DIRECT ESTERIFICATION OF α-METHOXY-α-(TRIFLUOROMETHYL)PHENYLACETIC ACID

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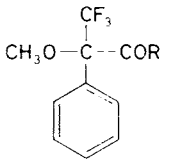
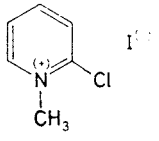
Esters of α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher acid, MTPA) were prepared in good yields from alcohols and the free acid *Ia* using 2-chloro-1-methylpyridinium iodide (*II*) as condensing agent.

Determination of optical purity of biologically active compounds represents an integral part of their investigation. Various methods are used for solution of this problem. Important among them are derivatization methods which convert pairs of enantiomers into diastereoisomers with different physical properties. The most widely used derivatives of alcohols and amines, used in this context, are their esters or amides with α-methoxy-α-(trifluoromethyl)phenylacetic acid[1] (Mosher acid, MTPA, *Ia*). Diastereoisomers, obtained in this way, were used for determination of absolute configuration and optical purity of esters of precocene-3,4-diols[2], for checking the optical purity in pheromone synthesis[3] and determination of absolute configuration of some pheromones[4].

Derivatives of alcohols or amines with Mosher acid are usually prepared from the corresponding chloride *Ib* whose preparation is rather complicated[5]. In several special cases the esterification was carried out in the presence of dicyclohexylcarbodiimide or its mixture with 4-dimethylaminopyridine[6,7]. The introduction of 2-halo-1-methyl-



Ia, R = OH
Ib, R = Cl



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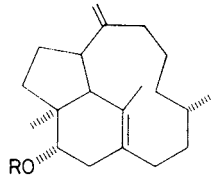
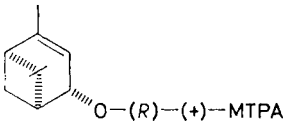


IIIa, R = (*R*)—(+)—MTPA
IIIb, R = (*S*)—(-)—MTPA



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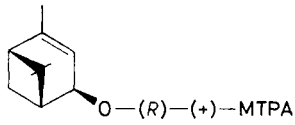

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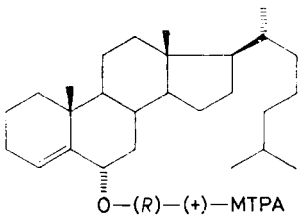

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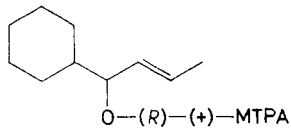

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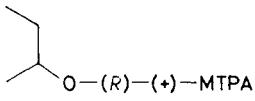

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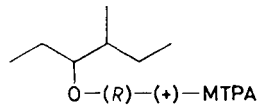

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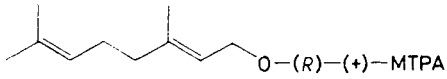

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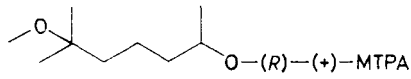
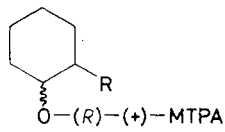


XI



XII, R = CH_3

XIII, R = CH_2—C$_6$H$_4$—OCH_3, *cis*

XIV, R = CH_2—C$_6$H$_4$—OCH_3, *trans*

XV, R = CH_2—C$_6$H$_4$—$O(CH_2)_2C(CH_3)_2OC_2H_5$, *cis*

XVI, R = CH_2—C$_6$H$_4$—$O(CH_2)_2C(CH_3)_2OC_2H_5$, *trans*

XVII, R = CH_2—C$_6$H$_4$—$O(CH_2)_2NHCO_2C_2H_5$, *cis*

XVIII, R = CH_2—C$_6$H$_4$—$O(CH_2)_2NHCO_2C_2H_5$, *trans*

TABLE I

Spectral data for esters *III*—*XVIII*, prepared in the presence of 4-dimethylaminopyridine as base

Compound (yield, %)	Formula (M. W.)	NMR (200 MHz) spectrum (δ; C^2HCl_3)	Mass spectrum (base peak)	IR spectrum (cm^{-1})
IIIa[a] (65)	$C_{30}H_{39}F_3O_3$ (504·6)	0·91 (d, 3 H), 0·92 (s, 3 H), 1·71 (bs, 3 H), 3·20 (m, 1 H), 3·59 (q, 3 H), 4·86 (t, 1 H), 4·96 (t, 1 H), 5·55 (dd, 1 H), 7·38—7·61 (m, 5 H)	M^+ = 504, (270), 255, 189, 119	3 070, 1 745, 1 631, 892
IIIb[a] (79)	$C_{30}H_{39}F_3O_3$ (504·6)	0·91 (d, 3 H), 0·96 (s, 3 H), 1·71 (bs, 3 H), 3·22 (m, 1 H), 3·55 (q, 3 H), 4·86 (t, 1 H), 4·96 (t, 1 H), 5·52 (dd, 1 H), 7·38—7·59 (m, 5 H)	M^+ = 504, (270), 255, 189, 119	3 075, 1 747, 1 635, 895
IV[a] (38)	$C_{20}H_{23}F_3O_3$ (368·4)	0·72 (s, 3 H), 1·25 (s, 3 H), 1·43 (d, 1 H), 1·75 (t, 3 H), 2·00 (m, 1 H), 2·34 (m, 1 H), 2·50 (m, 1 H), 3·57 (q, 3 H), 5·37 (m, 1 H), 5·76 (m, 1 H), 7·36—7·57 (m, 5 H)	M^+ = 368, (189), 134	1 745, 1 504, 1 498
V (51)	$C_{20}H_{23}F_3O_3$ (368·4)	0·83 (s, 3 H), 1·33 (s, 3 H), 1·60 (m, 1 H), 1·74 (t, 3 H), 2·01 (dt, 1 H), 2·40 (m, 1 H), 2·53 (ddd, 1 H), 3·53 (q, 3 H), 5·35 (m, 1 H), 5·76 (m, 1 H), 7·35—7·54 (m, 5 H)	M^+ = 368, 234, 215, 189, 134 (119)	2 855, 1 656, 1 260, 1 190, 1 126, 910
VI[a] (48)	$C_{37}H_{53}F_3O_3$ (602·8)	0·69 (s, 3 H), 0·86 (d, 6 H), 0·90 (d, 3 H), 3·60 (q, 3 H), 5·19 (m, 1 H), 5·60 (m, 1 H), 7·36—7·60 (m, 5 H)	M^+ = 602, (368), 353, 255, 247, 189	1 748, 1 497, 1 270, 1 258
VII (59)	$C_{19}H_{25}F_3O_3$ (358·1)	0·85—1·70 (m, 11 H), 1·69 (dd) and 1·72 (dd) (3 H), 3·55 (q, 3 H), 5·16 (dd) and 5·20 (dd) (1 H), 5·31 (ddq) and 5·44 (ddq) (1 H), 5·75 (dq) and 5·83 (dq) (1 H), 7·34—7·55 (m, 5 H)	189, 113, 71, (57), 43	2 935, 2 860, 1 450, 971
VIII[b,c] (43)	$C_{14}H_{17}F_3O_3$ (290·3)	1·25 (d, 3 H), 1·28 (t, 3 H), 1·62 (m, 2 H), 3·57 (q, 3 H), 7·40—7·61 (m, 5 H)	M^+ = 290, 221, (189), 77, 75 69, 31	2 850, 1 753, 1 271, 1 190, 1 165, 1 129, 1 033, 698

TABLE I
(*Continued*)

Compound (yield, %)	Formula (M. W.)	NMR (200 MHz) spectrum (δ; C^2HCl_3)	Mass spectrum (base peak)	IR spectrum (cm^{-1})
IX (93)	$C_{18}H_{25}F_3O_3$ (346·1)	0·76—0·94 (m, 9 H), 1·00—3·20 (m, 5 H), 3·57 (q, 3 H), 4·78 (m, 1 H), 7·36—7·63 (m, 5 H)	189, 113, 71, (57), 43	1 750, 1 749, 1 452, 1 370, 700
X[a] (32)	$C_{20}H_{25}F_3O_3$ (370·4)	1·59 (b, 3 H), 1·67 (b, 3 H), 1·71 (b, 3 H), 2·06 (b, 4 H), 3·56 (q, 3 H), 4·83 (m, 2 H), 5·06 (m, 1 H), 5·39 (m, 1 H)	M^+ = 370, 327, 301, (189), 69	1 750, 1 668, 1 499
XI (88)	$C_{19}H_{27}F_3O_4$ (376·4)	1·12 (s, 6 H), 1·12—1·76 (m, 6 H), 1·27 (d) and 1·35 (d) (3 H), 3·12 (s) and 3·15 (s) (3 H), 3·55 (q) and 3·57 (q) (3 H), 5·17 (m, 1 H), 7·36—7·58 (m, 5 H)	M^+ = 376, 361, 189, 143, 111, (73), 69	2 830, 1 665, 1 380, 1 365, 1 086
XII (60)	$C_{17}H_{21}F_3O_3$ (330·3)	0·92 (d) and 1·08 (d) (3 H), 1·17—1·83 (m, 8 H), 2·20 (m, 1 H), 3·69 (q) and 3·71 (q) (3 H), 4·75 (m) and 4·80 (m) (1 H), 7·49—7·72 (m, 5 H)	M^+ = 330, 189, (97)	2 940, 2 860, 1 450, 1 380
XIII (54)	$C_{24}H_{27}F_3O_4$ (436·5)	1·20—1·80 (m, 9 H), 2·09 (dd) and 2·19 (dd) (1 H), 2·71 (dd) and 2·90 (dd) (1 H), 3·56 (q) and 3·58 (q) (3 H), 3·77 (s) and 3·78 (s) (3 H), 4·80 (m, 1 H), 6·77—6·98 (m, 4 H), 7·35—7·64 (m, 5 H)	M^+ = 436, (188)	1 751, 1 250
XIV (55)	$C_{24}H_{27}F_3O_4$ (436·5)	1·20—1·80 (m, 9 H), 2·24 (dd) and 2·33 (dd) (1 H), 2·47 (dd) and 2·52 (dd) (1 H), 3·57 (q, 3 H), 3·78 (s, 3 H), 5·18 (m, 1 H), 6·78—6·99 (m, 4 H), 7·35—7·63 (m, 5 H)	M^+ = 436, (188)	1 751, 1 250

TABLE I
(*Continued*)

Compound (yield, %)	Formula (M. W.)	NMR (200 MHz) spectrum (δ; C^2HCl_3)	Mass spectrum (base peak)	IR spectrum (cm^{-1})
XV (46)	$C_{30}H_{31}F_3O_5$ (536·6)	0·86 (t, 3 H), 1·24 (t, 6 H), 1·99 (t, 2 H), 2·04 (dd) and 2·11 (dd) (1 H), 2·65 (dd) and 2·80 (dd) (1 H), 3·41 (q, 2 H), 3·61 (q, 3 H), 4·04 (t, 2 H), 6·80 (m, 2 H), 6·97 (m, 2 H), 7·40—7·53 (m, 5 H)	320, 316, 302, 274, 256, 241, 206, 201, (188), 175, 107	1 747, 1 247
XVI (55)	$C_{30}H_{31}F_3O_5$ (536·6)	1·16 (t, 3 H), 1·24 (s, 6 H), 1·98 (t) and 1·99 (t) (2 H), 2·07 (dd) and 2·17 (dd) (2 H), 2·70 (dd) and 2·89 (dd) (2 H), 3·41 (q. 2 H), 3·58 (q) and 3·61 (q) (3 H), 4·03 (t) and 4·04 (t) (2 H), 4·80 (m, 1 H), 6·77—6·97 (m, 4 H), 7·36—7·63 (m, 5 H)	$M^{\ddagger}$ = 536, 490, 436, 422, 303, 302, 257, 256, 202, (188), 107, 87	1 747, 1 247
XVII (30)	$C_{28}H_{34}F_3NO_6$ (537·6)	1·25 (t, 3 H), 2·33 (dd, 1 H), 3·08 (dd, 1 H), 3·57 (q, 2 H), 3·61 (q, 3 H), 4·01 (AB, 2 H), 6·81 (m, 2 H), 7·09 (m, 2 H), 7·40—7·58 (m, 5 H)	$M^{\ddagger}$ 537, 491, 304, 303, 258, 257, (189), 188, 116, 107, 88	3 465, 3 380, 1 747, 1 728, 1 709, 1 545, 1 246
XVIII (36)	$C_{28}H_{34}F_3NO_6$ (537·6)	1·24 (t, 3 H), 2·47 (dd, 1 H), 2·66 (dd, 1 H), 3·56 (q, 2 H), 3·62 (q, 3 H), 4·00 (AB, 2 H), 6·80 (m, 2 H), 7·10 (m, 2 H), 7·35—7·55 (m, 5 H)	$M^{\ddagger}$ = 537, 491, 304, 303, 258, 257, (189), 188, 116, 107, 88	1 747, 1 728, 1 709, 1 515, 1 246

[a] IR spectra recorded on a Perkin–Elmer 580 instrument; [b] 60 MHz ^1H NMR spectrum recorded on a Tesla BS-467 instrument, [c] the same yield with triethylamine.

pyridinium halides (*II*) as condensing agents for the preparation of hindered esters directly from alcohols and acids[8], amides[9], highly hindered steroid esters[10], sulfinamides and sulfinate esters[11] prompted us to try this method for the preparation of diastereoisomeric esters directly from the Mosher acid *Ia* and racemic alcohols. The experiments were performed with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, the only exception being the preparation of ester *IIIb* in which we used the (*S*)-enantiomer of the acid. The esterification gave good yields even with such

complicated compounds as trinervitane alcohols (*cf.* formula *III*) or hindered allyl alcohols (*cf.* formula *VII*). Whereas the ester *VI* was synthesized from cholest-4-en-6α-ol in very good yield, cholest-4-en-6β-ol gave no ester, probably for steric reasons. With tertiary alcohols (2-methyl-3-buten-2-ol and 3,7-dimethyl-1,6-octadien-3-ol) the reaction took another course and no corresponding MTPA esters were obtained. The described one-step reaction of alcohols with Mosher acid can be carried out also on the micro scale. Since no side-products are formed, the product isolation is very easy.

EXPERIMENTAL

Column chromatography was performed on silica gel Silpearl (Kavalier, Votice). Experiments with milligram quantities were carried out in closed 0·6 ml vials (Applied Science, Deerfield, IL, U.S.A.) and the compounds were separated on SEP-PAK cartridges (Waters Associates, Milford, MA, U.S.A.)[12]. The reaction course and purity of the compounds were followed by analytical thin-layer chromatography on silica gel G according to Stahl, type 60 (Merck, Darmstadt). Infrared spectra were taken in tetrachloromethane on Perkin–Elmer 580 (compounds *III*, *IV*, *VI*, and *X*) or UR-20 (Carl Zeiss, Jena) instruments. Mass spectra were measured on an AEI MS-902 spectrometer. ^{1}H NMR spectra were obtained in deuteriochloroform with Tesla BS-467 (60 MHz; compound *VIII*) or Varian XL-200 (200 MHz) instruments; internal standard tetramethylsilane, chemical shifts in ppm (δ-scale).

General Procedure

A solution of *Ia* (0·0214 mmol), the alcohol (0·0214 mmol) and the base (0·05 mmol; 4-dimethylaminopyridine or triethylamine) in dichloromethane (0·2 ml) was added dropwise to 2-chloro-1-methylpyridinium iodide (0·025 mmol) in dichloromethane (0·2 ml). The mixture was heated in a stoppered 0·6 ml vial for 3 h, diluted with water (0·6 ml) and extracted with ether (3 × 5 ml). After drying and evaporation of the solvent, the residue was dissolved in a nonpolar solvent (the total volume not exceeding 2 ml) and injected by a syringe into SEP-PAK cartridge. The desired fraction was then eluted with a solvent of appropriate polarity[12]. For characterization of the products see Table I.

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