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AN IMPROVED METHOD FOR THE SYNTHESIS OF OPTICALLY PURE EPOXIDE AND ALCOHOL DERIVATIVES OF CHIRAL BROMOHYDRINS

Suresh K. Balani, Derek R. Boyd,* E. Sally Cassidy, Ruth M.E. Greene,
Kenneth M. McCombe and Narain D. Sharma
Department of Chemistry, The Queen's University of Belfast, Belfast, BT9 5AG, N. Ireland.
and W. Brian Jennings,
Department of Chemistry, University of Birmingham, Birmingham, B15 2TT, England.

SUMMARY: The resolution of arene oxides, diols and other derivatives of bromohydrins has been markedly improved by the use of bromohydrin esters of (-)-(S)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).

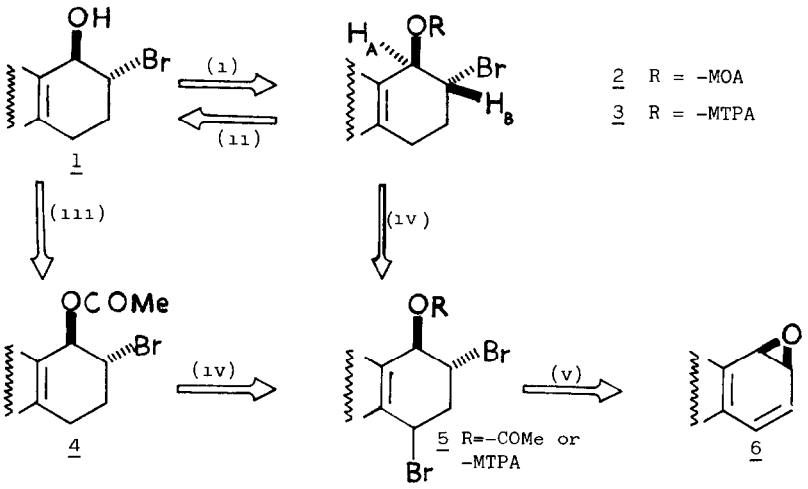
The metabolism of polycyclic aromatic hydrocarbons (PAHs) in mammals involves initially the addition of an oxygen atom to form an arene oxide intermediate. Some of the arene oxide metabolites of the carcinogenic PAHs benzo(a)pyrene,[1,2] benz(a)anthracene,[3,4] and chrysene[5] are considered to be formed in high optical yield during this enzyme controlled oxidation. A general route has been previously developed for the chemical synthesis of optically active arene oxides, tetrahydroepoxides, diols etc. in which the key resolution step involved the separation of menthyloxyacetate (MOA) esters (2) of bromohydrins (1)[1-7] (Scheme).

While the latter scheme has proved to be applicable to a wide range of arene oxides it can now be significantly improved upon by the use of commercially available (-)-(S) [or (+)-(R)] α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) as resolving agent to form the corresponding bromo MTPA esters (3). The bromo MTPA route to chiral epoxides and alcohols has a number of advantages over the original bromo MOA method including the following:

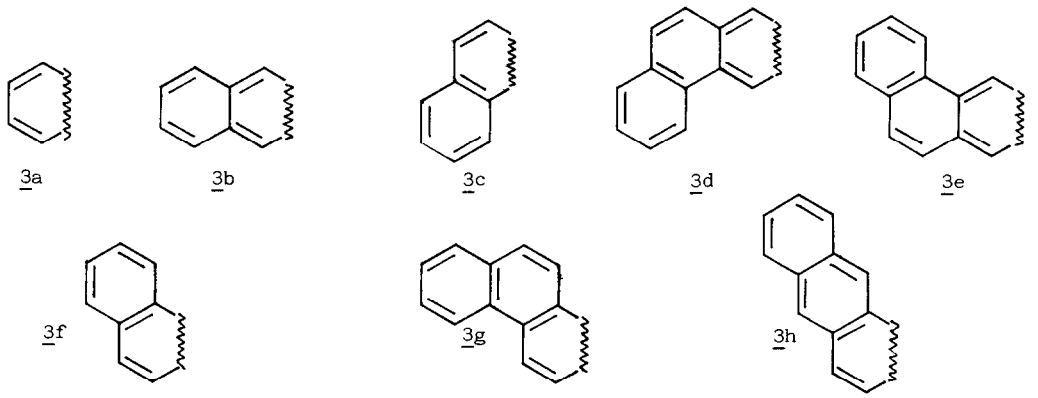
(a) The bromo MTPA esters were found to be more easily separated chromatographically than the corresponding bromo MOA esters. Thus, a complete separation by analytical and preparative t.l.c. on silica-gel into high (3H) and low (3L) R_f fractions was only possible using bromo MTPA esters. Similarly, the larger separation factors (α) observed for diastereoisomers of 3 (relative to 2) under identical h.p.l.c. conditions (Table 1) allowed both analytical and preparative h.p.l.c. separations to be more easily obtained. The MTPA chromophore was also found to be particularly useful for u.v. detection of lower molecular weight bromo MTPA ester diastereoisomers after separation by h.p.l.c.

(b) Separation of bromo MTPA ester diastereoisomers by fractional crystallization was generally achieved more readily. In examples where only one bromo MOA or MTPA ester diastereoisomer was obtained in the crystalline state it was often difficult to obtain the other isomer in a pure diastereoisomeric form. This problem was overcome by using MTPA of opposite chirality to obtain the alternative enantiomeric form of the crystalline diastereoisomer.

SCHEME



(i) (-) menthyloxyacetyl chloride/pyridine or (-) α-methoxy-α-trifluoromethylphenylacetyl chloride/pyridine (ii) 2/diborane (iii) acetic anhydride/pyridine (iv) N-bromosuccinimide (v) NaOMe/THF.



(c) Diastereoisomers of bromo MOA esters have previously been characterized by differences in the coupling constants of the exocyclic methylene protons in the MOA group. The MTPA esters of the non-bay region isomers (3a-e) may similarly be distinguished by a difference in coupling constants ($J_{A,B}$) for the H_A doublet i.e. the low R_f isomer (3L) had a larger $J_{A,B}$ value (Table 2). A small but significant and general trend in both ^1H and ^{19}F chemical shifts was observed. By analogy with previous reports on the relative values for protons in MTPA diastereoisomers of chiral secondary alcohols[7] equivalent to H_B in 3, a consistent difference in chemical shift values with absolute stereochemistry was observed i.e. low R_f isomer (3L) was further downfield from the reference. An analysis of the ^{19}F chemical shift positions again showed a consistent trend i.e. the low R_f isomer (3L) was further upfield from the reference.

TABLE 1: SEPARATION FACTOR (α), OPTICAL ROTATION ($[\alpha]_D$) AND ABSOLUTE STEREOCHEMISTRY OF 3

Compound[1]	α[2,3]	$[\alpha]_D$($CHCl_3$)		Configuration
		3H	3L	3H
a	1.48(1.15)	-93	+48	1R:2R
b	1.54(1.21)	+2	-35	1R:2R
c	1.56(1.18)	-93	+64	1R:2R
d	1.43(1.21)	+23[4]	+26[4]	8S:9S[4]
e	1.53(1.18)	+62	-93	11R:10R
f	1.75(1.31)	-22	+43	4R:3R
g	1.78(1.38)	+14	-1	4R:3R
h	1.83	+36	-21	1R:2R

1. Satisfactory spectral and microanalytical data obtained.
2. Using a Du Pont, 6.2 mm x 25 cm Zorbax-sil column and cyclohexane:ether (97:3) as eluant and flow rate of 2-4 ml/mm.
3. α values obtained for the bromo MOA esters (2) under identical h.p.l.c. conditions to those used for (3).
4. Bromoesters formed from (+)-R-MTPA and are thus of opposite configuration.

(d) The bromo MTPA diastereoisomers (3a-3h) were chemically converted into a range of chiral alcohols, diols, tetrahydroepoxides and arene oxides (some of which racemized[6,7] spontaneously) of known absolute stereochemistry by methods previously used for the corresponding bromo MOA diastereoisomers[1-7] and the configurations obtained are given in Table 1. Earlier synthetic routes from one diastereoisomeric bromo MOA ester (2) to the chiral arene oxide (6) proceeded via the bromoacetates 4 and 5 (R=-COMe) and required four steps (ii)→(v) since N-bromosuccinimide was found to attack the MOA group of 2. This problem did not occur with the bromo MTPA esters 3 which underwent direct benzylic bromination to yield 5 (R = MTPA) in good yield and thus allowed the arene oxide (6) to be obtained in two steps from (3) (vi,v).

The characteristic chromatographic and n.m.r. spectral data for individual bromo MTPA diastereoisomers of 3 can thus readily be correlated with their absolute stereochemistry for the examples shown and this method should now be applicable to analogous bromo MTPA esters of unknown configuration (e.g. 3h in the present report).

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TABLE 2: N.M.R. DATA FOR BROMO MTPA DIASTEREOISOMERS (3L AND 3H)

Compound	$J_{A,B}$ (Hz)[1]		$^1H_B\delta$(ppm)[1]		$^{19}F\delta$(ppm)[2]	
	3H	3L	3H	3L	3H	3L
a	4.2	4.6	4.46	4.53	-8.65[3]	-8.68[3]
b	4.2	5.1	4.55	4.60	-8.51	-8.59
c	3.7	4.4	4.54	4.62	-8.62[3]	-8.65[3]
d	4.2	5.4	4.58	4.63	-8.47	-8.55
e	4.2	4.9	4.60	4.66	-8.43	-8.54
f	2.75	2.7	4.64	4.78	-8.53	-8.79
g	2.9	2.7	4.65	4.84	-8.51	-8.81
h	- [4]	- [4]	4.68	4.83	-8.39	-8.73

1. In $CDCl_3$ solution using a Bruker WH-90 instrument (90 MHz) with TMS as reference.
2. In $CDCl_3$ solution at 33°C using a Varian XL-100 instrument (94.2 MHz) with α,α,α-trifluorotoluene as reference.
3. ^1H noise decoupling was used to reduce ^{19}F line width.
4. Signals obscured by aromatic protons.

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