_2$-promoted B-ring closure of **B** between C-9 and C-10 directly gave the abietane skeleton **A**. The *B*-alkyl Suzuki–Miyaura coupling reaction of the aryl fragment **C** and the optically active fragment **D** gave the intermediate **B**. This methodology would be useful for the synthesis of not only abietane diterpenoids but also various tricyclic terpenoids because it is easy to modify the functionalities and positions of the functionalities of the fragments. Optically active β-cyclohomogeranyl fragment **D** could be derived from known[14] alcohol **E**, obtained by the



Scheme 1. Retrosynthetic analyses of abietane diterpenes.

enzymatic enantioselective hydrolysis of the corresponding acetate. Because both of the enantiomers of **E** are available, this strategy would be useful for the enantioselective synthesis of various tricyclic diterpenes.

Scheme 2 summarizes our asymmetric synthesis of 12-deoxyroyleanone (**1**) and cryptoquinone (**2**). According to Meyers' method,[15] the regioselective bromination of commercially available 2-isopropylphenol (**3**) with *N*-bromosuccinimide (NBS) at room temperature gave **4a** in good yield. In the same manner, **3** was treated with *N*-iodosuccinimide (NIS) to give iodide **4b** in only 16% yield with 40–50% of the starting material recovery. At lower temperature, the yield of iodide was slightly improved but the formation of the 4-iodo-isomer was observed. The halogenated phenol derivatives were converted to the corresponding acetates (**5a** and **5b**). According to Mori's method,[14] the optically active alcohol **7** was prepared in the reported manner (90% ee). Alcohol **7** was halogenated in two steps to give optically active β-cyclohomogeranyl iodide[16] [(*S*)-**8**]. To connect (*S*)-β-cyclohomogeranyl iodide (**8**) and the phenol derivatives, one-pot *B*-alkyl Suzuki–Miyaura coupling reaction was undertaken under the established conditions.[7,8] The reaction with bromide **5a** gave a complex mixture and the desired coupling product (**9**) was isolated in <10% yield. But, with iodide **5b**, the reaction proceeded smoothly to give the coupling product (**9**) in 76% yield. The other key reaction of this synthesis, $BF_3 \cdot OEt_2$ in CH_3NO_2-promoted cationic cyclization without loss of the enantiomerical purity, was attempted with **9** to obtain the tricyclic compound (**10**). The mild exothermic reaction was observed and the desired product was obtained in 91% yield. The enantiomeric purity of **10** was estimated to be 87–88% ee by the HPLC analysis (Daicel CHIRALPAK IA, hexane/EtOAc=30:1, flow rate: 0.3 ml/min, at 0 °C). This result indicates that the racemization at the next position (C-5) of the resulting carbocation (C-9) is almost suppressed (1–1.5%). Fortunately, enantiomerically pure (>99% ee by HPLC analysis) **10** was obtained by simple recrystallization. Deacetylation of **10** gave the known compound **11**,[17] the common synthetic intermediate of 12-deoxyroyleanone (**1**) and cryptoquinone (**2**) in Alvarez-Manzaneda's and Matsushita's syntheses.[12,13] The physical properties, NMR spectra, and $[\alpha]_D$, of our synthetic **11** were compared with the reported data. Although ^1H and ^{13}C NMR spectra of our synthetic **11** and those reported by Matsushita were in good accord, we found that the reported ^1H and ^{13}C NMR data of compound **11** by Alvarez-Manzaneda and Matsushita were different. The selected chemical shifts of **11** reported by Alvarez-Manzaneda and Matsushita and our synthetic **11** are shown in Table 1. Obviously, the observed ^{13}C NMR spectrum of our synthetic **11** agrees with Matsushita's data but does not agree with Alvarez-Manzaneda's data. Our synthetic **11** shows $[\alpha]_D$ +27.9 (*c* 0.96, $CHCl_3$), and Matsushita's **11** was reported to show $[\alpha]_D$ +52.9 (*c* 0.507, $CHCl_3$).[13a] Since the $[\alpha]_D$ value of Alvarez-Manzaneda's **11** was not reported, a strict comparison of the $[\alpha]_D$ values is difficult. Our synthetic **11** is proved to be enantiomerically pure by the HPLC analysis of the precursor **10**, and Matsushita synthesized **11** from naturally occurring dehydroabietic acid. The phenomenon might arise from air oxidation of phenolic hydroxy group. In any case the reason for the disagreement is obscure. We turned to attempt further transformation with **11** to



Scheme 2. Synthesis of 12-deoxyroyleanone (**1**). Reagents, conditions, and yields: (a) for **4a**:[15] NBS, CS_2, rt (85%), for **4b**: NIS, CS_2, rt (16%, 32% based on recovered starting material); (b) Ac_2O, Py (95% for **5a**, 98% for **5b**); (c) lit.[16] (i) $MeC(OEt)_3$, EtCOOH, 140 °C (76%); (ii) LAH, ether (91%); (d) (i) TsCl, Py; (ii) NaI, acetone (66% in two steps); (e) (i) *t*-BuLi, ether, −78 °C; (ii) *B*-MeO-9-BBN, hexane, THF; (iii) 3 M K_3PO_4; (iv) $Pd(PPh_3)_4$, **5b**, DMF, 80 °C (76%); (f) (i) $BF_3{\cdot}OEt_2$, $MeNO_2$ (91%); (ii) recrystallization from MeOH (78%); (g) K_2CO_3, MeOH (94%); (h) CAN, MeCN, THF, H_2O (68%).

Table 1. ^{13}C NMR chemical shifts of **10**

Carbon number	This work[a] (ppm)	Matsushita[b] (ppm)	Alvarez-Manzaneda[c] (ppm)
8	123.20	123.24	130.9
9	149.04	149.05	149.1
11	116.34	116.38	116.5
12	120.55	120.62	123.3
13	129.88	129.96	130.9
14	150.16	150.20	150.3

[a] 100 MHz.
[b] 63 MHz.
[c] 75 MHz.

12-deoxyroyleanone (**1**). Although the details of the reaction condition were not reported, phenol derivative **11** was treated with excess amount of potassium nitrosodisulfonate (Fremy's salt) in MeOH according to Alvarez-Manzaneda's procedure. But we could not obtain 12-deoxyroyleanone (**1**), and no reaction was observed. We suspected that this might be due to the low solubility of Fremy's salt in MeOH. Heating the reaction mixture and addition of water as a co-solvent were undertaken but in vain. On the other hand, Matsushita's procedure of the oxidation of **11** with H_2O_2 catalyzed by $RuCl_3$ succeeded in giving 12-deoxyroyleanone (**1**) in 73% yield. An alternative procedure to oxidize **11** with ceric ammonium nitrate (CAN) gave **1** in 68% yield. The spectroscopic data of synthetic **1** are in perfect accordance with those of the natural product. Since the conversion of 12-deoxyroyleanone (**1**) to cryptoquinone (**2**) was reported by Matsushita, this synthesis is also a formal asymmetric total synthesis of **2**.

3. Conclusion

A simple and versatile methodology for enantioselective synthesis of tricyclic abietane diterpenoid was established by using one-pot *B*-alkyl Suzuki–Miyaura coupling reaction and $BF_3{\cdot}OEt_2$ in $MeNO_2$-promoted cationic cyclization. With this synthetic sequence, formal total asymmetric synthesis of an antileishmanial diterpene, 12-deoxyroyleanone (**1**), and an antifungal/cytotoxic diterpene, cryptoquinone (**2**), was achieved. Disagreements of the physical and chemical properties of the synthetic intermediate (**11**) between our synthetic product and the reported data were observed. The reason for the disagreement is obscure, but since the conversion of synthetic **11** to 12-deoxyroyleanone (**1**) was successful, the structure of our synthetic **11** should be correct. This established synthetic methodology would be a novel methodology of asymmetric synthesis of tricyclic diterpenes.

4. Experimental

4.1. General

Optical rotations were measured on a Jasco DIP-140. IR spectra were measured for samples as films for oils or as KBr plates for solids on a Jasco IR-4100 spectrometer. ^1H NMR spectra were taken with Jeol JNM-A400 (400 MHz) spectrometer using TMS at δ=0.00 as an internal standard. ^{13}C NMR spectra were taken with Jeol JNM-A400 (100 MHz) spectrometer using $CDCl_3$ at δ=77.0 as an internal standard. Elemental compositions were analyzed on a J-Science MICROCORDER JM10. HPLC analyses were performed with Jasco 880-PU as a pump and UV-2075 as a detector. Column chromatography was performed with silica gel Wakogel-C200.

4.1.1. 2-Iodo-6-isopropylphenol (4b). To a solution of **3** (1.00 g, 7.35 mmol) in CS_2 (20 ml), NIS (1.65 g, 7.35 mmol) was added at room temperature. After stirring overnight, the solvent was concentrated in vacuo and the residue was dissolved in ether. The organic layer was washed with 10% aq $Na_2S_2O_3$ and brine, and dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/EtOAc=60:1) to afford 300 mg (16%) of **4b** as a colorless oil. IR (film) ν_{max} (cm^{-1})=3490 (m, O–H), 2960, 2920, 2865 (m, C–H), 1590 (m), 1470 (s), 1435 (s), 1325 (s), 1235 (s), 1205 (s),

1175 (s), 1150 (s), 895 (s), 825 (s), 770 (s), 550 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (d, J=6.8 Hz, 6H, 2×CH_3), 3.31 (sep, J=6.8 Hz, 1H, CH–Ar), 5.29 (s, 1H, H–O), 6.66 (dd, J=8.0, 8.0 Hz, 1H, 4-H), 7.16 (d, J=8.0 Hz, 1H, 5-H), 7.49 (dd, J=1.6, 8.0 Hz, 1H, 3-H). This compound was immediately used in the next step without further purification.

4.1.2. Acetylation of 4a and 4b. To a stirred solution of **4a** or **4b** in dry pyridine was added dropwise acetic anhydride (1.2 equiv). After stirring for 1 h, the mixture was diluted with ether. The organic layer was washed with dil HCl, water and brine, and the organic layer was dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/EtOAc=100:1) to afford **5a** or **5b** as a colorless oil.

4.1.2.1. 2-Bromo-6-isopropylphenyl acetate (5a). Yield: 95%; IR (film) ν_{max} (cm^{-1})=3070 (w, H–C=C), 2965 (s, C–H), 2870 (m), 1770 (s, C=O), 1565 (w), 1470 (m), 1440 (s), 1370 (s), 1195 (s), 1085 (m), 1010 (m), 910 (s), 780 (s), 735 (w), 675 (w), 610 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20 (d, J=7.2 Hz, 6H, 2×CH_3), 2.40 (s, 3H, CH_3–C=O), 2.97 (sep, J=7.2 Hz, 1H, CH–Ar), 6.97 (dd, J=8.0, 8.0 Hz, 1H, 4-H), 7.29 (d, J=8.0 Hz, 1H, 5-H), 7.66 (dd, J=1.6, 8.0 Hz, 1H, 3-H). Found C, 51.38%; H, 5.09%. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38%; H, 5.09%.

4.1.2.2. 2-Iodo-6-isopropylphenyl acetate (5b). Yield: 99%; IR (film) ν_{max} (cm^{-1})=3060 (w, H–C=C), 2965 (s, C–H), 2870 (m), 1765 (s, C=O), 1560 (w), 1465 (m), 1430 (s), 1370 (s), 1190 (s), 1080 (m), 1010 (m), 905 (s), 780 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.19 (d, J=7.2 Hz, 6H, 2×CH_3), 2.40 (s, 3H, CH_3–C=O), 2.97 (sep, J=7.2 Hz, 1H, CH–Ar), 6.97 (dd, J=8.0, 8.0 Hz, 1H, 4-H), 7.29 (d, J=8.0 Hz, 1H, 5-H), 7.66 (dd, J=1.6, 8.0 Hz, 1H, 3-H). Found C, 43.44%; H, 4.30%. Calcd for $C_{11}H_{13}IO_2$: C, 43.44%; H, 4.31%.

4.1.3. (*S*)-β-Cyclohomogeranyl iodide (8). To a stirred and ice-cooled solution of **7**[14b] (11.0 g, 65.5 mmol) in dry pyridine (80 ml) was added portionwise *p*-toluenesulfonyl chloride (15.0 g, 78.6 mmol). After stirring overnight, the reaction mixture was poured into water, and extracted with ether. The combined organic extracts were washed with satd $CuSO_4$ aq, water, and brine. After concentration in vacuo, the residue was dissolved in dry acetone (100 ml). To the solution NaI (14.7 g, 98.2 mmol) was added, and the resulting suspension was heated under reflux. After stirring for 2 h, the reaction mixture was concentrated in vacuo, and the residue was diluted with pentane. The organic phase was washed with water and brine, and dried with Na_2SO_4. After concentration in vacuo, the residue was purified with column chromatography (pentane) to give **8** (12.0 g, 66% in two steps) as a colorless oil. $[\alpha]_D^{25}$ −120 (*c* 1.01, pentane); IR (film) ν_{max} (cm^{-1})=2955, 2920 (s, C–H), 1460 (m), 1385 (w), 1165 (m), 1025 (s), 820 (s), 765 (s), 590 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (s, 3H, 5-CH_3), 0.91 (s, 3H, 5-CH_3), 1.18 (m, 1H, 4-CHH), 1.37 (m, 1H, 4-CHH), 1.45 (m, 1H, 6-H), 1.70 (br d, J=1.4 Hz, 3H, CH_3–C=C), 1.85–2.10 (m, 4H, 3,1′-CH_2), 3.23 (t, J=7.8 Hz, 2H, CH_2I), 5.33 (br s, 1H, H–C=C). This compound was employed in the next step without further purification.

4.1.4. (*S*)-2′-Isopropyl-6′-[2″-(2‴,6‴,6‴-trimethyl-2‴-cyclohexenyl)ethyl]phenyl acetate (9). To a stirred and cooled (−78 °C) solution of **8** (90% ee, 777 mg, 2.80 mmol) in dry ether (8 ml) was added dropwise 1.47 M *t*-BuLi in pentane (4.19 ml, 6.16 mmol) under Ar. After stirring for 30 min, 1.0 M *B*-methoxy-9-borabicyclo[3.3.1]nonane in hexane (6.44 ml, 6.44 mmol) was added dropwise, followed by addition of dry THF (8 ml). After stirring for 10 min at the same temperature, the resulting solution was allowed to warm to room temperature for 75 min. To the mixture, aq 3 M K_3PO_4 solution (1.87 ml, 5.60 mmol) was added, followed by a solution of **4b** (850 mg, 2.80 mmol) in DMF (10 ml). After addition of $Pd(PPh_3)_4$ (162 mg, 0.14 mmol), the mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was diluted with ether. The organic layer was washed with water and brine, and the combined aqueous layers were extracted with ether three times. The combined organic layers were dried with Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (hexane/EtOAc=250:1) to afford **9** (694 mg, 76%) as a colorless oil. $[\alpha]_D^{25}$ −30.8 (*c* 0.31, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3030 (w, H–C=C), 2965 (s, C–H), 2870 (s, C–H), 1765 (s, C=O), 1455 (s), 1165 (s), 1210 (s), 1045 (s), 1095 (m), 1045 (w), 1010 (m), 910 (m), 790 (m), 750 (m), 700 (w), 600 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.88 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.19 (d, J=7.2 Hz, 6H, CH_3–CH), 1.2–1.5 (m, 5H, 2″,5‴-CH_2, 1‴-H), 1.96 (m, 2H, 4‴-CH_2), 2.33 (s, 3H, CH_3–C=O), 2.49 (m, 2H, 1″-CH_2), 2.91 (sep, J=7.2 Hz, 1H, CH–CH_3), 5.31 (br s, 1H, 3‴-H), 7.08 (dd, J=4.8, 4.8 Hz, 1H, 4′-H), 7.16 (d, J=4.8 Hz, 2H, 3′,5′-H). This compound was employed in the next step without further purification.

4.1.5. (5*S*,10*S*)-14-Acetoxyabieta-8,11,13-triene (10). To a stirred solution of **9** (45 mg, 0.14 mmol) in dry $MeNO_2$ (1 ml) was added dropwise $BF_3 \cdot OEt_2$ (67 μl, 0.55 mmol) under Ar. After stirring for 3 h, the solution was poured into satd $NaHCO_3$ aq and extracted with ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=1000:1) to give 41 mg (91%) of **10** as a colorless solid. The enantiomeric purity was estimated to be 87–88% ee by HPLC [Daicel CHIRALPAK IA column, hexane/EtOAc=30:1, flow rate=0.3 ml/min, 0 °C; t_R=14.9 (5*S*,10*S*), 21.0 (5*R*,10*R*)]. Recrystallization from MeOH gave 32 mg (78%) of pure **10** (colorless needles, >99% ee by HPLC). Mp 100–101 °C; $[\alpha]_D^{25}$ +42.5 (*c* 0.69, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1})=2925 (s, C–H), 2865 (s, C–H), 1760 (s, C=O), 1460 (m), 1365 (m), 1215 (s), 1205 (s), 1170 (m), 1140 (w), 1015 (m), 815 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.16 (d, J=7.0 Hz, 3H, CH_3–CH), 1.18 (s, 3H, CH_3), 1.19 (d, J=7.0 Hz, 3H, CH_3–CH), 1.1–1.8 (m, 8H, 1,2,3-CH_2, 6-CHH, 5-H), 1.86 (br dd, J=6.8, 13.2 Hz, 1H, 6-CHH), 2.25 (br d, J=12.4 Hz, 1H, 7-CHH), 2.33 (s, 3H, CH_3–C=O), 2.4–2.8 (br m, 1H, 7-CHH), 2.88 (sep, J=7.0 Hz, 1H, CH–CH_3), 7.09 (d, J=8.0 Hz, 1H, Ar–H), 7.14 (d, J=8.0 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.3, 19.3, 20.6, 21.6, 23.2 (br), 24.8, 27.2, 33.2, 33.3, 37.6, 38.7, 41.5, 49.6, 122.4, 123.4, 127.5, 136.5, 146.2, 149.3, 169.3. Found C, 80.43%; H, 9.82%. Calcd for $C_{22}H_{32}O_2$: C, 80.43%; H, 9.81%.

4.1.6. (5*S*,10*S*)-Abieta-8,11,13-trien-14-ol (11). A suspension of **10** (180 mg, 0.55 mmol) and K_2CO_3 (152 mg, 1.10 mmol) in MeOH/THF (2:1, 3 ml) was stirred at room temperature for 3 h. The suspension was poured into dil HCl and extracted with ether. The organic extracts were washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/EtOAc=1000:1) to furnish **11** (147 mg, 94%) as a colorless oil; $[\alpha]_D^{25}$ +27.9 (*c* 0.96, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3615, 3565 (br m, O–H), 2960 (s, C–H), 2865 (s, C–H), 1580 (w), 1455 (s), 1420 (s), 1375 (m), 1290 (w), 1205 (s), 1175 (s), 810 (s); ^1H NMR (400 MHz, $CDCl_3$): δ=0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.22 (d, *J*=7.0 Hz, 3H, C*H*$_3$–CH), 1.25 (d, *J*=7.0 Hz, 3H, C*H*$_3$–CH), 1.2–1.8 (m, 7H, 1,2,3-CH_2, 5-H), 1.98 (br dd, *J*=8.0, 13.4 Hz, 1H, 6-C*H*H), 2.27 (m, 1H, 6-CH*H*), 2.60 (ddd, *J*=7.6, 11.2, 16.2 Hz, 1H, 7-C*H*H), 2.81 (dd, *J*=7.0, 16.2 Hz, 1H, 7-CH*H*), 3.14 (sep, *J*=7.0 Hz, 1H, C*H*–CH_3), 4.63 (br s, 1H, H–O), 6.85 (d, *J*=8.0 Hz, 1H, Ar–H), 7.01 (d, *J*=8.0 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.36, 19.28, 21.57, 22.47, 22.75, 24.28, 24.82, 26.80, 33.27, 33.35, 37.46, 38.88, 41.57, 49.64, 116.34, 120.55, 123.20, 129.88, 149.04, 150.16. Found: C, 83.85%; H, 10.56%. Calcd for $C_{20}H_{30}O$: C, 83.85%; H, 10.55%.

4.1.7. 12-Deoxyroyleanone (1). To a stirred solution of **11** (70 mg, 0.24 mmol) in THF/MeCN/H_2O (2:2:1, 10 ml), CAN (1.34 g, 2.4 mmol) was added portionwise. After stirring for 48 h, the mixture was poured into water and extracted with EtOAc. The organic extracts were washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was filtered through short silica gel column to give crude **1**. Recrystallization from EtOH gave pure **1** (50 mg, 68%) as pale yellow needles. Mp 75–76 °C (lit.:[13a] yellow plate, 83.8–84.8 °C); $[\alpha]_D^{24}$ −71.0 (*c* 0.20, $CHCl_3$) [lit.:[9] $[\alpha]_D^{20}$ −60.0 (*c* 0.05, $CHCl_3$), lit.:[13a] $[\alpha]_D^{24}$ −65.3 (*c* 0.407, $CHCl_3$)]; IR (KBr) ν_{max} (cm^{-1})= 2955 (s, C–H), 2925 (s, C–H), 2855 (m, C–H), 1648 (s, C=O), 1595 (m), 1455 (w), 1370 (w), 1285 (w), 1240 (m), 900 (m); ^1H NMR (400 MHz, $CDCl_3$): δ=0.90 (s, 3H, 19-CH_3), 0.93 (s, 3H, 18-CH_3), 1.09 (d, *J*=7.0 Hz, 3H, 16-CH_3), 1.10 (d, *J*=7.0 Hz, 3H, 17-CH_3), 1.08–1.54 (m, 6H, 1,2,6-C*H*H, 3-CH_2, 5-H), 1.72 (ddd, 3.6, 3.6, 13.6 Hz, 1H, 2-CH*H*), 1.86 (dd, *J*=13.6, 7.6 Hz, 6-CH*H*), 2.30 (ddd, *J*=7.6, 12.0, 20.2 Hz, 1H, 7-C*H*H), 2.68 (dd, *J*=20.2, 5.6 Hz, 1H, 7-CH*H*), 2.72 (m, 1H, 1-CH*H*), 2.98 (sep, *J*=7.0 Hz, 1H, 15-H), 6.31 (br s, 1H, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.4 (C-6), 18.9 (C-2), 20.2 (C-20), 21.4 (C-16,17), 21.8 (C-19), 25.9 (C-7), 26.2 (C-15), 33.5 (C-18), 33.6 (C-19), 36.4 (C-1), 38.5 (C-10), 41.4 (C-3), 51.6 (C-5), 131.9 (C-12), 142.7 (C-8), 150.9 (C-9), 152.7 (C-13), 188.1 (C-14). Found C, 79.95%; H, 9.39%. Calcd for $C_{20}H_{28}O_2$: C, 79.95%; H, 9.39%. ^1H and ^{13}C NMR spectra are identical with those of reported natural product.

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