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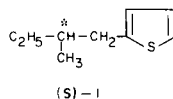
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Optically active (*S*)-2-(2-methylbutyl)thiophene was obtained by different procedures. Among them, the cross-coupling reaction between 2-methylbutylmagnesium chloride and 2-chlorothiophene proved to be the most efficient one. Compound **1** was thus obtained in satisfactory yield and rather high optical purity (82%).

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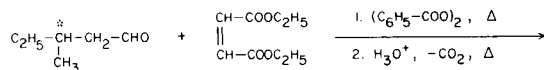
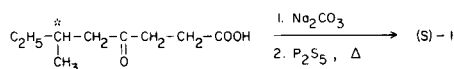
As a part of a synthetic project we needed a convenient and experimentally simple method for preparing a large amount of the optically active 2-(2-methylbutyl)thiophene (**1**).



Although several routes to 2-alkyl-substituted thiophenes are reported (1), the preparation of the title compound with high enantiomeric purity and the determination of the relationship between its rotatory power and minimum optical purity posed some problems.

The well documented (2,3) reaction sequence depicted in the Scheme 1 appeared quite unsatisfactory to prepare **1** because of the low yield ( $\leq 40\%$ ) and mainly the presence of a byproduct (20%), we were unable to identify and to separate from **1**.

Scheme 1

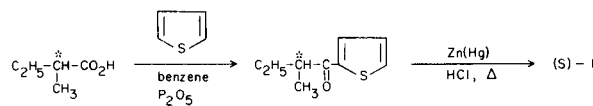
(*S*)-**2**(*S*)-**3**

On the other hand the classical two step-alkylation of thiophene (**4**) by (*S*)-2-methylbutanoic acid offered the possibility to prepare considerable amount of **1** from very accessible starting materials (Scheme 2) but with moderate overall yield ( $\sim 20\%$ ) and rather low optical purity.

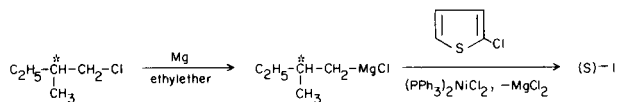
In this context it is interesting to note that the (*S*)-2-methylbutanoic acid recovered from the reaction mixture resulted in partial racemization (25%). The best alkyl-

ation method of the thiophene ring to **1** which we found consisted of the cross-coupling reaction between 2-chlorothiophene and (*S*)-2-methylmagnesium chloride catalyzed by nickel(II)-phosphine complexes (5,6) (Scheme 3). The only contaminant compound found in the reaction mixture of **1** was the 2,6-dimethyloctane, which was present in variable amounts (up to 20%) and was formed during the preparation of the Grignard reagent.

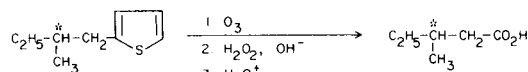
Scheme 2



Scheme 3



Scheme 4

[ $\alpha$ ]<sub>D</sub><sup>25</sup> +12.06 (n, C<sub>7</sub>H<sub>6</sub>)[ $\alpha$ ]<sub>D</sub><sup>25</sup> +7.23 (neat)

However, through the above one-pot reaction it was possible to obtain pure **1** in 45% overall yield after purification through the classical chloromercuriation method (7). In order to determine the relationship between its rotatory power and the minimum optical purity, **1** was cleaved by ozonolysis to (*S*)-3-methylpentanoic acid (Scheme 4) (8).

On this basis a minimum enantiomeric purity of 82% for **1** was calculated, corresponding to a 16% overall

racemization with respect to the starting (*S*)-1-chloro-2-methylbutane. Moreover, we were unable to reproduce the optical activity of **1** in two preparations starting from the same optically active chloride and following the same experimental procedure. Isomerization of the secondary alkyl group of the Grignard reagent in the presence of Ni(II)-phosphine complexes was reported in the literature (9). It was assumed that this isomerization takes place through an equilibration of the  $\sigma$ -alkylnickel complex with the corresponding  $\pi$ -complex. This process, which can be operative also in the case of primary alkyl groups, involves in our case the hydrogen atom in the  $\beta$ -position with respect to the metal and therefore lead to partial racemization of the asymmetric center.

### EXPERIMENTAL

All boiling points are uncorrected. The glc analysis were performed with a Perkin-Elmer F-30 gas chromatograph using the columns and the temperatures specified and the preparative glc with a Perkin-Elmer F-21 gas-chromatograph. The nmr spectra were obtained with a Jeol PS-100 spectrometer and the chemical shift in ppm was determined using tetramethylsilane as an internal standard. The ir spectra were recorded on a Perkin-Elmer 180 spectrometer; mass spectra were measured with Hitachi Perkin-Elmer RMU-6L and a Varian Mat CH 7 spectrometers operating at 70 eV. The optical rotations were determined on a Perkin-Elmer 241 polarimeter using 1 dm tube on pure liquids if not otherwise stated.

#### Materials.

Diethyl maleate, thiophene and 2-chlorothiophene were commercial products (Fluka AG); (*S*)-1-chloro-2-methylbutane (**10**), (*S*)-3-methylpentanal (**11**) and (*S*)-2-methylbutanoic acid (**12**) were prepared following standard procedures. The bis(diphenylphosphino)nickel(II) dichloride was obtained according to the method described by Hudson, *et al.*, (13).

#### (*S*)-6-Methyl-4-oxooctanoic Acid (**3**).

A mixture of 200 g. (2 moles) of (*S*)-3-methylpentanal (**2**),  $[\alpha]_{\text{D}}^{25} -7.01$ , 86 g. (0.5 mole) of diethyl maleate and 4 g. of benzoyl peroxide were refluxed for 22 hours under nitrogen (**3**). After cooling, the resulting solution was neutralized with aqueous sodium bicarbonate, washed with water and dried over anhydrous sodium sulfate. The excess of aldehyde (107 g., 1.07 moles) was removed by distillation; the oily residue (136 g.) was added to 560 ml. of 18% aqueous hydrochloric acid and refluxed for 22 hours under vigorous stirring. Compound **3** was isolated from this mixture and purified through its sodium salt. After acidification (pH = 4) the oxoacid **3** was extracted with ether; the solvent was removed and distillation of the oily residue gave pure **3**, 60.2 g. (70% yield calculated with respect to reacted aldehyde), b.p. 129-130° (10<sup>-3</sup> mm Hg);  $n_{\text{D}}^{25} 1.4463$ ; neutral equivalent, 172.2 (Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>3</sub>: 172.22);  $[\alpha]_{\text{D}}^{25} + 4.11$  (c, 2.747, chloroform).

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>3</sub>: C, 62.76; H, 9.36. Found: C, 62.84; H, 9.37.

The gas-chromatographic analysis (2m column packed with APZ 10% on Chromosorb P, heated at 190°) of the methyl ester, prepared by treatment with diazomethane, showed a single peak; m/e (%), 43 (100), 71 (97), 98 (91.5), 99 (74.3),

55 (68.5), 130 (65.7), 41 (60), 115 (57), 29 (48.5), 27 (45.7), 186 (M<sup>+</sup>, 5.7).

Cyclization of **3** with Phosphorus Pentasulfide to (*S*)-2-(2-methylbutyl)thiophene (**1**).

Compound **3** (20.0 g., 0.116 mole) was converted into the sodium salt by treatment with a 20% aqueous solution containing an equimolecular amount of sodium carbonate. The water was removed under reduced pressure and the solid residue dried *in vacuo* (10<sup>-3</sup> mm Hg). A mixture of 24 g. of the salt, 20 g. of phosphorus pentasulfide and 10 g. of sand, suspended on 100 ml. of high boiling mineral oil, was kept at 150° for 15 minutes. The yellow colour of this mixture turned red. The internal temperature was raised up to 200-210°; under reduced pressure (120 mm Hg) 10.5 g. of a pale-yellow liquid distilled off, b.p. 100-130°. This product was dissolved in 50 ml. of ethyl ether and was washed with a 20% aqueous solution of potassium hydroxide, then washed with water and dried over sodium sulfate. Evaporation of the solvent and distillation of the residue gave 1.7 g. (40% yield), b.p. 87-90° (13 mm Hg). Glc analysis (2 m column packed with 15% PPG on Chromosorb G and heated at 120°) showed the presence of ca. 20% of a byproduct having a very short retention time. Purification of the mixture through the chloromeric derivative (**7**) did not affect the ratio of the two components. This mixture was not further worked up.

#### (*S*)-2-(2-Methylbutanoyl)thiophene (**4**).

(*S*)-2-Methylbutanoic acid, 36.6 g. (0.358 mole),  $[\alpha]_{\text{D}}^{25} + 19.28$ , was added over 3 hours at room temperature to a vigorously stirred mixture of 46.6 g. (0.55 mole) of anhydrous thiophene, 52.5 g. of phosphorus pentoxide and 336 ml. of anhydrous benzene (**4**). After the addition was complete, the reaction mixture was refluxed for 4 hours. The benzene solution was decanted, and the sludge was repeatedly extracted with benzene. The collected benzene extracts were washed with a 10% aqueous solution and dried over anhydrous sodium sulfate. Removal of the solvent and distillation of the oily residue gave **4**, 28.0 g., b.p. 120° (23 mm Hg),  $[\alpha]_{\text{D}}^{25} + 41.13$  (c, 3.185, *n*-C<sub>7</sub>H<sub>16</sub>). Glc analysis of **4** (2 m column packed with 15% of polypropylenglycol on Chromosorb G and heated at 140°) showed the presence of only one peak. As from the alkaline washings pure (*S*)-2-methylbutanoic acid, 9.2 g., b.p. 90-92° (25 mm Hg),  $n_{\text{D}}^{25} 1.4044$ ,  $[\alpha]_{\text{D}}^{25} + 15.0$  was recovered, a 65% yield of **4** resulted (calculated with respect to reacted acid). In a further preparation from (*S*)-2-methylbutanoic acid (0.11 mole),  $[\alpha]_{\text{D}}^{25} + 19.28$ , compound **4** was obtained (50% yield), b.p. 96° (6 mm Hg),  $n_{\text{D}}^{25} 1.4952$ ,  $[\alpha]_{\text{D}}^{25} + 39.65$  (c, 2.963, *n*-C<sub>7</sub>H<sub>16</sub>). In this last case, the recovered acid showed  $[\alpha]_{\text{D}}^{25} + 13.37$ .

#### Clemmensen Reduction of **4** to **1**.

A mixture of 25.5 g. (0.15 mole) of **4**,  $[\alpha]_{\text{D}}^{25} + 41.13$  (*n*-C<sub>7</sub>H<sub>16</sub>), 100 ml. of methanol, 50 ml. of 37% aqueous solution of hydrochloric acid and 70 g. of zinc amalgam was refluxed for 3 hours (**14**). The organic product was separated by azeotropic distillation of the reaction mixture, the distilled liquid was extracted with ether and dried over sodium sulfate. Removal of the solvent and distillation over sodium of the residue gave **1**, 10.1 g. (40% yield), b.p. 105° (18 mm Hg),  $n_{\text{D}}^{25} 1.4975$ ,  $[\alpha]_{\text{D}}^{25} + 10.63$  (c, 1.787, *n*-C<sub>7</sub>H<sub>16</sub>). Glc analyse of **1** showed only one peak.

#### Cross-coupling Reaction Between 2-Methylbutylmagnesium Chloride and 2-Chlorothiophene to **1**.

To a stirred mixture of 12 g. (0.101 mole) of 2-chlorothiophene,

0.6 g. of bis(diphenylphosphino)nickel(II) chloride and 50 ml. of ethyl ether was added slowly at room temperature under a nitrogen atmosphere, 80 ml. of about a 2M ethereal solution of 2-methylbutylmagnesium chloride, prepared from (S)-1-chloro-2-methylbutane,  $[\alpha]_{\text{D}}^{25} + 1.61^{\circ}$  (10). After the addition was complete, the reaction mixture was refluxed for 20 hours. The emulsion obtained after hydrolysis with saturated aqueous solution of ammonium chloride, was treated with charcoal, the organic layer was separated and dried over anhydrous sodium sulfate. After evaporation of the solvent the residue was distilled *in vacuo* to give 7.7 g. of 85% pure **1** (43% yield), b.p. 100-105° (18 mm Hg). The reaction product showed by glc (2 m column packed with 2.5% Silicone gum rubber on Chromosorb G and heated at 108°) to contain 15% of 3,6-dimethyloctane. This byproduct was identified by mass spectrum  $M^+$ , and by comparison of the glc retention time of an authentic sample (15). By preparative glc (3 m column packed with 3% Silicone gum rubber on Chromosorb G) pure **1** was obtained, b.p. 107° (20 mm Hg),  $n_{\text{D}}^{25}$  1.4961-2; ms: 154 ( $M^+$ ); nmr ( $\delta$  ppm, neat) 0.7-0.9 (6H, m), 1.0-1.7 (3H, m), 2.2-2.7 (2H, m), 6.2-6.6 (3H, m); ir  $\nu$  max (neat)  $\text{cm}^{-1}$ : 3108 m, 3080 sh, 3070 m, 3045 m, 2960 vs, 2925 vs, 2875 s, 2860 sh, 1460 s, 1440 s, 1380 s, 850 m, 821 s, 808 m, 690 vs.

Anal. Calcd. for  $\text{C}_9\text{H}_{14}\text{S}$ : C, 70.06; H, 9.15; S, 20.79. Found: C, 70.12; H, 9.15; S, 20.70.

In a second preparation, starting from (S)-1-chloro-2-methylbutane (0.1 mole)  $[\alpha]_{\text{D}}^{25} + 1.61^{\circ}$ , compound **1** was obtained in 45% yield following the same experimental procedure,  $[\alpha]_{\text{D}}^{25} + 12.06$  (c, 2.604,  $n\text{-C}_7\text{H}_{16}$ ).

Ozonolysis of **1** to (S)-Methylpentanoic Acid.

A solution of **1**, 1.67 g. (0.011 mole),  $[\alpha]_{\text{D}}^{25} + 12.06$  ( $n\text{-C}_7\text{H}_{16}$ ), in 150 ml. of purified pentane was treated with a stream of ozonized oxygen at 0° for 10 hours (8). After removing the solvent, the oily residue was dissolved in 20 ml. of ethanol and the resulting solution was cautiously treated with a 10% aqueous sodium hydroxide and 10 ml. of 36% hydrogen peroxide at 0°. The mixture was refluxed for 24 hours. The volatile material was removed by distillation, and then the alkaline aqueous residue was extracted with ether, acidified, and extracted again *in continuum* with ethyl ether. The organic

phase was dried over anhydrous sodium sulfate. Removal of the solvent and distillation of the residue gave (S)-3-methylpentanoic acid (16), 0.98 g. (77% yield), b.p. 104° (20 mm Hg),  $n_{\text{D}}^{25}$  1.4139,  $[\alpha]_{\text{D}}^{25} + 7.23$ .

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