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A New Synthesis of a Chiral Ester Containing Phenylpyrimidine Ring as Liquid Crystal Dopant

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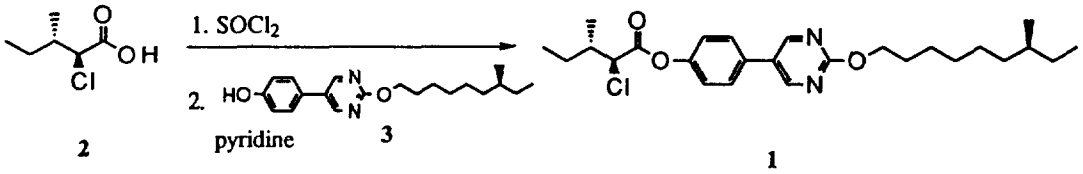
A new synthetic route to chiral liquid crystal dopant, 4-[2-(7*S*-methylnonanyl)oxy-5-pyrimidinyl]phenyl (2*S*,3*S*)-2-chloro-3-methylpentanoate (**1**), starting from 4-nitrophenylacetic acid is described. The key intermediate methylthiopyrimidine compound (**8**) has been synthesized from 4-nitrophenylacetic acid by Vilsmyer-Haack reaction followed by the formation of pyrimidine ring, and then converted to chiral ester (**1**) by the replacement of nitro group by (2*S*,3*S*)-2-chloro-3-methylpentanoic acid **2** through the formation of diazonium salt.

Introduction

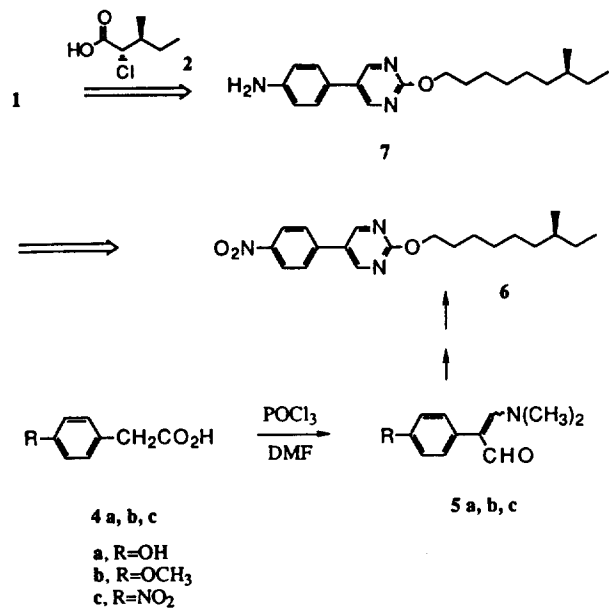
Recently, new liquid crystal display elements using a ferroelectric liquid crystal are actively studied because of their bistable and fast switching properties.[1] This liquid crystal display system utilizes a tilted smectic liquid-crystalline phases. if suitable chiral dopants are added to such tilted smectic phases, the phases can be transformed into a ferroelectric liquid crystalline phase.[2]

Accordingly, a lot of optically active dopants for ferroelectric liquid crystals were synthesized for the development of fast response display devices.[3] Among them, a chiral ester (**1**) containing phenylpyrimidine ring is known as a suitable dopant for tilted smectic liquid-crystalline phases.[3c] However, prior report merely gives a conventional preparation process of **1** by the reaction of acid chloride derivative, derived from (2*S*,3*S*)-2-chloro-3-methylpentanoic acid **2**, with pyrimidinylphenol derivative **3** without detailed experimental procedures as shown in Scheme 1.



Scheme 1

In connection with our efforts toward the synthesis of various chiral liquid crystal dopants, we report herein the details of a new and convenient synthesis of optically active ester (**1**) as outlined in the retro-synthetic scheme.



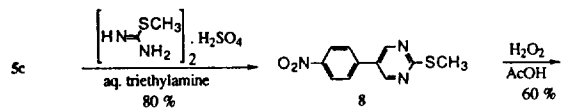
Retro-synthetic Scheme

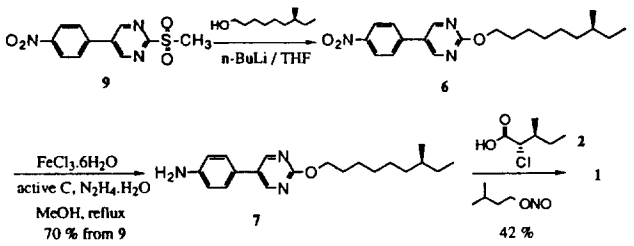
Synthesis

The pyrimidinylphenol derivative **3**, a key intermediate for the synthesis of the chiral liquid crystal dopant **1**, can be prepared by the cyclization reaction of acrolein derivatives (**5a** or **5b**) with isothiourea.[3d] In the previous report, Vilsmyer-Haack reaction of 4-hydroxy or 4-methoxyphenylacetic acid (**4a** or **4b**) with $POCl_3$ and N,N-dimethyl formamide (DMF) produced acrolein derivative (**5a** or **5b**) in modest yield (*ca.* 37%).[4] Furthermore, we could not isolate the pyrimidine compound by the reaction of acrolein derivative (**5a**, **5b**) with isothiourea. Here, we needed a new starting material for the efficient synthesis of **1**.

In preliminary experiments, acrolein derivative **5c** was obtained in quantitative yield by the reaction of 4-nitrophenylacetic acid (**4c**) with $POCl_3$ and DMF. Therefore, we expected that 4-nitrophenylacetic acid would be a good starting material on several reasons: (1) nitro group is tolerable to the next reaction conditions, (2) nitro group can be transformed to amino group, and (3) amino group in **7** can be readily converted to diazonium salt for the replacement of diazonium group with chiral carboxylic acid to afford the final product **1**.

The optically active ester (**1**) was synthesized by the reaction pathway shown in Scheme 2.



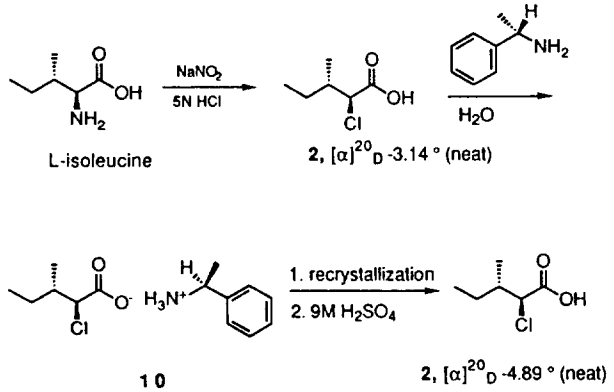


Scheme 2

The acrolein compound (**5c**) readily cyclized to afford methylthiopyrimidine compound (**8**) in 80% yield by the reaction with S-methyl isothiourea sulfate.[5] The methylthio group in methylthiopyrimidine compound was converted to methanesulfonyl group in 60% yield by treating **8** with hydrogen peroxide in acetic acid.

For the introduction of the chiral alkoxy side chain, the coupling of a chiral alkoxy side chain to pyrimidine ring was carried out by the reaction of **9** with an alkoxide solution, derived from (7*S*)-methylnonanyl alcohol[6] and *n*-butyllithium, to afford **6**. The nitro group in **6** was readily reduced by treatment of ferric chloride, hydrazine and activated carbon to give **7** in 70% yield from **9**.[7]

The remaining step is the replacement of diazonium salt derived from **7** by (2*S*,3*S*)-2-chloro-3-methylpentanoic acid (**2**) for obtaining the chiral ester (**1**). The chiral pentanoic acid (**2**) was prepared from L-isoleucine according to the known procedure.[8] However, the degree of optical rotation of **2** was low compared to the reported value ($[\alpha]_D^{20}$ −3.15°, neat; lit.,[8] $[\alpha]_D^{20}$ −4.78°, neat), Fortunately, the purification of crude acid **2** can be accomplished by formation of salt (**10**) and subsequent recrystallization of **10**, followed by the liberation of acid **2** by acidification with mineral acid as shown in Scheme 3.[9] Thus, obtained chiral pentanoic acid (**2**) was optically pure enough ($[\alpha]_D^{20}$ −4.89°, neat).



Scheme 3

The replacement of amino group in **7** by the alkoxy group of (2*S*,3*S*)-2-chloro-3-methylpentanoic acid (**2**) was attempted by the formation of diazonium salt with sodium nitrite or by the formation of phenyldiazonium borofluoride from **7** followed by treatment with **2**.[10] The attachment of the chiral pentanoic acid (**2**) to pyrimidinylphenyl ring did not proceed owing to the lower solubility of sodium nitrite to the chiral

pentanoic acid (**2**). On the other hand, the coupling reaction proceeded smoothly by the formation of diazonium salt using organic nitrite such as isoamyl nitrite[11] to afford the chiral ester (**1**) in 42% yield.

In conclusion, a new synthetic route to chiral liquid crystal dopant, 4-[2-(7*S*-methylnonanyl)oxy-5-pyrimidinyl]phenyl (2*S*,3*S*)-2-chloro-3-methylpentanoate (**1**), starting from 4-nitrophenylacetic acid has been developed. The efficacy of our synthesis relies upon efficient formation of the phenylpyrimidine ring and novel introduction of the chiral pentanoic acid into phenylpyrimidine ring.

Experimental

IR spectra were recorded on a Analect FX-6160 FT-IR spectrometer. NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer or JEOL JNM-60 (60 MHz) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at room temperature using the sodium D line. Melting points were determined on a Thomas-Hoover capillary melting apparatus and uncorrected. Analytical GC-MS work was performed with a Hewlett-Packard 5988A-GC-Mass using a capillary column of SE-54 (17 m×0.2 mm i.d.). N,N-Dimethylformamide (DMF) was distilled from CaH_2. Flash column chromatography was performed using E. Merck Kiesegel 60 (230-400 mesh) silica gel.

3-(N,N-Dimethylamino)-2-(4-nitrophenyl)acrolein (5c). N,N-Dimethylformamide (DMF, 200 g, 2.73 mol) was added to $POCl_3$ (381 g, 2,49 mol) dropwise under vigorous stirring at 15-20 ℃ over 1.5 h. To the mixture was added a solution of 4-nitrophenylacetic acid (150 g, 0.83 mol) in DMF (300 mL) for 10 min at the same temperature. The resulting solution was stirred at 70℃ for 18 h and poured into ice (800 g) followed by neutralization with K_2CO_3. The resulting mixture was made strong alkaline solution by addition of 50% aqueous NaOH solution (100 mL) (During the addition, the temperature was maintained at 50 ℃). After evolution of dimethylamine ceased, the mixture was cooled to 0 ℃ and the resulting precipitate was filtered and washed with water. The solid was recrystallized with water and methanol to afford **5c** in quantitative yield. mp 129 ℃; ^{1}H NMR ($CDCl_3$) δ 2.9 (S, 6H) 7.0 (s, 1H), 7.35 (d, J=8.0 Hz, 2H), 8.15 (d, J=8.0 Hz, 2H), 9,1 (s, 1H).

2-Methylthio-5-(4-nitrophenyl)pyrimidine (8). To S-methyl isothiourea sulfate (120 g, 0.43 mol) and triethylamine (120 mL, 0.86 mol) in water (400 mL) was added **5c** (170 g, 0.81 mol) portionwise at 60 ℃. The resulting solution was stirred at 15-25 ℃ for 48 h and treated with water (200 mL). The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* to afford **8** (122 g, 80%). mp 170-172 ℃; IR (KBr) 1597, 1581, 1514, 1412, 1377, 1343, 1199, 1176, 852 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.7 (s, 3H), 7.8 (d, J=8.0 Hz, 2H), 8.5 (d, J=8.0 Hz, 2H), 8.95 (s, 2H).

2-Methansulfonyl-5-(4-nitrophenyl)pyrimidine (9). To a solution of **8** (120 g, 0.43 mol) and triethylamine (32 g, 0.13 mol) in acetic acid (200 mL) was added dropwise 30% aqueous H_2O_2 solution (72 mL) at 10 ℃. After 2 h, the resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* to affford **9** (22 g, 60%). mp 278 ℃; IR (KBr) 1599, 1556, 1513, 1417, 1382, 1345, 1315, 1213, 1067, 954, 857 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.4 (s, 3H), 8.1 (d, J=8.0 Hz, 2H), 8.4 (d, J=8.0 Hz, 2H), 9.5 (s, 2H).

2-[(7*S*-Methylnonanyl)oxy]-5-(4-nitrophenyl)pyrimidine (6). To a solution of (*S*)-7-methylnonanyl alcohol (5.71 g, 36 mmol) in THF (700 mL) was added dropwise a solution of *n*-butyllithium (2.0 M in hexane, 18.5 mL) at room temperature. After 1 h, the solution of methanesulfonyl compound **9** (10.2 g, 36.1 mmol) in THF (100 mL) was added dropwise to the resulting lithium alkoxide solution under vigorous stirring. The reaction mixture was stirred at 60 ℃ for 12 h and quenched with 2 N HCl solution (50 mL) at 0 ℃. The organic layer was separated by centrifugation and concentrated. The residue was diluted with ethyl acetate (200 mL). The ethyl acetate layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography with short column (hexane/ethyl acetate=2 : 1) to afford **6** (*ca* 12 g) containing small amount of (*S*)-7-methylnonanyl alcohol. mp 62-63 ℃; IR (KBr) 2961, 2929, 2853, 1602, 1532, 1442, 1354, 1298, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8 (br d, 6H), 1.4 (m, 13H), 4.4 (t, J=7 Hz, 2H), 7.7 (d, J=0.8 Hz, 2H), 8.3 (d, J=8.0 Hz, 2H), 8.85 (s, 2H).

5-(4-Aminophenyl)-2-[(7*S*-methylnonanyl)oxy]pyrimidine (7). A solution of **6** (6 g, 16.6 mmol), activated carbon (1.2 g), and ferric chloride (III) hexahydrate (920 mg, 3.4 mmol) in methanol (50 mL) was heated to reflux for 10 min. To the refluxing mixture was added dropwise hydrazine hydrate (5.1 g, 102.2 mmol) over 10 min. After reflux for 12h, the mixture was evaporated and diluted with ether (100 mL). The ether layer was washed with water, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/ethyl acetate=2 : 1) to afford **7** (4.1 g, 70% from **9**) as a white solid. mp 86-87 ℃; ^{1}H NHR ($CDCl_3$) δ 0.84 (d, J=6.6 Hz, 3H), 0.86 (d, J=6.6 Hz, 2H), 1.32 (m, 12H), 1.84 (m, 1H), 4.38 (t, J=6.6 Hz, 2H), 6.70 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 8.64 (s, 2H).

(2*S*,3*S*)-2-chloro-3-methylpentanoic acid (2). L-Isoleucine (50 g, 0.38 mol) was dissolved in 5 N HCl solution (50 mL) and the solution was cooled to 3 ℃. To this solution was added dropwise a precooled (3 ℃) solution of $NaNO_2$, (63 g, 0.9 mol) in water (150 mL) under vigorous stirring and efficient cooling so that the temperature of the reaction mixture was kept below 5 ℃. After 5h, an additional $NaNO_2$ (10 g, 0.14 mol) in water (25 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. While the solution was stirred, Na_2CO_3 (38 g) was added carefully to prevent foaming. The reaction mixture was extracted with ethyl ether (1 L) in four portions. The combined organic phase was dried (Na_2SO_4), concentrated, and distilled (110-112 ℃/3 mmHg) to give crude **2** (40 g, 70%) as an oil $[\alpha]_D^{20}=-3.14$ (neat).

A solution of the above crude **2** in water (175 mL) was mixed with (*S*)-(−)-methylbenzylamine (45 g, 0.37 mol) and heated to 70 ℃ for 10 min. The mixture was allowed to cool to 10 ℃. After standing for 3 h at the same temperature, the crude salt was collected by filtration and washed with ice-water (25 mL). This crude salt was purified by recrystallization with methanol/ethyl acetate/hexane to afford pure (*S*)-(−)-methylbenzylammonium (2*S*,3*S*)-2-chloro-3-methylpentanoate (**10**, 33 g, 46%) as a white solid. mp 113.5-114 ℃;

^{1}H NMR ($CDCl_3$) δ 0.80 (m, 6H), 1.13 (m, 1H), 1.40 (m, 1H), 1.58 (d, J=6.8 Hz, 3H), 1.84 (m, 1H), 3.84 (d, J=6.0 Hz), 4.28 (q, J=6.8 Hz, 1H), 7.20 (br. s, 3H), 7.30 (m, 5H).

A solution of the above (*S*)-(−)-methylbenzylammonium (2 *S*,3*S*)-2-chloro-3-methylpentanoate (**10**, 33 g, 0.12 mol) in water (300 mL) was treated dropwise with 9M H_2SO_4 solution (8.1 mL) and stirred for 10 min. The mixture was extracted with ethyl ether (100 mL×2) and the combined ether solution was washed with brine, dried (Na_2SO_4), concentrated, and distilled (90 ℃/mmHg) to give optically pure **2** (16.3 g, 89%) as an oil. ($[\alpha]_D^{20}$= −4.89, neat; lit.[8] $[\alpha]_D^{20}$= −4.78, neat).

4-[2-(7*S*-methylnonanyl)oxy-5-pyrimidinyl]phenyl(2*S*,3*S*)-2-chloro-3-methylpentanoate (1). To a mixture of amine **7** (2 g, 6.1 mmol) and pentanoic acid **2** (10 g, 66.4 mmol) was added dropwise isoamyl nitrite (1.1 g, 9.4 mmol) at 70 ℃ and stirred for 15 min. After cooling to room temperature, the mixture was diluted with ether (200 mL) and treated with 2 N NaOH solution under vigorous stirring. The organic layer was separated, washed consecutively with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane /ethyl acetate=7 : 1) followed by recrystallization with methanol to afford liquid crystal dopant **1** (1.18 g, 42%, 100%, pure from GC) as a white needle. mp 71.7 ℃; $[\alpha]_D^{20}$= +6.8 (c=5, CH_2Cl_2); GC/Mass (70 eV) 462 (M^++2), 461 (M^++1), 460 (M^+), 375, 362, 328, 322, 321, 320, 243, 235, 189, 188 (base peak), 187; IR (KBr) 2961, 2929, 2858, 1760, 1595, 1550, 1442, 1378, 1333, 1202 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J=6.6 Hz, 3H), 0.86 (d, J=6.6 Hz, 3H), 1.00 (t, J=6.5 Hz, 3H), 1.15 (d, J=6.8 Hz, 3H), 1.34 (m, 12H), 1.86 (m, 8H), 2.23 (m, 1H), 4.39 (d, J=6.0 Hz, 1H), 4.41 (t, J=6.0 Hz, 2H), 7.24 (d, J=8.5 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 8.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.85, 11.37, 15.93, 19.18, 25.12, 25.99, 26.98, 28.87, 29.44, 29.69, 34.32, 36.51, 38.98, 65.45, 67.95, 122.08 (two carbons), 127.03, 127.59 (two carbons), 132.69, 150.36, 157.06, 151.16, 164.89, 167.70.

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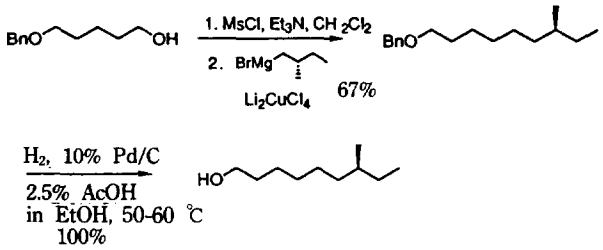
6. (*S*)-7-Methylnonyl alcohol was prepared as follows;



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