Chemical Synthesis and Optical Purity Determination of Optically Active 1,2-Epoxyindan and Alcohol Products which are also derived from Mammalian or Microbial Metabolism of Indene or Indanones

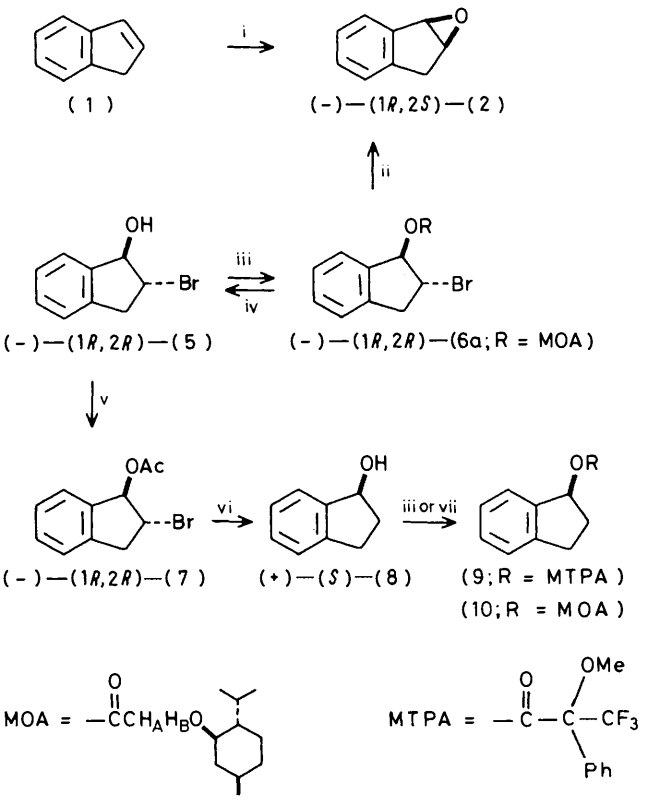
Derek R. Boyd,* Narain D. Sharma, and Alistair E. Smith
Department of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, N. Ireland

(+)-*trans*-2-Bromo-1-hydroxyindan (5) has been resolved into its enantiomers by preparative h.p.l.c. or fractional crystallization of the bromo-menthyloxy-acetoxydiastereoisomers (6a) and (6b). The bromohydrin (5) or bromo-esters (6a, 6b, and 7) have in turn been converted into (−)-(1*R*,2*S*)-1,2-epoxyindan (2), (−)-(1*R*,2*R*)-*trans*-1-acetoxy-2-bromoindan (7), (+)-(1*S*)-indanol (8), (−)-(1*R*,2*R*)-*trans*-indan-1,2-diol (3), and (−)-(1*S*,2*R*)-*cis*-indan-1,2-diol (4). The optical purity of the alcohol products (3), (4), and (8) was determined by n.m.r. and h.p.l.c. analysis of their 2-methoxy-2-phenyl-2-trifluoromethylacetates. The previously unknown optical purity of the chiral alcohols (3), (4), (5), and (8), which had been isolated in earlier mammalian and microbial metabolism studies, has also been deduced.

The metabolism of indene (1) by animals or animal-liver microsomes has been investigated extensively.[1–4] Early interest in the metabolic fate of indene arose from its presence in coal-tar products and from its classification as both an olefin and an arene substrate. The initially formed product of the metabolism of indene in animal-liver fractions (*in vitro*) was 1,2-epoxyindan (2), which was subsequently hydrolysed in the presence of liver-microsomal enzymes to *trans*-indan-1,2-diol (3).[2–4] This enzyme-catalysed epoxide ⟶ *trans*-diol sequence has also been observed in the metabolism of arenes.[5] The presence of the *cis*-diol (4) among the products recovered from early studies [1] on the metabolism of indene by animals (*in vivo*) was therefore unusual. The origin of this *cis*-diol during *in vivo* metabolism was unclear, since both *cis*- and *trans*-diols were recovered when 1,2-epoxyindan or either diol isomer was administered to rats.[6] The diols (3) and (4) are chiral and have been isolated in an optically active form (but of unspecified optical yield) from metabolism (by animal enzymes) of both indene [1] and a range of indan derivatives including (±)-(2),[6] (±)-(3),[6] (±)-(4),[6] indan-1-one,[6] indan-2-one,[7] and 2-hydroxyindan-1-one.[6]

Microbial enzyme-catalysed transformations have recently been found to provide a valuable synthetic route to chiral indan derivatives.[8–10] Thus, microbial reduction of indan-1-one [9] and 2-bromoindan-1-one [8] gave an enantiomeric excess of (+)-indan-1-ol (8) and (+)-*trans*-2-bromo-1-hydroxyindan (5), respectively. A predominance of the (−)-enantiomer of (5) resulted from enantioselective hydrolysis of *trans*-1-acetoxy-2-bromoindan (7) in the presence of *Rhizopus nigricans*.[10] Of the isolated optically active products (3)—(5) and (8) resulting from enzyme-catalysed reactions,[1–4,8–10] only the last-named product has to date been chemically resolved into its enantiomers.[11–14] Unfortunately, however, a significant variation between the maximum observed $[\alpha]_D$ values for the indanol (8) was reported (−30.1° and +38.9°,[11] +34.0 [14]) and thus it has not to date proved possible to obtain any reliable estimate of optical purity.[9,10,12,13] In view of the factors discussed, and earlier reports from these laboratories on the chemical resolution of optically active epoxide and diol metabolites,[15–21] a chemical synthesis of optically pure metabolites (2)—(5) and (8) was undertaken.

(±)-*trans*-2-Bromo-1-hydroxyindan (5) was esterified by treatment with (−)-menthyloxyacetyl chloride in pyridine. The resulting menthyloxyacetate (MOA) diastereoisomers (6a) and (6b) were found to be separable by careful preparative h.p.l.c. (α 1.08, Zorbax-Sil, cyclohexane–diethyl ether 98 : 2). Using some of the diastereoisomerically pure (≥98%) fraction of the ester (6b) ([α] +82°) as seed crystals, it was subsequently possible to obtain (6b) as the less soluble diasteroisomer from fractional recrystallization of the original mixture of (6a) and (6b). Thus, by a combination of preparative h.p.l.c. [which more readily yielded a pure sample of the (−)-isomer (6a), $[\alpha]_D$ −183.3°] and recrystallization [which yielded pure (6b)] each diasteroisomer could be obtained in pure (≥98%) form.



Scheme 1. Reagents: i, Mono-oxygenase–O_2; ii, NaOMe–Et_2O; iii, (−)-menthyloxyacetyl chloride–pyridine; iv, diborane–THF; v, Ac_2O–pyridine; vi, $LiAlH_4$–THF; vii, (−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride–pyridine

Table 1. Optical rotations, optical yields and absolute stereochemistry of chiral indan derivatives

Compound	Optical rotation [a] $[\alpha]_D$ (°)	Configuration	Optical rotation [b] $[\alpha]_D$ (°)	Optical yield [b] (%)	Configuration [b]
(5)	−64.4 [c]	(1*R*,2*R*)	+29.0 [c,d]	45	(1*S*,2*S*)
(6 A)	−183.3 [e,f]	(1*R*,2*R*)			
(2)	−55.0 [e]	(1*R*,2*S*)	+17.5 [e,d]	32	(1*S*,2*R*)
(3)	−29.4 [c,g]	(1*R*,2*R*)	−10.7 [c,d]	35	(1*R*,2*R*)
			+30.0 [c,h]	100	(1*S*,2*S*)
(4)	−51.6 [e,g]	(1*S*,2*R*)	+41.0 [e,h]	79	(1*R*,2*S*)
			+43.0 [e,i]	83	(1*R*,2*S*)
(7)	−167.5 [c]	(1*R*,2*R*)	+79.2 [c,d]	47	(1*S*,2*S*)
(8)	+30.8 [e]	(*S*)	−18.0 [e,d]	58	(*R*)
			+22.6 [e,j]	73	(*S*)

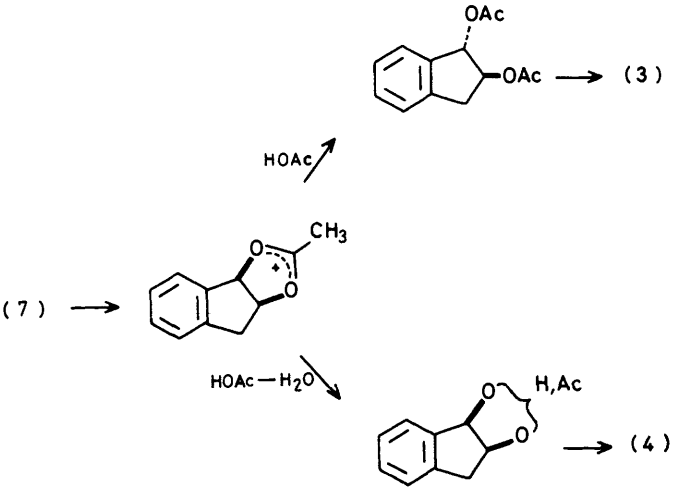
[a] Optical purity ≥98% (see Table 2). All compounds are derived from (6 a) except (3) and (4) which come from (6b). [b] Mammalian or microbial metabolites and derivatives. [c] EtOH solvent. [d] Ref. 9. [e] $CHCl_3$ solvent. [f] Diastereoisomer (6b) gave $[\alpha]_D$ +82.0° ($CHCl_3$). [g] Derived from (6b). [h] Ref. 7. [i] Ref. 1. [j] Ref. 8.

The absolute stereochemistry of the isomers (6a) and (6b) was deduced from their n.m.r. spectra using a method which has previously proved totally successful for a number of comparable cyclic bromo-menthyloxyacetate diastereoisomers.[15–21] The exocyclic methylene group (H_A, H_B) appeared in the ^1H n.m.r. spectrum as an AB quartet (J_{AB} 16.9 Hz) for the more polar isomer (6b) (which was eluted as the later peak in the h.p.l.c. trace) and by analogy with earlier studies [15–21] was assigned a (1*S*,2*S*)-configuration. Similarly, (6a) was assumed to have a (1*R*,2*R*)-configuration, since the signal for $H_{A'}$ and $H_{B'}$ appeared as a singlet (C_6D_6; 250 MHz).

The chemical interconversion and stereochemical correlation of ester (6a) or (6b) to the corresponding enantiomeric forms of the bromohydrin (5), bromoacetate (7), alcohol (8), and epoxide (2) was again carried out using similar methods to those used for the analogous tetrahydro-derivatives of naphthalene,[15] anthracene,[15] phenanthrene,[16,17] chrysene,[18] benz[*a*]anthracene,[19,20] and benzo[*a*]pyrene [21] series (Scheme 1 and Table 1). The formation of (+)-indanol (8) ($[\alpha]_D$ +30.8°) from the (−)-isomer (6a) (≥98%diateroisomeric purity) *via* (−)-(5) and (−)-(7) occurred by a reaction sequence in which the absolute configuration at C-1 remained unaltered. The optical purity of (+)-(8) was confirmed to be ≥98% by h.p.l.c. and n.m.r. analyses of the MTPA or MOA ester (Table 2). On the basis of these results, optically pure indanol (5) should be considered to have a maximum $[\alpha]_D$ value of ±31.4° ($CHCl_3$). This stereochemical correlation of the (−)-ester (6a) with (−)-(5), (−)-(7), and (+)-(8) is in total accord with an earlier study on enantiomerically enriched samples [(+)-(5) ⟶ (+)-(7) ⟶ (−)-(8) [9]] and with the present n.m.r. assignment of configuration of (1*R*,2*R*) to (6a).

From the diastereoisomers (6a) and (6b), the only compound to have been synthesised in both enantiomeric forms was *trans*-2-bromo-1-hydroxyindan ($[\alpha]_D$ −64.4°, +64.0°). The synthesis of optically pure (−)-(1*R*,2*S*)-1,2-epoxyindan (2) (and the ready availability of the opposite enantiomer by the present method) will facilitate stereochemical studies on the action of epoxide hydrolase enzyme in the indene series.

The chemical conversion of *trans*-1-acetoxy-2-bromoindan (7) into the *cis*- (4) and *trans*-diols (3) using silver acetate has been reported, using both the racemic [23] and enantiomerically enriched [9] samples. The mechanism proposed [23] involved a cyclic cationic structure (Scheme 2) which opens up in dry acetic acid solution to give the essentially pure *trans*-diacetate which could be hydrolysed to the *trans*-diol. In acetic acid solvent containing more than one equivalent of water, an ortho-monoacetate product yielded the *cis*-diol as the major (*ca.* 98%) isomer with total retention of configuration. The



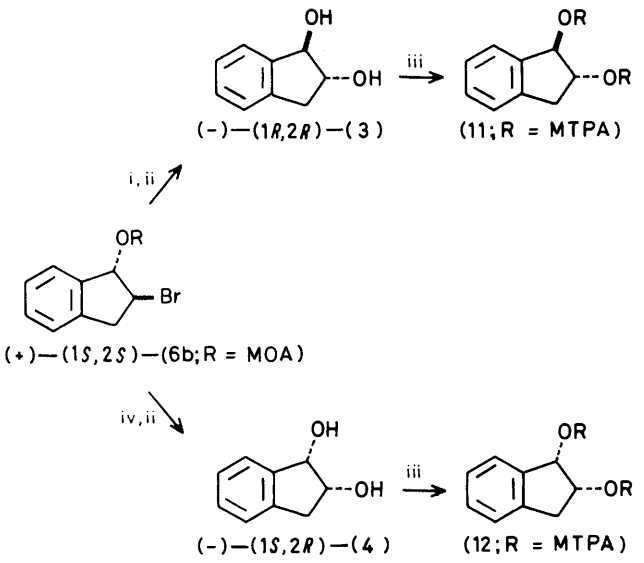
Scheme 2.

high optical yield (≥98%) obtained for (−)-(3) after treatment of the (+)-isomer (6b) with silver acetate in dry acetic acid (Scheme 2) suggests that attack of the acetate anion on the cyclic intermediate cation is virtually 100% regioselective, *i.e.* almost exclusive attack at the C-1 centre. Optical purity determinations of (−)-(3) and (−)-(4) formed from (6b) (Scheme 3) led to estimates of ≥98% enantiomeric excess by h.p.l.c. and n.m.r. analysis of their respective MTPA esters (Table 2).

Based upon the present results it is now possible to estimate the optical yields of chiral derivatives (2)—(5) and (7)—(8) resulting from the earlier metabolism studies (Table 1). It is noteworthy that in only one example, the (+)-diol (3),[7] was the isolated product from mammalian or microbial metabolism optically pure.

Experimental

N.m.r. spectra were obtained using a Bruker (Model WM-250) 250 MHz instrument with deuteriochloroform as solvent and tetramethylsilane as reference unless stated otherwise. Mass spectra were recorded on an AEI-MS902 instrument operating at 70 eV. H.p.l.c. analyses were carried out using a Spectra-Physics 3500B Model coupled to a Cecil Instruments CE272 u.v. detector and a Water Associates Differential Refractometer (Model R401). Analytical and preparative separations



Scheme 3. *Reagents:* i, AgOAc–CH_3CO_2H; ii, KOH–MeOH; iii, (−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride–pyridine; iv, AgOAc–CH_3CO_2H–H_2O

column and cyclohexane–diethyl ether (98 : 2) as eluant (α 1.08) initially gave a partial separation of diastereoisomers (6a) and (6b) (Found: C, 61.8; H, 7.2. $C_{21}H_{28}BrO_3$ requires C, 61.55; H, 7.1%). Repeated preparative h.p.l.c. separation finally yielded the isomers (6a) and (6b) in ⩾98% diastereoisomeric purity. Fractional crystallization of the unresolved mixture (6a)–(6b) [seeded with a crystal of (6b)] from light petroleum, (b.p. 40—60 °C) resulted in a convenient route for the separation of the less soluble isomer (6b). Compound (6a) was eluted early from h.p.l.c., m.p. 48—50 °C (light petroleum) $[\alpha]_D$ −183.3° ($CHCl_3$); δ (C_6H_6) 2.87 (dd, 1 H, 3-H, $J_{3,3'}$, 16.9 Hz, $J_{3,2}$ 4.4 Hz), 3.18 (dd, 1 H, 3'-H), $J_{3,3'}$ 16.9 Hz, $J_{3',2}$ 6.6 Hz), 3.90 (s, 2 H, H_A and H_B), 4.26 (m, 1 H, 2-H), 6.53 (d, 1 H, 1-H, $J_{1,2}$ 3.7 Hz), 6.18 (m, 1 H, Ar), 6.98 (m, 2 H, Ar), and 7.36 (m, 1 H, Ar). Compound (6b) was eluted late from h.p.l.c., m.p. 70—72 °C (light petroleum), $[\alpha]_D$ +82.0 ($CHCl_3$); δ (C_6D_6) 2.87 (dd, 1 H, 3-H, $J_{3,3'}$ 16.9 Hz, $J_{3,2}$ 4.4 Hz), 3.19 (dd, 1 H, 3'-H, $J_{3,3'}$ 16.9, $J_{3',2}$ 6.6 Hz), 3.84 (d, 1 H, H_A, J_{AB} 16.2 Hz), 3.95 (d, 1 H, H_B, J_{AB} 16.2 Hz), 4.27 (m, 1 H, 2-H), 6.51 (d, 1 H, 1-H, $J_{1,2}$ 3.3 Hz), 6.81 (m, 1 H, Ar), 6.91 (m, 2 H, Ar), and 7.38 (m, 1 H, Ar).

(−)-(1R,2R)- *and* (1S,2S)-trans-2-*Bromo*-1-*hydroxyindan* (5).—The synthesis of the (−)-isomer (5) was carried out in 75% yield from the ester (6a) ($[\alpha]_D$ −183.3°) using the diborane

Table 2. Optical purity determination of chiral alcohols [a] by analysis of their MOA or MTPA esters

Alcohol	MOA or MTPA ester [b]	α-Values [b]	N.m.r.[c]	Optical purity [a,d]	Configuration
(+)-(8)	(9a) [e]	1.20	3.50 [f]	⩾98%	(1*S*)
(−)-(8)	(9b) [e]	1.20	3.53 [f]		(1*R*)
(+)-(8)	(10a) [g]	1.11	3.93 [h]	⩾98%	(1*S*)
(−)-(8)	(10b) [g]	1.11	3.94 [h]		(1*R*)
(+)-(3)	(11a) [i]	1.38	3.56,[f] 6.61 [j]	⩾98%	(1*S*,2*S*)
(−)-(3)	(11b) [i]	1.38	3.50,[f] 6.51 [j]		(1*R*,2*R*)
(−)-(4)	(12a) [k]	1.08	3.35,[f] 6.32 [l]	⩾98%	(1*S*,2*R*)
(+)-(4)	(12b) [k]	1.08	3.45,[f] 6.48 [l]		(1*R*,2*S*)

[a] Optical rotations of samples of (−)-(3), (−)-(4), and (+)-(8) are given in the Experimental section. [b] a = early isomer and b = late isomer eluted from Zorbax-Sil h.p.l.c. column with 2—3% diethyl ether in cyclohexane. [c] Selected δ values for each diastereoisomer (250 MHz; $CDCl_3$). [d] The observed optical purity values were obtained by both n.m.r. and h.p.l.c. analysis of the appropriate peak areas. [e] Found: M^+, 350.112 85. $C_{19}H_{17}F_3O_3$ requires *M*, 350.112 97. [f] OMe. [g] Found: M^+, 330.219 41. $C_{21}H_{30}O_3$ requires *M*, 330.219 48. [h] In C_6D_6; exocyclic methylene protons H_A, H_B and $H_{A'}$,$H_{B'}$ (dd, $J_{AB} = J_{A'B'} = 16.9$ Hz). [i] Found: M^+, 582.147 48. $C_{29}H_{24}F_6O_6$ requires *M*, 582.147 68. [j] H_1 [d, $J_{1,2}$ 4.4 (11a) or 3.7 (11b) Hz]. [k] Found: *M*, 582.149 21. $C_{29}H_{24}F_6O_6$ requires *M*, 582.147 68. [l] H_1 (d, $J_{1,2}$ 5.2 Hz).

were carried out using Du-Pont Zorbax-Sil columns (6.2 mm × 25 mm and 9.4 × 25 mm respectively) and cyclohexane–diethyl ether mixtures. Optical rotations were determined using a Perkin-Elmer automatic polarimeter (Model 242) with chloroform or ethanol solvents and a concentration of *ca.* 10 mg ml^{-1}.

trans-1-Hydroxy-2-bromoindan, (−)-menthyloxyacetic acid (MOAA), and (−)-2-methoxy-2-phenyl-2-trifluoromethylacetic acid (MTPAA) were purchased from Aldrich Chemical Co. Ltd.

(−)-(1R,2R)- *and* (+)-(1S,2S)-trans-2-*Bromo*-1-(*menthyloxyacetoxy*)*indan* (6a) *and* (6b).—The diastereoisomeric mixture (6a)–(6b) was obtained in 95% yield by treatment of the hydroxy-compound (5) with (−)-menthyloxyacetyl chloride in pyridine. Preparative h.p.l.c. separation using a Zorbax-Sil

method.[15] Recrystallization of the (−)-indan (5) from chloroform–light petroleum (b.p. 40—60 °C) gave colourless crystals, m.p. 116—118 °C (lit.,[23] m.p. 129.5—130 °C), $[\alpha]_D$ −64.4° (EtOH). The n.m.r. spectrum was identical with that of the racemic sample and with that reported.[9] The enantiomer of opposite chirality, the (+)-indan (5), $[\alpha]_D$ +64.0° (EtOH), was obtained by similar treatment of the (+)-isomer (6b).

(−)-(1R,2S)-1,2-*Epoxyindan* (2).—Treatment of either bromo-ester (6a) ($[\alpha]_D$ −183.3°) or (7) ($[\alpha]_D$ −167.5°) with sodium methoxide in diethyl ether by the normal method [15] gave the (−)-isomers of (2) (80%) which was purified by distillation, b.p. 40 °C at 0.1 mmHg (lit.,[9] b.p. 78 °C at 1.0 mmHg), $[\alpha]_D$ −55° ($CHCl_3$); δ 2.94 (dd, 1 H, 3-H, $J_{3,3'}$ 18.0 Hz, $J_{3,2}$ 2.9 Hz), 3.22 (d, 1 H, 3'-H, $J_{3',3}$ 18.0 Hz), 4.13 (dd, 1 H, 2-H, $J_{2,1}$ 2.6 Hz, $J_{2,3}$ 2.9 Hz), 4.27 (d, 1 H, 1-H, $J_{1,2}$ 2.6 Hz), 7.22 (m,

3 H, Ar), and 7.50 (d, 1 H, Ar, J 7.0 Hz) (Found: M^+, 132.0575. C_9H_8O requires M, 132.057 51).

(−)-(1R,2R)-trans-1-*Acetoxy*-2-*bromoindan* (7).—Reaction of the hydroxy-compound (5) ($[\alpha]_D$ −64.4°) with acetic anhydride in pyridine gave (−)-(1R,2R)-*trans*-1-acetoxy-2-bromoindan (7) (90%) as a colourless, high b.p. oil (lit.,[23] b.p. 124—126 °C at 1.7 mmHg) which was purified by preparative t.l.c., $[\alpha]_D$ −167.5° (EtOH). The sample gave an n.m.r. spectrum identical with the racemic compound and with that reported.[9]

(+)-(1S)-*Indanol* (8).—Reduction of the (−)-isomer of (7) by $LiAlH_4$ in dry THF at ambient temperature gave (+)-indanol (8) in 60% yield. Recrystallization from light petroleum (b.p. 40—60 °C) gave (+)-(8), m.p. 72 °C (lit.,[11] m.p. 72 °C), $[\alpha]_D$ +30.8° ($CHCl_3$).

(−)-(1R,2R)-trans-*Indan*-1,2-*diol* (3).—A mixture of acetic acid, acetic anhydride, and silver acetate was refluxed with the ester (6b) ($[\alpha]_D$ +82°) to form a diester intermediate which was hydrolysed *in situ*, using aqueous methanolic KOH, and worked up to yield the (−)-isomer of (3) using conditions previously reported for the reaction on the acetate (7).[9,23] Purification by preparative t.l.c. (silica gel eluted with $CHCl_3$–MeOH, 92 : 8) followed by recrystallization from chloroform–methanol gave (−)-(3) (55%), m.p. 184—186 °C (lit.,[9] 182—184 °C), $[\alpha]_D$ −29.4° (EtOH).

(−)-(1S,2R)-cis-*Indan*-1,2-*diol* (4).—Using conditions similar to those reported for the reaction of the acetate (7),[9,23] the bromo-ester (6b) ($[\alpha]_D$ +82°) was treated with silver acetate in aqueous acetic acid. Direct hydrolysis of the intermediate (KOH–MeOH–H_2O) yielded the (−)-isomer of (4) which was worked up and purified by preparative t.l.c. as for (−)-(3). Recrystallization from chloroform–hexane gave (−)-(4) (10%), m.p. 109—111 °C (lit.,[9] 99—100 °C), $[\alpha]_D$ −51.6°.

Optical Purity Determination of the Chiral Alcohols (3), (4), *and* (8) *by N.m.r. and H.p.l.c. Analyses of their MOA* (10) *or MTPA* (9), (11), (12) *Esters* (*Table* 2).—The alcohols (3), (4), and (8) were converted into their corresponding MTPA esters using the acid chloride from (−)-MTPA in pyridine by the normal method. The products (9), (11), and (12) were viscous, high b.p. oils which were separated from impurities by preparative t.l.c. and characterized by h.p.l.c., and their n.m.r. and mass spectra methods (Table 2). The MOA ester (10) was prepared in a similar manner using the acid chloride of (−)-MOAA.

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References

1 C. J. W. Brooks and L. Young, *Biochem. J.*, 1956, **63**, 264.
2 K. C. Leibman and E. Ortiz, *Mol. Pharmacol.*, 1968, **4**, 201.
3 K. C. Leibman and E. Ortiz, *J. Pharmacol. Exp. Ther.*, 1970, **173**, 243.
4 T. J. R. Francis, R. J. Rick, P. Callaghan, and R. P. Hopkins, *Biochem. Soc. Trans.*, 1975, **3**, 1244.
5 D. M. Jerina and J. W. Daly, *Science*, 1974, **185**, 573.
6 D. A. Lewis, *Biochem. J.*, 1966, **99**, 694.
7 D. A. Lewis, *Nature*, 1966, **210**, 1046.
8 K. Kabuto, M. Imuta, E. S. Kempner, and H. Ziffer, *J. Org. Chem.*, 1978, **43**, 2357.
9 M. Imuta and H. Ziffer, *J. Org. Chem.*, 1978, **43**, 4540.
10 K. Kawai, M. Imuta, and H. Ziffer, *Tetrahedron Lett.*, 1981, 2527.
11 W. Hückel and F. Mössner, *Ann.*, 1960, **637**, 57.
12 D. Battail and D. Gagnaire, *Bull. Soc. Chim. Fr.*, 1964, 3076.
13 J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.*, 1966, **88**, 2233.
14 G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4667.
15 M. N. Akhtar, D. R. Boyd, and J. G. Hamilton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2437.
16 D. R. Boyd, J. D. Neill, and M. E. Stubbs, *J. Chem. Soc., Chem. Commun.*, 1977, 873.
17 D. R. Boyd and R. M. E. Greene, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1535.
18 D. R. Boyd, M. G. Burnett, and R. M. E. Greene, *J. Chem. Soc., Chem. Commun.*, 1981, 838.
19 D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malone, and N. D. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1981, 94.
20 D. R. Boyd, G. S. Gadaginamath, N. D. Sharma, A. F. Drake, S. F. Mason, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2233.
21 D. R. Boyd, G. S. Gadaginamath, A. Kher, J. F. Malone, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2112.
22 W. G. Dauben and P. Baumann, *Tetrahedron Lett.*, 1961, 565.
23 S. Winstein and R. M. Roberts, *J. Am. Chem. Soc.*, 1953, **75**, 2298.

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