Synthesis of (R)-(−)-3-Methoxymethyl-3-propyl-3,4-dihydrocoumarin from a Chiral Michael Adduct: Absolute Configurations of the Allylated Products of Enantioselective Radical-Mediated Reactions

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(1R,2S)-3-Methoxymethyl-3-propyl-3,4-dihydrocoumarin was synthesized, starting from a chiral Michael adduct ([S]-methyl 2,3-dihydro-1-oxo-2-(3-oxobutyl)-1H-indene-2-carboxylate), in order to determine the absolute configurations of the products obtained by enantioselective radical-mediated allylation. Aldol cyclization of the Michael adduct proceeded smoothly with suppression of the retro Michael reaction to afford an optically active cyclized product. The Baeyer–Villiger reaction of (R)-2-methoxymethyl-2-propylindanone in the presence of BF₃·Et₂O afforded the desired dihydrocoumarin.

Key words absolute configuration; 3-methoxymethyl-3-propylidihydrocoumarin; aldol reaction; Baeyer–Villiger reaction

In the field of asymmetric synthesis, construction of chiral quaternary carbon centers has received wide attention. 1,2) Asymmetric induction in radical-mediated reactions is also a current topic in synthetic organic chemistry. 3,4) We have reported the efficient creation of chiral quaternary carbon centers by enantioselective radical-mediated reactions catalyzed by a chiral Lewis acid. For example, the reactions of 3-alkyl-3-iododihydrocoumarins 1 with allyltirbutyltin in the presence of a chiral aluminum reagent proceeded enantioselectively to afford optically active 3-alkyl-3-allyldihydrocoumarins 2 as shown in Chart 1. 3) The absolute configurations of the allylated products 2 were determined by circular dichroism measurements of their derivatives. 2a) To confirm the result of such an empirical method for determining the absolute configurations of 2, a direct chemical correlation of 2 with a configurationally defined compound seemed necessary. The present paper deals with the synthesis of (R)-3-methoxymethyl-3-propyldihydrocoumarin starting from a chiral Michael adduct, ([S]-methyl 2,3-dihydro-1-oxo-2-(3-oxobutyl)-1H-indene-2-carboxylate 3), in order to determine the absolute configurations of 2 obtained by enantioselective radical-mediated allylation.

In our synthetic strategy, the methoxycarbonyl and 3-oxobutyl groups of a Michael adduct (S)-3, which is prepared by the asymmetric reaction reported by Wynberg and other workers, 4) are converted into methoxymethyl and propyl groups, respectively. In this study, the crucial steps are as follows: an aldol cyclization of (S)-3 with suppression of the retro Michael reaction, and the Baeyer–Villiger reaction of an indanone, having a chiral quaternary carbon center, to afford an optically active dihydrocoumarin (Chart 2).

To protect the ketone moiety, conversion of (S)-3 into enone 4 was considered. At first, aldol cyclization of a chiral Michael adduct (S)-3 was carried out as described in the literature. 4b) Namely, treatment of (S)-3 with NaOMe in MeOH provided enone 4, the specific rotation of which, however, had a lower value ([α]_D^27 +75.3° (c = 2.58, benzene) than that reported in the literature. 5) This result suggested that partial racemization, which is attributed to a retro Michael reaction and recombination of the side chain under basic conditions, occurred easily through the cyclization reaction. Indeed, cleavage of the side chain of the 3,3-oxobutyl group, took place quantitatively on treatment with tert-BuOK in tert-BuOH to give the carbomethoxyindanone. To improve the optical purity of the enone, we examined the cyclization under mild conditions. The aldol cyclization of (S)-3 in benzene with pyrrolidine and acetic acid was found to give 4 in 61% isolated yield. The degree of specific rotation of this product was [α]_D^27 +279.3° (c = 2.44, benzene).

With the optically active 4 available, we next focused our attention on the preparation of indanone 13. Protection of the carbonyl group in the enone moiety in 4 provided ketal 5 in 53% yield. For conversion of the ester moiety, reduction of 5 with LiAlH₄ was carried out to give alcohol 6 in 92% yield, and methylation of this with Mel and NaH gave 7 in 93% yield. Deprotection of the ketal group in 7, using SiO₂–10% aqueous oxalic acid, gave enone 8 in 97% yield. 6) Oxidative cleavage of the enone moiety in 8, by ozone–H₂O₂, gave acid 9 to regenerate the indanone structure and remove one carbon atom. Selective reduction of the carboxyl group was carried out using borane–tetrahydrofuran complex (BH₃·THF) to give indanone 10 having an alcohol moiety, in 96% yield. Chlorination of alcohol 10 gave 11, but reduction with tributyltin hydride did not produce a propyl group. Therefore, 11 was converted into iodide 12 in 88% yield. Reduction of 12 with tributyltin hydride successfully afforded (R)-2-methoxymethyl-2-propylindanone 13.

Next, conversion of indanone 13 into dihydrocoumarin 14 by the Baeyer–Villiger oxidation was examined. 7,8) It is known that the reaction of indanone with CF₃CO₂H–Na₂HPO₄ gives the corresponding M verdadeckos acid or AcOH–H₂O₂, gives dihydrocoumarin. 7a–c) It is also reported that reaction of 2-methylindanones with CF₃CO₂H–NaHPO₄ gives the corresponding dihydrocoumarins. 7d) Recently, we reported that oxidation

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of 2-methoxymethylindanone using m-chloroper oxybenzoic acid (m-CPBA) afforded 3-methoxymethylhydroxy coumarin.\(^{10}\) However, indanone 13 under these conditions did not afford the desired product. Other agents, such as m-CPBA–CF\(_3\)COOH, m-CPBA–NaHPO\(_4\), AcOOH, AcOOH–NaHPO\(_4\), K\(_2\)S\(_2\)O\(_8–\)H\(_2\)SO\(_4\), ceric ammonium nitrate or O\(_2–\)PhCHO–m-CPBA, were also found to be unsuitable for the oxidation of 2-methoxymethylindanone using m-CPBA–NaHPO\(_4\), the resulting mixture was extracted with benzene (15 ml) and AcOH (20 ml, 349 mmol). The mixture was stirred for 20 h at room temperature. After addition of water, the resulting mixture was extracted with benzene (50 ml×2). The extracts were washed successively with 10% aqueous HCl, saturated NaHCO\(_3\), and saturated NaCl, and dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene : acetone 5 : 1) followed by rinsing with Et\(_2\)O–hexane to afford (S)-5 (10.0 g, 41.0 mmol) in benzene (150 ml) and AcOH (20 ml, 349 mmol). The mixture was stirred for 20 h at room temperature. After addition of water, the resulting mixture was extracted with benzene (50 ml×2). The extracts were washed successively with water and saturated NaCl, and dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene : acetone 5 : 1) to afford (S)-5 (10.0 g, 38.5 mmol, [\(\alpha\])\(_D\)\(^{178}\) = -2.02 (c = 2.0, benzene)) in benzene (15 ml) and AcOH (20 ml, 349 mmol). The mixture was stirred for 20 h at room temperature. After addition of water, the resulting mixture was extracted with benzene (50 ml×2). The extracts were washed successively with 10% aqueous HCl, saturated NaHCO\(_3\), and saturated NaCl, and dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene : acetone 5 : 1) to afford (S)-5 (10.0 g, 38.5 mmol, [\(\alpha\])\(_D\)\(^{178}\) = -2.02 (c = 2.0, benzene)).

**Experimental**

**General**

All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi FT-210 spectrophotometer. \(^1\)H-NMR \((270\text{ MHz})\) and \(^{13}\)C-NMR \((67.5\text{ MHz})\) spectra were recorded with a JEOL EX-270 spectrometer in CDCl\(_3\) solution using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS D-300 or a JEOL JMS-SX102A spectrometer. Specific rotations were measured on a JASCO DIP-360 digital polarimeter. The enantiomeric excess (ee) of 14 was determined by HPLC using chiral columns (DAICEL). Column chromatography was performed on silica gel.

A chiral Michael adduct (S)-3 was prepared according to the method reported by Wynberg and his co-workers.\(^{11}\) After recrystallization from benzene–Et\(_2\)O, conversion of (S)-3 was carried out.

**Methyl (S)-1,2,9a-Tetrahydro-3-oxo-3H-fluorene-9a-carboxylate (4)**

To a solution of (S)-3 \((10.0\text{ g}, 38.5\text{ mmol}, [\(\alpha\])\(_D\)\(^{178}\) = -2.02, benzene) in benzene (15 ml) and AcOH (20 ml, 349 mmol). The mixture was stirred for 20 h at room temperature. After addition of water, the resulting mixture was extracted with benzene (50 ml×2). The extracts were washed successively with 10% aqueous HCl, saturated NaHCO\(_3\), and saturated NaCl, and dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene : acetone 5 : 1) to afford (S)-5 (10.0 g, 38.5 mmol, [\(\alpha\])\(_D\)\(^{178}\) = -2.02, benzene).

**Chart 2**

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On the other hand, hydrogenation of 2a afforded 14, the specific rotation of which was identical to that of (R)-14 prepared from (S)-3 (Chart 2). Thus, the absolute configuration of all the alylated products obtained by our enantioselective radical-mediated reactions was found to be R, because 2b–d had already been correlated with 2a by a chemical method.\(^{20}\)

In conclusion, the absolute configuration of 2a was unequivocally established. The result is consistent with the previously assigned configuration using circular dichroism measurements. It was also demonstrated that a chiral Michael adduct was useful as a synthon for the synthesis of optically active indanones and dihydrocoumarins. These findings should provide an efficient approach to the syntheses of five- and six-membered optically active cyclic compounds bearing quaternary carbon centers.
then more water (3.6 ml) at 0 °C. The resulting mixture was dried over K₂CO₃. The solvent was removed under reduced pressure, and the crude product was purified by rinsing with Et₂O–hexane to afford (S)-6 (4.74 g, 92%), mp 143—144 °C (iso-Pr₂O). [α]D₂⁰ +161.4° (c = 1.02, benzene). IR (Nujol) cm⁻¹: 3435, 3029, 1542, 1332, 1305, 1260, 1178, 1161, 1104, 840, 740. ¹H-NMR: δ = 1.71—2.01 (1H, m), 2.44—2.72 (3H, m), 2.74 (1H, d, J = 17.5 Hz), 3.91—4.10 (4H, m), 5.82 (1H, d, J = 8.6 Hz). ¹³C-NMR: δ = 28.8, 29.2, 35.9, 52.9, 59.3, 77.0, 124.1, 126.5, 127.5, 132.9, 135.2, 153.2, 178.7, 208.3. MS: m/z 248 (M⁺). HR-MS Calcd for C₁₇H₁₉O₃: 272 (M⁺) c = +0.7° (c = 1.08, benzene). IR (Nujol) cm⁻¹: 3429, 2924, 2854, 1670, 1648, 1604, 1586, 1572, 1475, 1442, 1378, 1305, 1253, 1240, 1171, 1134, 1098, 928, 754, 740. ¹H-NMR: δ = 1.91—2.01 (1H, m), 2.44—2.72 (3H, m), 2.74 (1H, d, J = 16.5 Hz), 3.13 (1H, d, J = 9.2 Hz), 3.27 (1H, d, J = 16.5 Hz), 3.32 (3H, s), 3.46 (1H, d, J = 9.2 Hz), 6.32 (2H, s), 7.03—7.58 (4H, m). ¹³C-NMR: δ = 29.8, 34.1, 41.7, 48.2, 59.3, 75.7, 118.7, 123.0, 126.0, 127.3, 131.8, 137.8, 147.1, 168.0. MS: m/z 228 (M⁺). HR-MS Calcd for C₁₄H₁₈O₃: 228.1185. Found 228.1147. Anal. Calcd for C₁₄H₁₈O₃: C, 79.82; H, 7.06. Found: C, 79.03; H, 7.05.

(R)-5-(3-Methoxyl-1-propyl)-5-oxo-3-oxo-7H-furoene (2) A solution of silica gel (60 ml, 145 g) in hexanes (20 ml) was added to the mixture at 0 °C.

(R)-5-(2-Methoxyl-1-propyl)-5-oxo-3-oxo-7H-furoene (2) A solution of silica gel (60 ml, 145 g) in hexanes (20 ml) was added to the mixture at 0 °C.

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room temperature. After addition of hexane, the mixture was filtered. The filtrate was washed with saturated NaHCO₃, saturated NaCl, and dried over MgSO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) followed by distillation to afford (R)-14 (83.9 mg, 52%) as an oil. bp 130—140 °C (1 mmHg) (bulb-to-bulb distillation). 92% ee; HPLC [chiralcel OD; hexane : 2-propanol = 50 : 1; flow rate 0.5 ml/min]. \[\delta^2_{H} = 16.5^\circ = c(1.13, \text{acetone})\] H-NMR and mass spectra were identical to those for the product obtained from 2a.

References and Notes


5) The specific rotation of (S)-3 in our study showed \[\alpha^2_{D} = -70.4^\circ (\epsilon = 2.16, \text{benzene})\]. \[\alpha^2_{D} = -77^\circ (\epsilon = 2, \text{benzene})\] for (S)-3 has been reported, see: ref. 4a and b. It has also been reported in ref. 4b that enone 4 was obtained as two crops of crystals (major crop: \[\alpha^2_{D} + 41^\circ (\epsilon = 2, \text{benzene})\], minor crop: \[\alpha^2_{D} + 313^\circ (\epsilon = 2.0, \text{benzene})\]) by the cyclization of (S)-3 under basic conditions (using NaOMe) followed by fractional recrystallization.


9) For reports of the rate of the Baeyer–Villiger reaction, see: refs 7a and b.