  Bull. Chem. Soc. Jpn., 57, 1902—1907 (1984) [Vol. 57, No. 7

Total Synthesis of Racemic and Optically Active Coronafacic Acids

Susumu OHIRA
Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Naka-ku, Hiroshima 730
(Received November 17, 1983)

(±)-Methyl 3-ethyl-4-oxotricyclo[4.3.0.0^{1,5}]nonane-5-carboxylate (**4**), prepared by the stereoselective alkylation of methyl 4-oxotricyclo[4.3.0.0^{1,5}]nonane-5-carboxylate, was reduced with zinc borohydride, and the resultant hydroxy ester was treated with *p*-toluenesulfonyl chloride to give a mixture of α,β-unsaturated esters, having hydrindan skeletons. The mixture was submitted to hydroboration-oxidation to afford a keto ester, which was hydrolyzed to (±)-coronafacic acid (**2**). A diastereomeric mixture of *l*-menthyl 3-ethyl-4-oxotricyclo-[4.3.0.0^{1,5}]nonane-5-carboxylates, prepared by a modification of the synthesis of (±)-**4**, was resolved by column chromatography on silica gel, and each diastereomer was converted into (+)-**2** and (−)-**2** in a similar way as (±)-**2**.

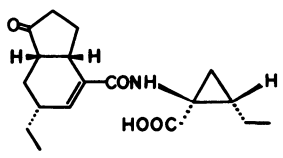
Coronatine (**1**), a phytotoxin produced by *Pseudomonas syringae pv. atropurpurea*, induces chlorosis on the leaves of Italian ryegrass and a hypertrophy on potato tuber tissues at a very low concentration.[1] The structure of **1** was established by the combination of a single-crystal X-ray analysis of coronafacic acid (**2**)[2a] and partial synthesis of **1**, which was achieved from natural **2** and synthesized coronamic acid (**3**).[2b] Determination of the absolute configuration of **1** was based on the ORD measurement of **2**[2b] and X-ray diffraction analysis of the *N*-acetyl derivative of the enantiomer of **3**.[2c] The first synthesis of (±)-**2**,[3a] which means the total synthesis of coronatine in a formal sense, was reported by Ichihara *et al.* in 1977. Since then many different syntheses have been accomplished constructing the hydrindan skeleton by characteristic methods, namely the intermolecular or intramolecular Diels-Alder reaction,[3,4b] the anionic oxy-Cope rearrangement,[4a] and the palladium-catalyzed cyclization followed by the Dieckmann condensation.[5] In this paper, I describe the total synthesis of racemic and optically active coronafacic acids,[6] including the transformation of the tricyclo[4.3.0.0^{1,5}]nonane system to the hydrindan skeleton *via* the cleavage of the cyclopropane ring.

Synthesis of (±)-Coronafacic Acid.[6a] As C_{7a}-epimer of **2** is easily convertible to **2**,[2-4] the major stereochemical problem in the synthesis of (±)-**2** was the introduction of the C_6-ethyl group *trans* to the C_{3a}-proton. A tricyclo[4.3.0.0^{1,5}]nonane derivative (**4**) appeared to be a suitable synthetic intermediate, because (±)-**4** was expected to be thermodynamically more stable than its C_3-epimer (**5**), which may have a significant interaction between the ethyl group and the cyclopropane ring. Transformation of the similar tricyclic compound to the fused bicyclic one was reported by Ruppert and White,[7] although there has been no application to the synthesis of the natural product.

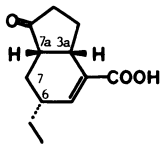
1-Cyclopentenecarbaldehyde (**6**)[8] was reduced with lithium aluminium hydride to give an alcohol (**7**). Treatment of **7** with *p*-toluenesulfonyl chloride (TsCl) under the phase-transfer catalyzed conditions (benzene–aqueous sodium hydroxide)[9] gave a sensitive sulfonate (**8**), which was not obtainable in the standard way (TsCl–pyridine). Without purification, **8** was subjected to reaction with the dianion of methyl acetoacetate, giving a β-keto ester (**9**)[10] in 66% yield from **6**. Treatment of **9** with *p*-toluenesulfonyl azide in acetonitrile in the presence of triethylamine afforded a diazo compound, which was heated in refluxing toluene with a catalytic amount of trimethyl phosphite–copper(I) iodide complex to give a 60% yield of the cycloadduct (±)-**10**.

Alkylation of (±)-**10** with 1 equiv of lithium diisopropylamide (LDA) and ethyl bromide in tetrahydrofuran provided a mixture of the monoalkylation product (±)-**4** and the dialkylation product (±)-**11** in various ratios depending on the reaction conditions. Although (±)-**5** was not produced as was expected, the yield of (±)-**4** was generally unsatisfactory due to production of (±)-**11** and recovery of (±)-**10**. After some considerable investigation, a 68% yield of (±)-**4** was obtained using a small excess of LDA, 4 equiv of hexamethylphosphoric triamide (HMPA) as a cosolvent, and 5 equiv of ethyl iodide in place of the bromide. The stereochemistry of (±)-**4** was confirmed by single-crystal X-ray analysis as shown in Fig 1.[11]

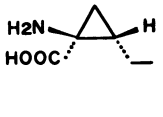
(±)-**4** was reduced with sodium borohydride in methanol to give an epimeric mixtur (*a* 3:1 ratio) of the hydroxy ester (±)-**12** and (±)-**13**; these were separated by chromatography on silica gel. The major product was assumed to be (±)-**12**, produced by the attack of the hydride from the less hindered side. Evidently, the ^{1}H NMR spectrum of the minor product (**13**) showed the CHOH proton at δ 4.06 as a double doublet, coupled with the adjacent methine proton (J= 3.5 Hz) and the OH proton (J=6.5 Hz), suggesting the intramolecular hydrogen bonding between the hydroxyl group and the ester carbonyl group. On



(1)



(2)



(3)

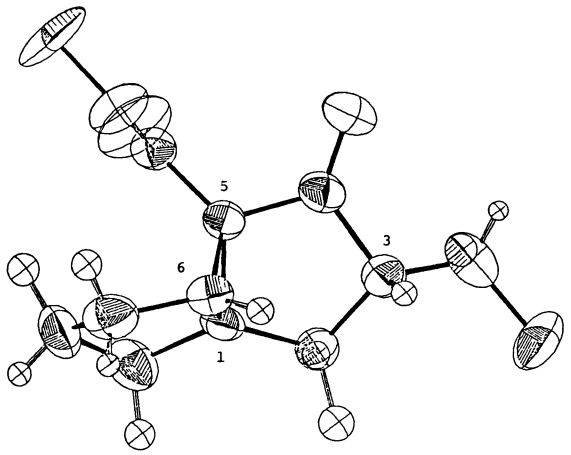


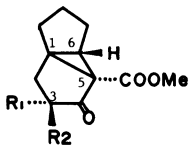
Fig. 1. Computer-generated perspective drawing of compound **4**.

the other hand, the ^{1}H NMR spectrum of the major product (**12**) showed the CHOH proton at δ 4.16 as a doublet with a larger coupling (J=6.5 Hz) than that of the minor product. Reduction of (±)-**4** with zinc borohydride gave a 86% yield of (±)-**12** as a single isolated product by the attack of the hydride from the same side as the ester carbonyl group.[11]

Transformation of (±)-**12** to the fused bicyclic system was attempted using HMPA or TsCl. Treatment with refluxing HMPA for a few minutes, or a large excess of TsCl for a few days at room temperature, afforded an unseparable mixture of α,β-unsaturated esters (±)-**14a—c**, contaminated with the aromatized product (**15**). Their structures were determined by GC-MS spectra and the ^{1}H NMR spectrum of the mixture, which showed the C_1-proton of (±)-**14a** and the C_7-proton of (±)-**14b** at δ 5.17 and 5.40 (each bs), the C_5-proton of (±)-**14a—c** at δ 6.5—6.9 (m), and two aromatic protons of **15** at δ 7.15 and 7.56 (each bs). After standing for a week at room temperature, almost all of the (±)-**14a—c** changed to **15**. When (±)-**12** was treated with 2—3 equiv of TsCl in pyridine at 90 °C for 1 h, a 1:1:1 mixture (glc analysis) of (±)-**14a—c** was obtained without **15**.

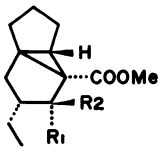
The unseparable mixture was then submitted to hydroboration and subsequent oxidation with pyridinium chlorochromate to give a complex mixture, from which a methyl ester of (±)-coronafacic acid (**16**) was isolated in 8% yield based on (±)-**12**. The ^{1}H NMR spectrum of (±)-**16** was identical with that of the methyl ester derived from the natural product. The hydroboration-oxidation process was investigated under various reaction conditions; but the yield of (±)-**16** could not be improved. Epoxidation of (±)-**14a—c** with *m*-chloroperbenzoic acid and subsequent treatment with boron trifluoride etherate afforded an undesired mixture, from which (±)-**16** could not be isolated.

Hydrolysis of (±)-**16** with refluxing aqueous hydrochloric acid[4] gave an 80% yield of (±)-**2**, whose spectral and analytical properties were identical with those of the natural product.[12]

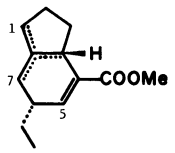


(4) R_1=Et, R2=H
(5) R_1=H, R2=Et
(10) R_1=R2=H
(11) R_1=R2=Et

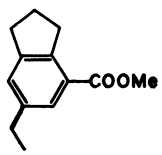
(6) R=CHO
(7) R=CH2OH
(8) R=CH2OTs
(9) R=CH2CH2COCH2COOMe



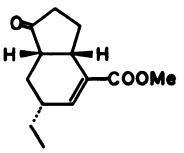
(12) R_1=H, R2=OH
(13) R_1=OH, R2=H



(14a) $\Delta^{1,7a}$
(14b) $\Delta^{7,7a}$
(14c) $\Delta^{3a,7a}$



(15)

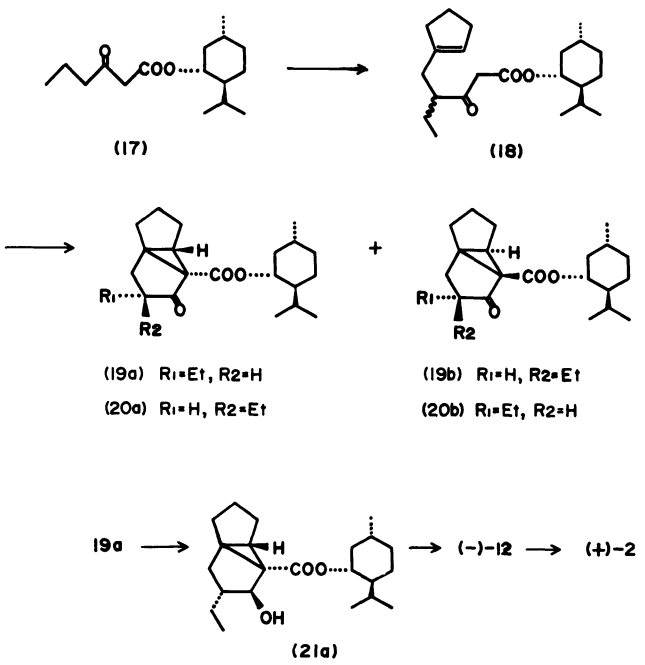


(16)

Synthesis of Optically Active Coronafacic Acids.[6b] Although the overall yield of (±)-**2** (0.9% from **6**) was not very satisfactory, the short process fror. (±)-**4** was attractive for the synthesis of optically active coronafacic acids, as there has been no approach to (+)- and/or (−)-**2** in contrast to (+)- and (−)-**3** which were prepared by resolution of the racemate.[2b] It was decided to try the resolution of the *l*-menthyl ester derivative[14] corresponding to (±)-**4**.

To circumvent the late alkylation step (**10**→**4**) in this study, the dianion of *l*-menthyl acetoacetate was first alkylated with 1 equiv of ethyl bromide to give the 3-oxohexanoate (**17**) in 88% yield. Reaction of **8** with the dianion of **17** afforded a 75% yield of a β-keto ester (**18**), whose diazotization and subsequent carbenoid addition gave a stereoisomeric mixture of the desired diastereomers (**19**) and its isomers (**20**) in 56% yield. Isolation of each isomer was difficult; however treatment of the mixture with sodium methoxide in refluxing methanol caused epimerization of **20** to afford only **19**. Fortunately, it could be resolved cleanly by column chromatography on silica gel and recrystallization from methanol gave **19a** and **19b** in a 1:1 ratio. The absolute configurations of **19a** and **19b** became clear after completion of the synthesis of (+)- and (−)-**2**.

Although **19a** could be converted to *l*-menthyl ester of (+)-**2** in three steps as described above, the ester resisted hydrolysis under mild acidic conditions (aqueous hydrochloric acid, aqueous sulfuric acid–acetic acid. To avoid the possibility of epimerization at the C_6-



position under vigorous conditions of hydrolysis, the hydroxy ester (**21a**), which was obtained by reduction of **19a** with zinc borohydride in 90% yield, was converted beforehand into the corresponding methyl ester. Hydrolysis of **21a** was not achieved by refluxing in aqueous sodium hydroxide–methanol or ethanol, but was effected on refluxing with aqueous sodium hydroxide–dimethyl sulfoxide. The resultant carboxylic acid was esterified with ethereal diazomethane to give (−)-**12** in 88% yield from **21a**. By a similar transformation as described for the synthesis of (±)-**2**, (−)-**12** was led to (+)-**2** ($[\alpha]_D^{20}$+109°, lit,[2a] +119°) whose optical rotation showed the same sign as the natural product. (−)-**2** ($[\alpha]_D^{20}$−119°) was obtained from **19b** on a similar four-step process.

Experimental

All melting points were uncorrected. IR spectra were recorded on a Hitachi EPI-G3 spectrometer. The ordinary mass spectra were determined on a Hitachi RMU-6L mass spectrometer, using a direct inlet system with a prove temperature of 60—100 °C, an ionizing energy 70 eV and an accelerating voltage 3.2 kV. The high resolution mass spectra were taken using a Hitachi RMU-7L double focussing mass spectrometer. ^{1}H NMR spectra were recorded on Varian T-60 (60 MHz) and Hitachi R-22 (90 MHz), employing tetramethylsilane as an internal standard. Optical rotations were measured on a Yanako OR-50 polarimeter. Column chromatography and preparative TLC were performed on Merck silica gel 60 (70—230 mesh ASTM) and 60 PF_{254}, respectively.

*Methyl 3-Oxo-5-(1-cyclopentenyl)pentanoate (**9**).* 1-Cyclopentenecarbaldehyde (**6**)[8] (6.79 g, 70.6 mmol) was added to a suspension of lithium aluminium hydride (1.0 g, 26.4 mmol) in anhydrous ether (100 ml), and the reaction mixture was stirred at room temperature for 2 h. After the excess reagent was destroyed with ethyl acetate, aqueous sodium hydroxide was added to the mixture until aluminium oxide separated. The organic layer was washed with brine, and dried ($MgSO_4$). Removal of the solvent gave **7** (6.59 g) as a colorless oil, which was used directly in the next reaction: IR ($CHCl_3$) 3620, 3420 (OH), and 1670 cm^{-1} (-CH=C-); ^{1}H NMR (CCl_4) δ=3.76 (1H, bs, OH), 4.07 (2H, bs, CH_2OH), and 5.55 (1H, bs, -CH=C-); MS *m/z* (rel intensity) 98 (M^+; 64), 80 (29), 70 (86), 67 (100), 57 (63), and 31 (85).

To a solution of **7** (6.59 g, 67.1 mmol) and *p*-toluenesulfonyl chloride (15.4 g, 80.6 mmol) in benzene (100 ml), was added 30% aqueous sodium hydroxide (100 ml) and benzyltriethylammonium chloride (0.8 g), with vigorous stirring at 20 °C (water bath). After the heterogeneous mixture was stirred for 5 h, the organic layer was washed with water, dil hydrochloric acid and brine, and dried (Na_2SO_4). The solvent was carefully evaporated *in vacuo* at *ca.* 30 °C to give the sensitive *p*-toluenesulfonate **8** as a colorless oil, which was used immediately in the next reaction: ^{1}H NMR (CCl_4) δ=2.43 (3H, s, CH_3), 4.54 (2H, bs, CH_2OTs), and 5.65 (1H, bs, -CH=C-).

To a suspension of 55% sodium hydride (4.85 g, 111 mmol) in tetrahydrofuran (100 ml), was added a solution of methyl acetoacetate (11.7 g, 101 mmol) in tetrahydrofuran (300 ml) at 0—20 °C, and subsequently 1.6 M (1M=1 mol dm^{-3}) butyllithium in hexane (69 ml, 110 mmol) under nitrogen at −5—0 °C (ice-ethanol bath). To the yellow solution of the dianion, was added a solution of the sulfonate **8** in tetrahydrofuran (200 ml) at 0 °C, and the reaction mixture was stirred for 3 h. After quenching with aqueous ammonium chloride, the solvent was evaporated and the residue was extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a crude product. Purification of the mixture by column chromatography on silica gel (300 g) using ethyl acetate–hexane (1:3) as eluent, gave **9** (9.09 g, 66% yield from **6**) as an oil: IR ($CHCl_3$) 1740 (ester C=O) and 1710 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ=3.33 (2H, s, $COCH_2CO$), 3.71 (3H, s, $COOCH_3$), and 5.32 (1H, bs, -CH=C-); MS *m/z* (rel intensity) 196 (M^+; 17), 178 (26), 122 (60), 95 (80), 94 (70), 80 (97), and 79 (100). Found: C, 67.14; H, 8.44%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

*(±)-Methyl 4-Oxoticyclo[4.3.0.0^{1,5}]nonane-5-carboxylate (**10**).* The keto ester **9** (3.39 g, 17.3 mmol) was dissolved in acetonitrile (70 ml) and mixed with triethylamine (2.62 g, 25.9 mmol) and *p*-toluenesulfonyl azide (3.57 g, 19.0 mmol) at room temperature. After standing overnight, the solvent was removed and the residue was treated with ether and water. The organic layer was washed with aqueous sodium hydroxide, water, and brine, and dried (Na_2SO_4). Removal of the solvent gave a crude product as an oil which was dissolved in toluene (200 ml) and refluxed for 5 h with trimethyl phosphite–copper (I) iodide complex (0.5 g). After cooling, the mixture was filtered and evaporated *in vacuo* to give a dark brown oil. Purification of the mixture by column chromatography on silica gel (160 g) using ethyl acetate–hexane (1:3) as eluent, gave (±)-**10** (2.02 g, 60% yield), which was recrystallized from ether–hexane as colorless prisms: Mp 68.5—69.5 °C; IR ($CHCl_3$) 1735 (ester C=O) and 1710 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ=0.6—1.4 (1H, brm, -CH-) and 3.68 (3H, s, $COOCH_3$); MS *m/z* (rel intensity) 194 (M^+; 10), 166 (36), 162 (100), 152 (48), 135 (28), and 93 (77). Found: C, 67.81; H, 7.38%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%.

*(±)-Methyl 3-Ethyl-4-oxotricyclo[4.3.0.0^{1,5}]nonane-5-carboxylate (**4**).* To a solution of lithium diisopropylamide in tetrahydrofuran (20 ml), prepared from diisopropylamine (450 mg, 4.38 mmol) and 1.6 M butyllithium in hexane (2.0 ml, 3.2 mmol) at 0 °C, was added a solution of (±)-**10** (567 mg, 2.93 mmol) and hexamethylphosphoric triamide (2.1 g, 11.7 mmol) in tetrahydrofuran (5 ml). The mixture was stirred for 15 min and ethyl iodide (2.3 g, 16 mmol) was

added to the solution. After stirring at 0 °C for 3 h, the reaction mixture was quenched with aqueous ammonium chloride. The solvent was evaporated *in vacuo* and the residue was extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a crude product. Purification by column chromatography on silica gel (30 g) using ethyl acetate–hexane (1:5) as eluent, gave (±)-**4** (442 mg, 68% yield), which was recrystallized from ether–hexane as colorless prisms: Mp 71.5—73 °C; IR ($CHCl_3$) 1740 (ester C=O) and 1715 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=0.87 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$) and 3.66 (3H, s, $COOCH_3$); MS *m/z* (rel intensity) 222 (M^+; 12), 194 (80), 166 (100), 152 (54), 134 (36), and 93 (70). Found: C, 69.96; H, 8.12%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

A mixture from less polar fractions was purified by preparative TLC, using ethyl acetate–hexane (1:10) as solvent, to give the dialkylation product (±)-**11** (99 mg) as a colorless oil: IR ($CHCl_3$) 1735 (ester C=O) and 1710 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=0.78 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), 0.83 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), and 3.67 (3H, s, $COOCH_3$); MS *m/z* (rel intensity) 250 (M^+; 3), 222 (19), 190 (10), 166 (100), and 98 (78). Found: C, 72.00; H, 9.10%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

X-Ray Analysis of (±)-4. (±)-**4** crystallized as a monoclinic crystal with a=8.617(2), b=9.737(3), c=15.070(6) Å, β=103.19(3)°. All unique diffraction intensities with $2\theta<50.0°$ were collected in a variable speed ω-scan mode on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation (0.7107 A). 1420 were judged to be observed after correction for Lorentz, polarization, and background effects. A phasing model which was obtained from the program MALTAN[14] was defined using Syntex XTL program system. Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and isotropic ones for the hydrogen atoms converged to a final R factor of 0.082 for 1420 reflections.

Reduction of (±)-4 with Sodium Borohydride. A stirred solution of (±)-**4** (78 mg, 0.35 mmol) in methanol (3 ml) was treated with sodium borohydride (67 mg, 1.8 mmol) for 2 h at room temperature. After the solvent was removed *in vacuo*, the residue was taken up in ether, washed with dil hydrochloric acid, aqueous sodium hydrogencarbonate and brine, and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a crude product, which was purified by preparative TLC, developed twice, using ethyl acetate–hexane (1:5) as solvent, to give (±)-**12** (47 mg, 60% yield) and (±)-**13** (17 mg, 22% yield). (±)-**12**: a colorless oil; R_f 0.45 (ethyl acetate–hexane=1:2); IR ($CHCl_3$) 3600 (OH) and 1710 cm^{-1} (ester C=O); ^1H NMR (CCl_4) δ=0.90 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.61 (1H, bs, OH), 3.71 (3H, s, $COOCH_3$), and 4.16 (1H, d, J=6.5 Hz, $-C\underline{H}OH$); MS *m/z* (rel intensity) 224 (M^+; 14), 206 (18), 191 (25), 177 (43), 165 (48), 147 (56), and 136 (100). Found: C, 69.33; H, 9.16%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%. (±)-**13**: a colorless oil; R_f 0.52 (ethyl acetate–hexane=1:2); IR ($CHCl_3$) 3600 (OH) and 1710 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=2.57 (1H, d, J=6.5 Hz, OH), 3.70 (3H, s, $COOCH_3$), and 4.06 (1H, dd, J=6.5, 3.5 Hz, $-C\underline{H}OH$). Found: C, 69.23; H, 9.12%. Calcd for $C_{13}H_{20}O_3$: C, 69.01; H, 8.99%.

Reduction of (±)-4 with Zinc Borohydride. To a solution of (±)-**4** (155 mg, 0.697 mmol) in ether (5 ml), was added 0.33 M zinc borohydride in ether (2.1 ml, 0.69 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched with ice and dil hydrochloric acid. The organic layer was washed with aqueous sodium hydrogencarbonate and brine, and dried (Na_2SO_4). Removal of the solvent gave a crude product which was purified by preparative TLC, developed twice, using ethyl acetate–hexane (1:5) as solvent, to give (±)-**12** (135 mg, 86% yield).

Methyl Ester of (±)-Coronafacic Acid (16). A solution of (±)-**12** (135 mg, 0.602 mmol) and *p*-toluenesulfonyl chloride (344 mg, 1.80 mmol) in pyridine (2 ml) was stirred at 90 °C under nitrogen for 1 h. The solvent was removed *in vacuo*, and the residue was treated with ether and water. The organic layer was washed with dil hydrochloric acid and brine, and dried (Na_2SO_4). Removal of the solvent gave a crude product, which was purified by preparative TLC, using ethyl acetate–hexane (1:5) as solvent, to give the unseparable mixture of (±)-**14a—c** (93 mg) as a colorless oil: IR ($CHCl_3$) 1710 (ester C=O) and 1630 ($-CH=\underset{|}{C}-$); ^1H NMR (CCl_4) δ=3.66, 3.67 (3H totally, each s, $COOCH_3$), 5.17, 5.40 (each *ca.* 0.3H, bs, C_1-or C_7-olefin proton), and 6.5—6.9 (1H, m, C_5-olefin proton).

To a solution of (±)-**14a—c** (93 mg, 0.46 mmol) in tetrahydrofuran (5 ml) was added 2.6 M borane in tetrahydrofuran (0.6 ml, 1.56 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 1 h at 0 °C and excess borane was destroyed with a small portion of water. Dichloromethane (10 ml) and pyridinium chlorochromate (0.8 g, 3.6 mmol) was added to the mixture succesively at 0—20 °C, and the mixture was stirred at room temperature for 2 h. The dark brown solution was passed over silica gel using ethyl acetate as eluent. After removal of the solvent, the residue was treated with ether and water. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a complex mixture of many products. Isolation by preparative TLC, developed three times, using ethyl acetate–hexane (1:8) as solvent, and further purification by preparative TLC, developed twice, using ether–hexane (1:5) as solvent, provided (±)-**16** (11 mg, 8% yield from (±)-**12**), as a colorless oil: IR ($CHCl_3$) 1740 (ester C=O), 1710 (C=O), and 1640 cm^{-1} ($-CH=\underset{|}{C}-$); ^1H NMR ($CDCl_3$: 90 MHz) δ=0.99 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), and 6.93 (1H, bs, $-CH=\underset{|}{C}-$); MS *m/z* (rel intensity) 222 (M^+; 100), 193 (14), 190 (26), 145 (20), 133 (28), and 119 (74). Found: *m/z* 222.1272. Calcd for $C_{13}H_{18}O_3$: M, 222.1255. The ^1H NMR spectrum of (±)-**16** was identical with that of the methyl ester of natural coronafacic acid.

(±)-Coronafacic Acid (2). A suspension of (±)-**16** (12 mg, 0.054 mmol) in 2.4 M hydrochloric acid (10 ml) was refluxed for 2 h with vigorous stirring. After cooling, the mixture was extracted with dichloromethane and the organic layer was dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by preparative TLC, developed twice, using ethyl acetate–hexane (1:2) as solvent, to give (±)-**2** (9 mg, 80% yield), which was recrystallized from diisopropyl ether as colorless prisms: mp 130—132 °C (lit,[3b] 115—127 °C); IR ($CHCl_3$) 3400—2500 (COOH), 1735 (C=O), 1685 (COOH), and 1635 cm^{-1} ($-CH=\underset{|}{C}-CO$); ^1H NMR ($CDCl_3$: 90 MHz) δ=0.99 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.96—3.23 (1H, m, $-\underset{|}{C}=CHC\underline{H}-$), 7.11 (1H, bs, $-\underset{|}{C}=CH-$), and 10.28 (1H, bs, COOH); MS *m/z* (rel intensity) 208 (M^+; 100), 190 (20), 163 (29), 151 (33), 133 (48), 119 (71), 105 (47), 91 (64), and 79 (88). Found: C, 69.13; H, 7.66%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. The ^1H NMR spectrum of (±)-**2** was identical with that of the natural product. The IR spectrum of (±)-**2** was identical with that of an authentic sample.[12]

l-Menthyl 3-Oxohexanoate (17). A similar procedure to the preparation of **9**, using *l*-menthyl acetoacetate[13] (13.94 g, 58 mmol), 55% sodium hydride (3.04 g, 70 mmol), 1.6 M butyllithium in hexane (40 ml, 64 mmol), and ethyl bromide (7.6 g, 69.7 mmol), gave a crude product, which was chromatographed on silica gel (400 g), using ethyl acetate–hexane (1:30) as eluent, to give **17** (13.7 g, 88% yield) as an oil; $[\alpha]_D^{20}$ −63.5 ° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 1730 (ester C=O) and 1705 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=2.47 (2H, t, J=7 Hz, $CH_2C\underline{H}_2CO$), 3.28 (2H, s, $COCH_2CO$), and 4.64 (1H, dt,

J=10, 4 Hz, COOCH–); MS m/z (rel intensity) 268 (M^+; 1), 155 (5), 138 (76), 123 (30), 113 (15), 95 (68), 71 (72), and 43 (100). Found: C, 71.67; H, 10.73%. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%.

1-Menthyl 3-Oxo-4-(1-cyclopentenylmethyl)hexanoate (18). A similar procedure to the preparation of **9**, using **17** (1.29 g, 4.81 mmol), 55% sodium hydride (230 mg, 5.27 mmol), 1.6 M butyllithium in hexane (3.3 ml, 5.3 mmol), and **8** prepared from **7** (380 mg, 3.88 mmol) gave a crude product, which was chromatographed on silica gel (60 g), using ethyl acetate–hexane (1:50) as eluent, to give **18** (1.016 g, 75% yield from **7**) as an oil: IR ($CHCl_3$) 1735 (ester C=O), 1710 (C=O), and 1645 cm^{-1} (–CH=C–), ^1H NMR (CCl_4) δ=2.70 (1H, m, COCH–), 3.27 (2H, s, $COCH_2CO$), 4.67 (1H, m, COOCH–), and 5.35 (1H, bs, –CH=C–); MS m/z (rel intensity) 348 (M^+; 3), 210 (56), 192 (33), 130 (40), 123 (87), 83 (65), and 81 (100). Found: C, 75.51; H, 10.53%. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41%.

Preparation of 1-Menthyl 3-Ethyl-4-oxotricyclo[4.3.0.0^{1,5}]-nonane-5-carboxylates (19) and (20). A similar procedure to the preparation of (±)-**10**, using **18** (8.21 g, 23.6 mmol), triethylamine (2.86 g, 28.3mmol), *p*-toluenesulfonyl azide (4.88 g, 24.8 mmol), and a catalytic amount of trimethyl phosphite–copper(I) iodide complex, gave a crude product, which was chromatographed on silica gel (300 g), using ethyl acetate–hexane (1:15) as eluent, to give a mixture of cycloadducts **19** and **20** (4.54 g, 56% yield).

Epimerization of 20 and Resolution of 19. To a solution of sodium methoxide in methanol, prepared by addition of sodium (0.5 g, 22 mmol) into methanol (200 ml), was added the mixture of **19** and **20** (4.20 g, 12.1 mmol), and refluxed for 2 h. After cooling, aqueous ammonium chloride was added to the mixture and the methanol was evaporated *in vacuo*. The residue was extracted with ether and the organic layer was dried (Na_2SO_4). Removal of the solvent gave the mixture of **19a** and **19b**, which was chromatographed on silica gel (200 g) using ether–hexane (1:10) as eluent. Repeated column chromatography on silica gel and final purification by recrystallization from methanol gave pure **19a** (1.65 g, 21% yield from **18**) and **19b** (1.61 g, 21% yield from **18**). **19a**: Mp 70—71 °C (colorless prisms); R_f 0.26 (ether–hexane=1:5); $[\alpha]_D^{20}$ −86.7° (*c* 4.65, $CHCl_3$); IR (CCl_4) 1740 (ester C=O) and 1720 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=4.65 (1H, dt, J=10, 4 Hz, COOCH–); MS m/z (rel intensity) 346 (M^+; 1), 209 (52), 191 (100), 180 (21), 164 (44), 152 (20), 138 (40), 123 (19), and 95 (45). Found: C, 76.54; H, 10.19%. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89%. **19b**: mp 100—101.5 °C (colorless prisms); R_f 0.31 (ether–hexane=1:5); $[\alpha]_D^{20}$ +5.4° (*c* 3.68, $CHCl_3$); IR (CCl_4) 1740 (ester C=O) and 1715 cm^{-1} (C=O); ^1H NMR (CCl_4) δ=4.62 (1H, dt, J=10, 4 Hz, COOCH–). Found: C, 76.54; H, 9.96%. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89%.

Reduction of 19 with Zinc Borohydride. A similar procedure to the reduction of (±)-**4**, using **19a** (1.016 g, 2.93 mmol) and 0.33 M zinc borohydride in ether (6.8 ml, 2.24 mmol), gave a crude product, which was chromatographed on silica gel (50 g), using ethyl acetate–hexane (1:8) as eluent, to give **21a** (0.918 g, 90% yield) as a colorless oil: $[\alpha]_D^{20}$ −67.5° (*c* 1.53, $CHCl_3$); IR (CCl_4) 3600 (OH) and 1705 cm^{-1} (ester C=O); ^1H NMR (CCl_4) δ=2.26 (1H, s, OH), 4.05 (1H, d, J=6.5 Hz, –CHOH), and 4.68 (1H, dt, J=10, 4 Hz, COOCH–); Found: C, 75.64; H, 10.69%. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41%.

Hydrolysis of 21a and Subsequent Esterification. A solution of **21a** (769 mg, 2.21 mmol) in 2.5 M aqueous sodium hydroxide (15 ml) and dimethyl sulfoxide (30 ml) was refluxed for 3 h. After addition of water, the mixture was extracted with ether. The aqueous layer was acidified with crashed ice and 6 M hydrochloric acid, and extracted with ether. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent gave a crude carboxylic acid, which was treated with ethereal diazomethane. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (60 g), using ethyl acetate–hexane (1:5) as eluent, to give (−)-**12** (436 mg, 88% yield) as a colorless oil: $[\alpha]_D^{20}$ −43.5° (*c* 1.82, $CHCl_3$); the physical data (IR, ^1H NMR, and TLC analysis) of (−)-**12** were identical with those of (±)-**12**. Found: C, 69.72; H, 9.08%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

(+)-Coronafacic Acid (2). A similar three-step procedure to the preparation of (±)-**2** from (±)-**12**, using (−)-**12** (1.22 g), gave (+)-**2** (15 mg), which was recrystallized from diisopropyl ether: Mp 142—143 °C (colorless prisms) (authentic sample[12]: 142—143 °C, mmp 142—143 °C, lit,[2a] 125—126 °C); $[\alpha]_D^{20}$ +109° (*c* 0.75, MeOH, lit,[2a] +119.1°); IR and ^1H NMR spectra were identical with those of the natural product and (±)-**2**. Found: C, 69.09; H, 7.81%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

(−)-Coronafacic Acid (2). A similar five-step procedure to the preparation of (+)-**2** from **19a**, using **19b** (1.151 g), gave (−)-**2** (17 mg), which was recrystallized from diisopropyl ether: Mp 142—143 °C (colorless prisms); $[\alpha]_D^{20}$ −119° (*c* 0.86, MeOH); IR and ^1H NMR spectra were identical with those of the natural product and (±)-**2**. Found: C, 69.31; H, 7.93%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

The author wishes to express his hearty thanks to Associate Professor Mitsuru Nakayama of Hiroshima University for his encouragement and guidance during the course of this research. The author is grateful to his laboratory staff, for useful suggestions and continual encouragement, and also to Professor Akitami Ichihara, Hokkaido University, for kindly providing him with an authentic sample, as well as spectral data of natural coronafacic acid and its methyl ester. Thanks are also due to Dr. Shizuko Eguchi (MS) and Dr. Sachihiko Imai (NMR), Hiroshima University, for the spectral measurement. The author is grateful to Dr. Hiroshi Nozaki, Okayama University of Science, for the help and advice with X-ray analysis.†

References

1) K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi, M. Ogasawara, H. Sato, and S. Sakamura, *Ann. Phytopath. Soc. Jpn.*, **42**, 613 (1976); K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi, and S. Sakamura, *ibid.*, **43**, 219 (1977).

2) a) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, and T. Matsumoto, *J. Am. Chem. Soc.*, **99**, 636 (1977); b) A. Ichihara, K. Shiraishi, S. Sakamura, K. Nishiyama, and R. Sakai, *Tetrahedron Lett.*, **1977**, 269; c) A. Ichihara, K. Shiraishi, S. Sakamura, A. Furusaki, N. Hashiba, and T. Matsumoto, *ibid.*, **1979**, 365.

3) a) A. Ichihara, R. Kimura, K. Moriyasu, and S. Sakamura, *Tetrahedron Lett.*, **1977**, 4331; b) A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, *J. Am. Chem. Soc.*, **102**, 6353 (1980).

4) a) M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, **102**, 2463 (1980); b) M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, **22**, 2735 (1981).

† The complete F_o–F_c data are deposited as Document No. 8412 at the Office of the Editor of Bull. Chem. Soc. Jpn.

5) J. Tsuji, *Pure Appl. Chem.*, **53**, 2371 (1981).
6) A part of this work has already been briefly communicated: a) M. Nakayama, S. Ohira, Y. Okamura, and S. Soga, *Chem. Lett.*, **1981**, 731; b) M. Nakayama and S. Ohira, *Agric. Biol. Chem.*, **47**, 1689 (1983).
7) J. F. Ruppert and J. D. White *J. Am. Chem. Soc.*, **103**, 1808 (1981).
8) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, **1950**, 3634.
9) W. Szeja, *Synthesis*, **1979**, 822.
10) M. J. Bullivant and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 249.
11) T. Nakata and T. Oishi, *Tetrahedron Lett.*, **1980**, 1641.
12) The authentic sample of (+)-**2** was supplied by Professor A. Ichihara, Hokkaido University, and the characteristics (mp, TLC, IR) were measured in this laboratory.
13) D. F. Taber, S. A. Saheh, and R. W. Korsmeyer, *J. Org. Chem.*, **45**, 4699 (1980).
14) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **24**, 274 (1970).