Enantioconvergent Synthesis of (−)-3-Methyl-3-phenylcyclopentanone

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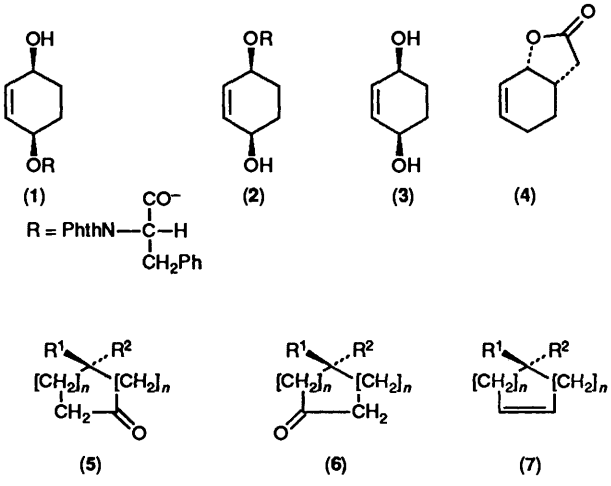
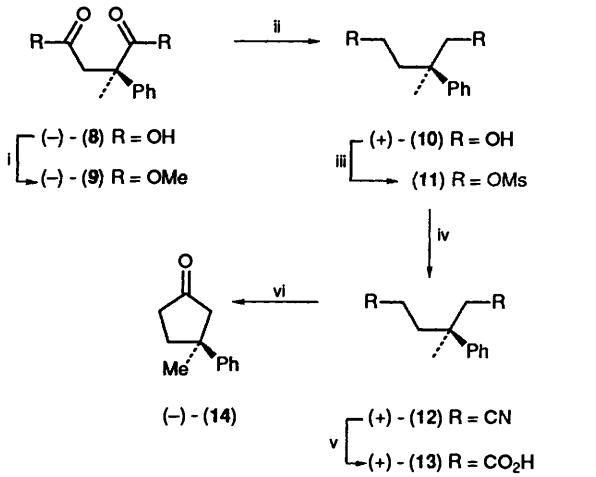
(+)-3-Methyl-3-phenylhexanedioic acid, prepared through homologation of (−)-2-methyl-2-phenylbutanedioic acid, has been cyclized to furnish (−)-3-methyl-3-phenylcyclopentanone. Chiral inversion of (+)-3-methyl-3-phenylcyclopentanone synthesized from (+)-2-methyl-2-phenylbutanedioic acid has been effected through regiospecific 1,2-ketone transposition.

The synthesis of enantiomerically pure compounds is important in synthetic organic as well as in medicinal chemistry as is evident from the publication of a number of monographs[1] and from the existence of the journal *Chirality*. One of the classical methods employed for the preparation of an enantiomerically pure compound utilizes the resolution of either the final racemic product or the resolution of a suitable racemic intermediate.[2] This route is not currently favoured since (i) methods used until recently for the resolution of racemates are neither general nor efficient and (ii) normally, only one of the enantiomeric intermediates obtained *via* resolution has the proper configuration to furnish the required enantiomer of the target molecule, while the other enantiomeric intermediate cannot be transformed to the required enantiomer of the product. However, recent developments[3] make it possible to achieve efficient and rapid resolution of a wide range of racemates by utilization of medium-pressure liquid chromatography (MPLC) on a column packed with a suitable chiral stationary phase. A synthesis is enantioconvergent if both enantiomers of a racemic intermediate are ultimately transformed into a single enantiomeric product.[4] Enantioconvergent synthesis can be carried out when the 'wrong' enantiomeric intermediate has (i) one chiral centre and (ii) an enolizable hydrogen attached to the chiral centre, since such an intermediate can be racemized and recycled.[2] Starting independently from the enantiomers (**1**) and (**2**) which can be regarded as derivatives of the *meso* compound (**3**), Terashima *et al.*[5] have synthesized the enantiomer (**4**). This is an example of



enantioconvergent synthesis. In a recent review, Seebach and Hungerbuhler[6] have given many examples of synthetic studies which employ the concept used by Terashima.

Inspection of the structures (**5**) and (**6**) makes it evident that it may be possible to effect chiral inversion of a monocarbocyclic ketone having an odd number of carbon atoms in the ring‡ [for example ketone (**5**)] *via* regiospecific 1,2-ketone transposition. It is essential that, for the chiral inversion to be successful, one has to avoid the use of *meso* intermediates such as compound (**7**). This paper deals with the chiral inversion of the ketone (+)-(**16**) by employment of 1,2-ketone transposition, and based on this chiral inversion the enantioconvergent synthesis of the ketone (−)-(**14**) starting from the racemic acid (**8**) has been achieved.



Scheme 1. *Reagents and conditions:* i, MeOH, H_2SO_4; ii, $LiAlH_4$, Et_2O; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2; iv, NaCN, HMPA; v, KOH, ethanediol; vi, $Ba(OH)_2$, heat.

The enantiomeric acids (−)-(**8**) and (+)-(**15**) have been obtained by resolution of the corresponding racemic mixture.[7] The enantiomer (−)-(**8**) has been transformed to the ketone (−)-(**14**) by employing the series of reactions shown in Scheme 1. Mesylation of the diol (+)-(**10**) and subsequent reaction of the mesyl diester (**11**) with NaCN furnished the dinitrile (+)-(**12**) in higher yields than the sequence of reactions (i) tosylation and (ii) reaction of tosyl diester with NaCN. The ketone (+)-(**16**) was prepared from the enantiomer (+)-(**15**) by again employing the sequence of reactions in Scheme 1. Aldol condensation of the ketone (+)-(**16**) with benzaldehyde is regioselective; the reaction takes place at the less hindered

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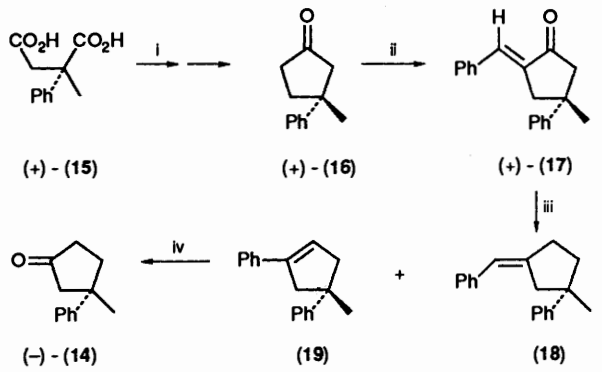
‡ Chiral inversion is not limited to carbocyclic ketones having an odd number of carbon atoms in the ring. In principle, it should be possible to effect chiral inversion of a ketone, whose deoxy compound is of *meso* configuration, by appropriate ketone transposition.

carbon atom C-5 to furnish the crystalline benzylidene derivative (**17**). The mixture of hydrocarbons (**18**) and (**19**) obtained through reduction of the ketone (**17**) with $LiAlH_4$–$AlCl_3$ furnished, after ozonolysis and oxidative work-up, the ketone (−)-(**14**) identical in all respects (IR; NMR; specific rotation) with a sample prepared from the acid (−)-(**8**). The synthesis of the ketone (−)-(**14**) from the (−)-enantiomer (**8**) (according to Scheme 1) and also from the (+)-enantiomer (**15**) (according to Scheme 2) constitutes an enantioconvergent synthesis. This



Scheme 2. *Reagents:* i, Sequence of reactions given in Scheme 1; ii, PhCHO, NaOH, MeOH, H_2O; iii, $LiAlH_4$, $AlCl_3$, Et_2O; iv, O_3/CrO_3, acetone.

synthesis utilizes the chiral inversion of the ketone (+)-(**16**) by employing 1,2-ketone transposition. The concept developed for the synthesis of ketone (−)-(**14**) has been employed recently[8] for an enantioconvergent synthesis of the naturally occurring (−)-α-cuparenone.

Experimental

IR spectra were recorded on a Perkin-Elmer 599B infra-red spectrophotometer. ^1H NMR spectra were recorded on a Varian T-60, Varian FT-80A, or Brucker WH-90 spectrometer, with tetramethylsilane as internal standard. Optical rotations were determined at the sodium D-line with a JASCO DIP-181 digital polarimeter at ambient temperature. All m.p.s were measured on a Büchi apparatus, and, together with b.p.s, are uncorrected.

(−)-*Dimethyl 2-Methyl-2-phenylbutanedioate* (**9**).—A mixture of (−)-diacid (**8**)[7] (0.208 g, 1.0 mmol), methanol (10 ml), and H_2SO_4 (0.2 g) was heated under reflux for 3 h. Usual work-up furnished the *diester* (**9**) (0.212 g, 90%), b.p. 120–130 °C (bath)/1 mmHg; $[\alpha]_D^{27}$ −16° (*c* 1.5, EtOH) (Found: C, 66.0; H, 6.75. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); δ(CCl_4) 1.70 (3 H, s, MeC), 2.87 (2 H, ABq, *J* 16 Hz, CH_2CO), 3.63 (3 H, s, OMe), 3.70 (3 H, s, OMe), and 7.23 (5 H, s, Ph).

(+)-2-*Methyl-2-phenylbutane*-1,4-*diol* (**10**).—A mixture of diester (**9**) (0.236 g, 1.0 mmol), $LiAlH_4$ (0.152 g), and dry diethyl ether (20 ml) was stirred at 0 °C for 24 h, heated under reflux for 4 h, cooled, and poured on ice. The reduction product was chromatographed on grade II alumina to furnish the *diol* (**10**) (0.153 g, 85%), $[\alpha]_D^{27}$ +6° (*c* 0.9, EtOH) (Found: C, 73.3; H, 8.8. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%); δ($CDCl_3$) 1.30 (3 H, s, MeC), 1.96 (2 H, t, *J* 6 Hz, CH_2CH_2OH), 3.50–3.70 (4 H, m, 2 × CH_2OH), and 7.29 (5 H, m, Ph).

(+)-3-*Methyl-3-phenylhexanedinitrile* (**12**).—A mixture of the diol (**10**) (0.135 g, 0.75 mmol), triethylamine (0.166 g), and CH_2Cl_2 (5 ml) was added during 10 min to a solution of mesyl chloride (0.22 g, 1.91 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred for 30 min and poured onto ice. The aqueous layer was extracted with methylene dichloride. The combined extracts were dried (Na_2SO_4). Evaporation of the solvent furnished the mesyl diester (**11**) (0.268 g, 80%).

A mixture of compound (**11**) (0.241 g), NaCN (0.06 g), hexamethylphosphoric triamide (HMPA) (10 ml), and water (0.1 ml) was heated at 90 °C for 24 h. The reaction mixture was diluted with water, then extracted with diethyl ether, and the extract was dried (Na_2SO_4). Evaporation of the solvent furnished the *dinitrile* (**12**) (0.094 g, 88%); $[\alpha]_D^{27}$ +27° (*c* 1.1, EtOH) (Found: C, 78.7; H, 7.1; N, 14.0. $C_{13}H_{14}N_2$ requires C, 78.75; H, 7.1; N, 14.1%); ν_{max} 2 220 cm^{-1} (CN); δ($CDCl_3$) 1.56 (3 H, s, Me), 1.90–2.35 (4 H, m, CH_2CH_2CN), 2.66 (2 H, s, ArCCH_2CN), and 7.28 (5 H, m, Ph).

(+)-3-*Methyl-3-phenylhexanedioic Acid* (**13**).—A mixture of dinitrile (**12**) (0.082 g, 0.41 mmol), KOH (0.23 g, 4.1 mmol), and ethane-1,2-diol (5 ml) was heated under reflux for 6 h. The reaction mixture was diluted with water, acidified, extracted with chloroform, and the extract was dried and evaporated to furnish the *diacid* (**13**) (0.088 g, 90%), m.p. 147 °C (from EtOH); $[\alpha]_D^{27}$ +16° (*c* 1.2, EtOH) (Found: C, 66.0; H, 6.7. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); δ($CDCl_3$) 1.50 (3 H, s, Me), 2.05 (4 H, m, $CH_2CH_2CO_2H$), 2.60 (2 H, s, ArCCH_2), and 7.24 (5 H, m, Ph).

(−)-3-*Methyl-3-phenylcyclopentanone* (**14**).—A mixture of diacid (**13**) (0.088 g) and $Ba(OH)_2$ (0.02 g) was placed in a distillation flask which was immersed in a graphite covered tin–lead bath maintained at 320 °C. The distillate was redistilled to furnish the *ketone* (**14**) (0.048 g, 73%), b.p. 110 °C (bath)/1 mmHg; $[\alpha]_D^{27}$ −10° (*c* 1.1, EtOH) (Found: C, 82.7; H, 8.1. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%); ν_{max} 1 740 cm^{-1} (CO); δ($CDCl_3$) 1.38 (3 H, s, Me), 2.28 (4 H, m, CH_2CH_2CO), 2.56 (2 H, ABq, *J* 15 Hz, ArCCH_2), and 7.24 (5 H, m, Ph).

(+)-2-*Benzylidene-4-methyl-4-phenylcyclopentanone* (**17**).—A sample of (+)-ketone (**16**), $[\alpha]_D^{27}$ +10° (*c* 1.1, EtOH), was prepared starting from (+)-diacid (**15**) following the sequence of reactions described above. A mixture of (+)-ketone (**16**) (0.048 g, 0.26 mmol), benzaldehyde (0.028 g, 0.26 mmol), NaOH (0.005 g), water (2 ml), and MeOH (2 ml) was heated under reflux for 6 h, diluted with water, and extracted with diethyl ether, and the extract was dried (Na_2SO_4). The residue obtained after evaporation of the solvent was recrystallized from light petroleum (60–80 °C)–ethanol (1:1) to furnish *compound* (**17**) (0.035 g, 48%), m.p. 96 °C; $[\alpha]_D^{27}$ +260° (*c* 2.0, EtOH) (Found: C, 86.75, H, 7.0. $C_{19}H_{18}O$ requires C, 87.0; H, 6.9%); δ($CDCl_3$) 1.30 (3 H, s, Me), 2.72 (2 H, ABq, *J* 16 Hz, CH_2CO), 3.22 (2 H, d, *J* 2 Hz, $CH_2C{=}CH$), and 7.15–7.7 (11 H, m, Ph and vinyl H).

(−)-*Ketone* (**14**) *from the Benzylidene Derivative* (+)-(**17**).—A mixture of compound (**17**) (0.024 g), diethyl ether (5 ml), $AlCl_3$ (0.019 g), and $LiAlH_4$ (0.006 g) was stirred at 25 °C for 4 h. The reduction product was purified through preparative TLC (PLC) [silica gel; chloroform–light petroleum (60–80 °C)] to furnish a 70:30 mixture of compounds (**18**) and (**19**) (0.02 g); the composition of the mixture was determined by comparison of the areas of the signals due to the vinyl H of each compound in the NMR spectrum.

The mixture of compounds (**18**) and (**19**) (0.02 g) was dissolved in ethyl acetate (10 ml) and treated with ozone at 0 °C until no starting material remained (TLC). A mixture of the ozonized solution and Jones' reagent[9] (5 ml) was stirred at 0–10 °C for 2 h. The excess of Jones' reagent was destroyed by addition of EtOH. The reaction product was separated into acidic and neutral fractions. Purification of the neutral fraction through PLC furnished compound (**14**) (0.008 g, 47%), $[\alpha]_D^{27}$ −10° (*c* 0.9, EtOH). The IR and NMR spectra of ketone (**14**)

thus obtained were identical with those spectra of a sample prepared according to Scheme 1.

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Paper 0/01035I
Received 7*th March* 1990
Accepted 13*th June* 1990