Enantioselective Synthesis of Monofluorinated Chiral Building Blocks from Malonic Acid

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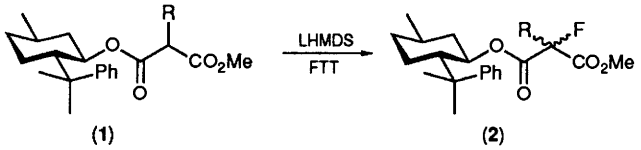
A general method for the preparation of monofluorinated chiral building blocks has been developed by fluorination of methyl phenylmenthyl monoalkylmalonates using lithium hexamethyldisilazide and 1-fluoro-2,4,6-trimethylpyridinium triflate.

Since important physical and biological properties,[1] are shown by compounds containing a fluorine atom, the regio- and stereoselective introduction of the latter is also important. In this respect, although chiral compounds fluorinated at the asymmetric centre have considerable potential in synthesis, there are few reports of their preparation.[2,3] We have, therefore, studied

the enantioselective construction of a quaternary asymmetric centre,[4] and report here a versatile methodology for the synthesis of optically pure monofluorinated compounds.

Chiral esters of monosubstituted malonates are fluorinated in excellent yield with 1-fluoro-2,4,6-trimethylpyridinium triflate (FTT)[5] under basic conditions. Thus, treatment of methyl phenylmenthyl methylmalonate (**1a**) with lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF), followed by reaction of the resulting enolate anion with the reagent[5] at −78 °C to room temperature for 15 h produced two diastereoisomers of the monofluorinated esters (**2a**) (87%) in a ratio of 79:21. Fluorination of the esters (**1b–d**) under the same conditions furnished epimeric mixtures of (**2b**) (96% yield; 67:33), (**2c**) (95% yield; 67:33), and (**2d**) (88% yield; 62:38), respectively. However reaction of the corresponding phenylmenthyl half esters[4] with the triflate[5] in the presence of 2 mol equiv. of LHMDS, followed by methylation with CH_2N_2 gave poorer results. For example, the half ester of methylmalonate gave a mixture of two epimers (**2a**) in 32% yield in a ratio of 3:2.

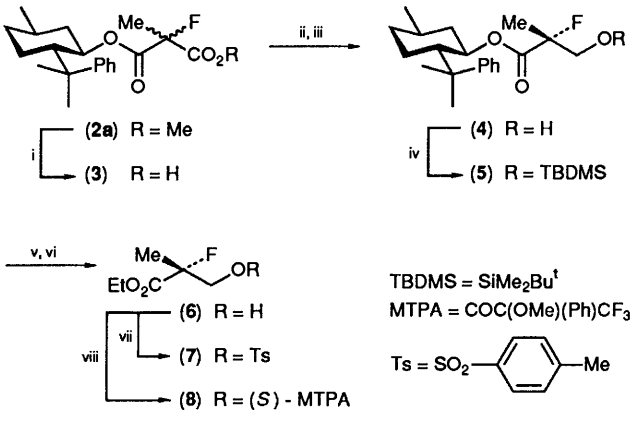


(1) (2)

a; R = Me
b; R = Et
c; R = Pr
d; R = $PhCH_2$

Scheme 1.

The 79:21 mixture of the above esters (**2a**) was selectively hydrolysed with $LiOH{\cdot}H_2O$ in aqueous MeOH at room temperature to give the carboxylic acids (**3**) (89%). Conversion of (**3**) into the corresponding acid chloride, followed by reduction with Bu_4NBH_4 in CH_2Cl_2 gave an epimeric mixture of the primary carbinols in 67% overall yield. The hydroxy group of the major component (**4**), separated by HPLC, was protected with TBDMS group to give the ether (**5**), $[\alpha]_D^{24}$ −3.46° (*c* 1.1 in $CHCl_3$), in 98% yield. Removal of the phenylmenthyl group of (**5**) using potassium superoxide in the presence of 18-crown-6,[6] followed by a treatment of the resulting carboxylic acid with 10% HCl–EtOH, provided the hydroxy ester (**6**), which was treated with tosyl chloride in pyridine. The (*R*)-configuration of the tosylate (**7**), obtained in 72% overall yield from (**5**), was determined by a comparison of its specific rotation, $[\alpha]_D^{24}$ +1.90° (*c* 0.21 in MeOH), with the reported one for the (*S*)-isomer,[3a] $[\alpha]_D$ −1.79° (*c* 1.34 in MeOH, 91% ee). The optical purity (100% ee) of the hydroxy ester (**6**) was confirmed by conversion into the (*S*)-MPTA ester (**8**). The fact indicates that the geometry (**A**) of the enolate anion, shown in the Figure, is preferred for the fluorination of the methylmalonate (**1a**).



Scheme 2. *Reagents and conditions:* i, LiOH, room temp.; ii, $(COCl)_2$; iii, Bu_4NBH_4; iv, TBDMSCl, Et_3N, DMAP; v, KO_2, 18-crown-6, room temp.; vi, HCl, EtOH; vii, TsCl, pyridine, viii, (*S*)-MTPAOH, DCC, DMAP.

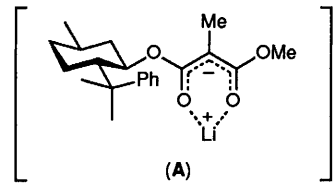


Figure.

Experimental

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* 2-*Fluoro*-2-*methylmalonate* (**2a**).—To a stirred solution of the methylmalonate (**1a**) (250 mg, 0.72 mmol) in dry THF (5 ml) was added at −78 °C under argon 1M LHMDS in THF (1.1 ml, 1.1 mmol). The mixture was stirred for 30 min at −78 °C, after which 1-fluoro-2,4,6-trimethylpyridinium triflate (FTT) (310 mg, 1.1 mmol) was added to it in small portions. The resulting mixture was stirred for 15 h at −78 °C to room temperature, before dilution with benzene. The mixture was washed with 5% aqueous $KHSO_4$ and brine, dried ($MgSO_4$), and evaporated. Silica gel column chromatography of the residue with hexane–AcOEt (95:5) as eluant gave an epimeric mixture of the fluorides (**2a**) (225 mg, 87%) as an oil; ν_{max} 1 753 cm^{-1} (C=O); δ 1.56 and 1.69 [3 H(21:79), each d, *J* 23.0 Hz, CFMe] and 3.80 and 3.81 [3 H(21:79), each s, OMe].

Compound (**2b**) ν_{max} 1 752 cm^{-1} (C=O); δ 0.95 and 1.00 [3 H(67:33), each t, *J* 7.3 Hz, CH_2Me] and 4.92 and 4.94 [1 H(33:67), each dt, *J* 4.3 and 8.0 Hz, CHO_2C].

Compound (**2c**) ν_{max} 1 752 cm^{-1} (C=O); δ 0.94 and 0.97 [3 H(67:33), each t, *J* 7.9 Hz, CH_2Me] and 4.92 and 4.94 [1 H(33:67), each dt, *J* 4.9 and 10.2 Hz, CHO_2C].

Compound (**2d**) ν_{max} 1 752 cm^{-1} (C=O); δ 3.74 and 3.77 [3 H(62:38), each s, OMe].

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