# A Novel One-pot Synthesis of Homochiral (*R*)-(−)- and (*S*)-(+)-Fe(CO)($\eta^5$-$C_5H_5$)($PPh_3$)$COCH_3$

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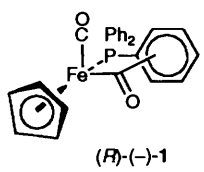
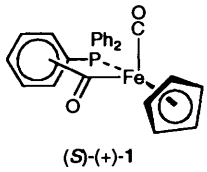
Treatment of the salt [$Fe(CO)_2(\eta^5$-$C_5H_5)(PPh_3)$]Br with potassium L-mentholate followed by lithium bromide and methyllithium generates, after work-up and crystallisation, homochiral (*S*)-(+)-[Fe(CO)($\eta^5$-$C_5H_5$)($PPh_3$)$COCH_3$] in ≥30% yield.

The iron chiral auxiliary [Fe(CO)($\eta^5$-$C_5H_5$)($PPh_3$)] has been shown to be versatile and effective for reactions involving attached acyl ligands.[1] The parent acetyl complex [Fe(CO)($\eta^5$-$C_5H_5$)($PPh_3$)$COCH_3$] **1** is the key compound in this area since all other acyl complexes may be derived from it. For applications to asymmetric synthesis significant quantities of the homochiral enantiomers (*R*)-(−)-**1** and (*S*)-(+)-**1** are required.


(*R*)-(−)-**1**

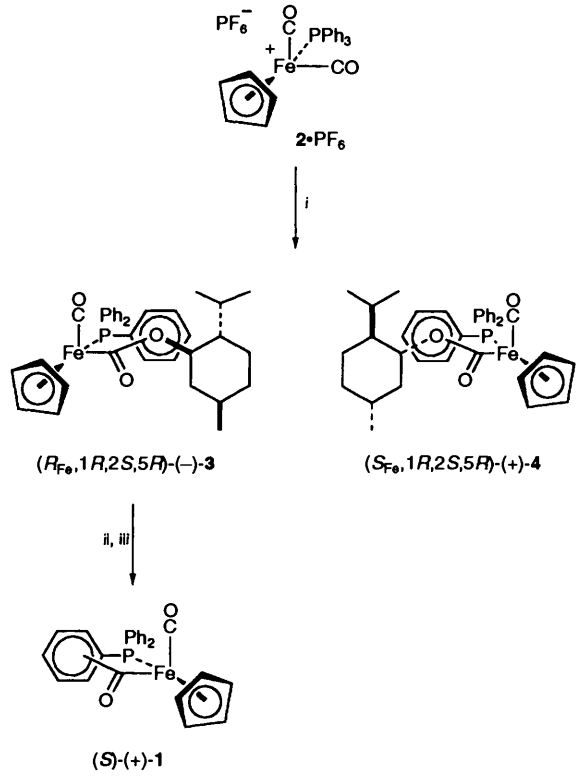

(*S*)-(+)-**1**

In an early series of elegant experiments, Brunner *et al.*[2] were the first to prepare (*R*)-(−)-**1** and (*S*)-(+)-**1**, albeit in low overall yields. Their method involved the reaction of the dicarbonyl salt [$Fe(CO)_2(\eta^5$-$C_5H_5)(PPh_3)$][$PF_6$] **2**•$PF_6$ with sodium L-mentholate† to form the two diastereoisomeric esters ($R$‡$_{Fe}$,1*R*,2*S*,5*R*)-**3** and ($S_{Fe}$,1*R*,2*S*,5*R*)-**4**. One of these esters ($R_{Fe}$,1*R*,2*S*,5*R*)-(−)-**3** could be isolated pure and reacted further with methyllithium to generate, with inversion of configuration at iron, (*S*)-(+)-**1** (Scheme 1). An identical sequence using sodium D-mentholate generated (*R*)-(−)-**1**. Unfortunately, this method is not viable for the large-scale preparation of homochiral **1**, because of the low yields reported (3–4% for the conversion of **2** into homochiral **1**). Indeed, in our hands the yields were found to be even lower on a large scale.

As part of an extensive programme[4] aimed towards achieving practical methods for the synthesis of homochiral (*R*)-(−)-**1** and (*S*)-(+)-**1** we have reinvestigated the procedure reported by Brunner,[2] and report here a simple and efficient one-pot synthesis.

## Results

The salt dicarbonyl(cyclopentadienyl)(triphenylphosphine)iron bromide **2**•Br was treated with potassium L-mentholate (Scheme 2). The intermediate esters **3** and **4** were *not* isolated, but the mixture was treated directly with lithium bromide followed by methyllithium. Quenching with methanol gave, after chromatographic separation, the iron acetyl complex (*S*)-(+)-**1** in 35% yield with an enantiomeric excess of >90%. A single recrystallisation from dichloromethane by addition of hexane gave homochiral (*S*)-(+)-**1** in 30% overall yield from **2**.




**Scheme 1** *Reagents:* i, L-NaOMenthyl; ii, crystallise; iii, MeLi

The enantiomeric excesses of samples of **1** were determined by optical rotation, and by treatment of a sample with butyllithium followed by alkylation of the resultant enolate with (+)-chloromethyl menthyl ether[5] and HPLC analysis (normal phase, cyclohexane–tetrahydrofuran, 3%) of the resultant diastereoisomers. Similar analysis of the racemate demonstrated that this method of derivatisation did not effect kinetic resolution.

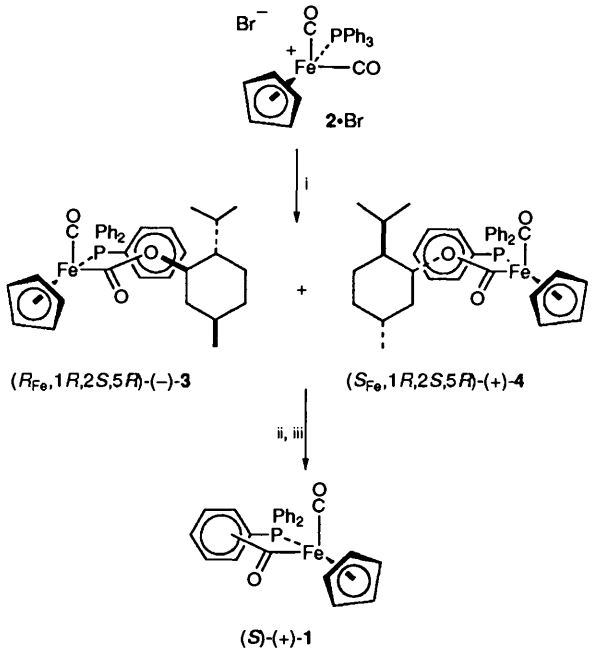
A number of other chiral alcohols and diols were also found to promote the conversion of **2**•Br into homochiral **1**. The results are listed below in Table 1.

Using the CHEMX§ molecular modelling package, the

† L-(−)-Menthol is (1*R*,2*S*,5*R*)-(−)-2-isopropyl-5-methylcyclohexanol. Menthyl is the radical formed by loss of the 1-hydroxy group. All numbering quoted for carbons refer to the IUPAC descriptors for menthol.

‡ Ligand priority is cyclopentadienyl, phosphine, carbon monoxide with the ester or acetyl ligand having the lowest priority.[3]

§ CHEMX, designed and distributed by Chemical Design Limited, Roundway House, Cromwell House, Chipping Norton, Oxon OX7 5SR, UK.




**Scheme 2** *Reagents:* i, L-KOMenthyl; ii, LiBr, MeLi; iii, crystallise

complex ($R_{Fe}$,1*R*,2*S*,5*R*)-**3** was constructed using standard bond lengths and angles for the menthyloxy fragment, and crystallographically derived data associated with (*R*)-**1** for the iron fragment.[6] A computational model was generated by driving the bond C(1)–O through 0–360°, in 2° increments. The ester function was confined to the s-*trans* geometry, and the dihedral angle FeC(O)–O[C(1)] was constrained to 0°. For each conformation generated, the van der Waals energy was minimised by independent rotations about the cyclopentadienyl centroid–Fe, C(2)–C(7), C(5)–C(10), Fe–C(=O), Fe–P and P–$C_{ipso}$ bonds. The calculation clearly indicated that only one well-defined energy minimum was accessible to the complex, and the lowest energy conformation is shown in Fig. 1. This global minimum was found to be in excellent agreement with the X-ray crystal structure of ($R_{Fe}$,1*R*,2*S*,5*R*)-**3** reported by Brunner *et al.*,[7] as shown in Fig. 2. Repeating the above calculations on the crystal structure data for ($R_{Fe}$,1*R*,2*S*,5*R*)-**3** generated essentially the same conformation observed in the crystal.

In a precisely analogous manner, the complex ($R_{Fe}$,1*S*,2*R*,5*S*)-**4**, the enantiomer of ($S_{Fe}$,1*R*,2*S*,5*R*)-**4**, was generated using the CHEMX package. The same calculations as described above were performed upon ($R_{Fe}$,1*S*,2*R*,5*S*)-**4**, which again indicated a single accessible well-defined energy minimum for which the lowest energy conformation is presented in Fig. 3.

## Discussion

Treatment of **2**•Br with potassium L-mentholate generates a mixture of the diastereoisomeric esters **3** and **4** (Scheme 2), consistent with the disappearance of the metal carbonyl stretch characteristic of **2**•Br in the IR spectrum of the crude reaction mixture. One of these diastereoisomers reacts with methyllithium at least 20 times faster than the other since on treatment with an excess of lithium bromide–methyllithium the iron acetyl (*S*)-(+)-**1** is formed with >90% ee. Since Brunner *et al.* have shown that the reaction of isolated **3** with methyllithium proceeds with inversion of configuration at iron,[10] ($R_{Fe}$,1*R*,2*S*,5*R*)-(−)-**3** must be the faster reacting diastereoisomer.

The yield and ee of the product were very sensitive to the reaction conditions. In general, when the reaction temperature was kept at −60 °C or below, the ee increased but the yield was lowered. Higher reaction temperatures (−30 to −20 °C) gave better yields but lower ee's. Using methyllithium in the absence of lithium bromide gave much lower ee's. Optimal conditions involved the prior addition of 2 or more equivalents of lithium bromide to the ester mixture, before addition of methyllithium–lithium bromide solution. One crystallisation of the crude acetyl product **1** was generally sufficient to produce homochiral material.

**Table 1** One-pot conversion of **2**•Br into homochiral acetyl **1** by treatment with alkoxide and methyllithium (LiBr) followed by crystallisation

| Alcohol | Base | Yield of homochiral **1** (%) | Confign. |
|---|---|---|---|
| (1*R*,2*S*,5*R*)-L-Menthol | KH | 30–45 | (*S*)-(+) |
| (1*S*,2*R*,5*S*)-D-(+)-Menthol | KH | 30–45 | (*R*)-(−) |
| (2*R*,3*R*)-Butane-2,3-diol | KH | 40 | (*S*)-(+) |
| (2*R*,3*R*)-Butane-2,3-diol | NaH | 38 | (*S*)-(+) |
| (2*R*,4*R*)-Pentane-2,4-diol | NaH | 29 | (*S*)-(+) |
| (1*S*,2*S*,5*S*)-(−)-Myrtanol | KH | 11 | (*S*)-(+) |
| (−)-2,3-*O*-Isopropylidene-D-threitol | KH | 26 | (*S*)-(+) |
| (*S*)-Butan-2-ol | KH | 22 | (*R*)-(−) |

Addition of potassium L-mentholate to **2**•Br in [$^2H_8$]tetrahydrofuran and with monitoring of the resultant mixture by $^1H$ NMR spectroscopy showed formation of the diasteroisomeric esters **3** and **4** as a 1:1 mixture, *i.e.* no stereoselectivity is imparted to this process by the mentholate. Since Brunner *et al.* have already demonstrated that **3** and **4** do not equilibrate,[2a] the yields obtained here are striking since the theoretical maximum is only 50%; using the procedure detailed in the Experimental section, yields of homochiral **1** in the range 30–45% were achieved consistently. L-Menthol produced (*S*)-(+)-**1** while D-menthol gave (*R*)-(−)-**1**. A range of other homochiral alcohols proved effective in this transformation (Table 1). We had hoped that the use of $C_2$ symmetric diols would allow intramolecular switching of the corresponding ester diastereoisomers, however no evidence for this could be found since the yields never exceeded 50%. On the basis of economy and availability, the alcohol of choice is menthol.

In order to probe the difference in reactivity between the diastereoisomers **3** and **4** we undertook molecular modelling studies. To simplify the visualisation and comparison of the diastereoisomeric structures, calculations were performed upon ($R_{Fe}$,1*R*,2*S*,5*R*)-**3** and ($R_{Fe}$,1*S*,2*R*,5*S*)-**4**, the former being the reactive diastereoisomer in the L-menthol pair and the latter being the unreactive diastereoisomer in the D-menthol pair. Thus, the *R* configuration at the iron centre affords the frame of reference for the purpose of comparison. The calculations, which were designed to probe the complete conformational energy map for the complexes, indicated that, in each case, only a single well-defined energy well was accessible with, in each case, the ester carbonyl *anti* to the carbon monoxide ligand; such conformations are very similar to that preferred for the iron acetyl complex **1** itself.[9] The calculated minimum energy conformation for ($R_{Fe}$,1*R*,2*S*,5*R*)-**3** (Fig. 1) was essentially identical with the conformation in the solid state (Fig. 2), lending credence to the qualitative validity of the calculations.

The established inversion of configuration at iron in the reaction requires that the methyl nucleophile must be adding to the carbon monoxide ligand and not to the ester carbonyl moiety. Our calculations suggest that essentially equal energy pathways are available for free $CH_3$ to approach the carbon monoxide ligand in both the reactive and unreactive

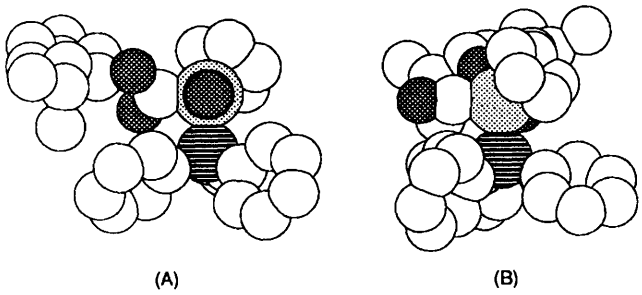



**Fig. 1** The calculated lowest energy conformation of ($R_{Fe}$,1*R*,2*S*,5*R*)-**3**, viewed along; (A) the axis of the O≡C–Fe bond, and (B) the Fe–C(O)O bond. Hydrogen atoms have been omitted for clarity.

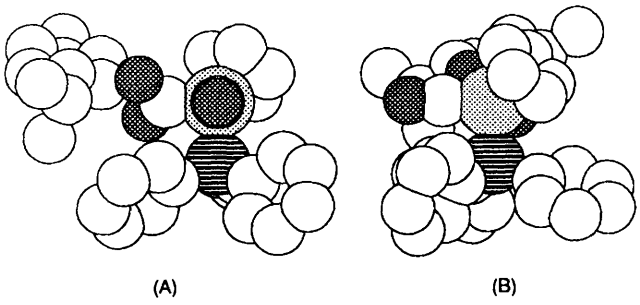



**Fig. 2** The crystal structure of ($R_{Fe}$,1*R*,2*S*,5*R*)-**3**, viewed along; (A) the axis of the O≡C–Fe bond, and (B) the Fe–C(O)O bond. Hydrogen atoms have been omitted for clarity.

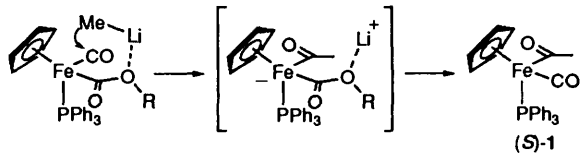
diastereoisomers (see Figs. 1–3). However, if lithium chelation to the ester is invoked (Scheme 3) a striking difference is apparent. Chelation of methyllithium to the menthyloxy oxygen of the ester would deliver the methyl nucleophile *via* a six-membered transition state to the carbon monoxide ligand. In the reactive diastereoisomer (Figs. 1 and 2) one face of the ester is hindered by the triphenylphosphine ligand while the other is relatively unencumbered. In contrast, the unreactive diastereoisomer (Fig. 3) has both faces of the ester hindered, one by the triphenylphosphine ligand and the other by the sterically demanding isopropyl moiety associated with the menthyl fragment. Hence a chelation-controlled mechanism (Scheme 3) would be strongly disfavoured in the latter case.

In conclusion, a one-pot synthesis of either homochiral iron acetyl complex (*S*)-(+)- or (*R*)-(−)-**1** has been established from the prochiral bromide salt of **2** and L- or D-menthol, respectively.* Yields up to 45%, close to the maximum of 50%, have been achieved.

## Experimental

*General.*—Reactions and purifications involving organometallic compounds were carried out under an atmosphere of nitrogen using vacuum-line and Schlenk-tube techniques and all solvents for organometallic reactions were deoxygenated. Melting points are uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methyllithium·LiBr complex was used as supplied by Aldrich (1.5 mol $dm^{-3}$ solution in diethyl ether). For organometallic complexes chromatography was performed under a positive pressure using deoxygenated solvents. $^1$H NMR spectra were recorded on a Bruker WM-300 (300 MHz), using $CDCl_3$ as solvent and referenced to residual $CHCl_3$ with chemical shifts being reported as $\delta$ (ppm) from tetramethylsilane; *J* values are

* This method constitutes the commercial preparation of homochiral iron acetyl **1**.




**Scheme 3** Mechanism for the conversion of esters ($R_{Fe}$,1*S*,2*R*,5*S*)-**3** and ($R_{Fe}$,1*R*,2*S*,5*R*)-**4** into (*S*)-**1**: R = menthyl

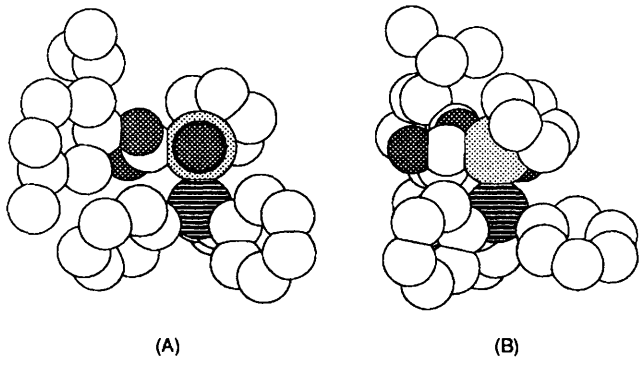



**Fig. 3** The lowest energy conformation of ($R_{Fe}$,1*S*,2*R*,5*S*)-**4**, the enantiomer of ($S_{Fe}$,1*R*,2*S*,5*R*)-**4**, viewed along; (A) the axis of the O≡C–Fe bond, and (B) the Fe–C(O)O bond. Hydrogen atoms have been omitted for clarity.

measured in Hz. $^{31}$P NMR spectra were recorded on a Bruker AM-250 spectrometer operating at 101.26 MHz using $CDCl_3$ as solvent and chemical shifts were reported as $\delta$ (ppm) from an external reference of 85% orthophosphoric acid. IR spectra were obtained as chloroform solutions in 1 mm cells on a Perkin-Elmer 297 instrument calibrated against polystyrene (1601 $cm^{-1}$).

*Preparation of* [$Fe(CO)_2(\eta^5$-$C_5H_5)(PPh_3)$]Br **2**·Br.—The complex **2**·Br was prepared by a modification of the literature procedure.[10] [$Fe(CO)_2(\eta5$-$C_5H_5)]_2$ (12 g, 33.9 mmol) was dissolved in dichloromethane (45 $cm^3$) and the solution cooled to 0 °C before the slow addition to it of a solution of bromine (5.42 g, 33.9 mmol) in dichloromethane (2.5 $cm^3$). The mixture was stirred at 18 °C for 16 h and then triphenylphosphine (18.7 g, 71.4 mmol) was added to it in small portions with stirring. The resulting solution was stirred under nitrogen at 40–45 °C for 12 h. On cooling, yellow crystals of the title compound **2**·Br were precipitated. These were filtered off, washed with diethyl ether and dried *in vacuo* (yield 26 g). Combination of the filtrate and washings precipitated a second crop (6.25 g) of product: total yield 32.25 g (90%); $\nu_{max}$/$cm^{-1}$ 2013 and 2057 vs (C≡O). This procedure works consistently and on scales up to 100 times those reported above.

*Homochiral* (*S*)-(+)-[$Fe(CO)(\eta^5$-$C_5H_5)(PPh_3)COCH_3$)] **1**. —In a 250-$cm^3$ 3-neck flask fitted with a nitrogen inlet, KH (895 mg, 21.9 mmol) [washed with light petroleum (3 × 10 $cm^3$)] and L-(−)-menthol (1.70 g, 10.9 mmol) was heated and stirred in THF (40 $cm^3$) for 4 h; the mixture was then evaporated and stored overnight at −20 °C. The solid was redissolved in THF (160 $cm^3$), and dicarbonyl(cyclopentadienyl)(triphenylphosphino)iron bromide **2**·Br (5.07 g, 9.8 mmol) was added to the solution. The mixture was stirred (2.5 h) and slowly warmed to −30 °C; it was then re-cooled to −60 °C. LiBr (1.75 g, 20.2 mmol) was added to the mixture which was then stirred for a further 0.25 h. MeLi as a complex with LiBr [25 $cm^3$, 37.5 mmol; prediluted with THF (25 $cm^3$) and precooled to −50 °C] was added slowly *via* a cannula to the reaction mixture which was then stirred for a further 3.5 h at −50 °C before being quenched with methanol (25 $cm^3$).

Chromatography (5% deactivated alumina, hexane–$CH_2Cl_2$, 4:1 v/v ⟶ $CH_2Cl_2$) afforded analytically pure (*S*)-(+)-**1** (1.54 g, 35%, ee > 90%). Recrystallisation of the product from $CH_2Cl_2$–hexane gave homochiral (*S*)-(+)-**1** (30% overall yield); $[\alpha]_{546}^{25}$ = +288 (*c* 0.04, $C_6H_6$); m.p. 154–155 °C, $\delta_H(CDCl_3)$ 2.32 (3 H, s, $CH_3$), 4.43 (5 H, d, $J_{PH}$ 1.2, $C_5H_5$) and 7.25–7.75 (15 H, m, Ph); $\delta_P$ 72.8; $\nu_{max}/cm^{-1}$ 1917 vs (C≡O).

*Determination of the ee of* **1**.—BuLi (1.4 mol $dm^{-3}$; 60 $mm^3$ * 0.084 mmol) was added dropwise to a THF (7 $cm^3$) solution of the acetyl complex **1** (43 mg, 0.095 mmol) at −78 °C. The blood red solution was stirred for 0.5 h after which (+)-chloromethyl-menthyl ether (35 $mm^3$, 0.15 mmol) was added to it. The solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature; after concentration under reduced pressure, the crude product was purified by preparative TLC ($SiO_2$), eluting with hexane–diethyl ether (9:1 v/v). HPLC Analysis on a normal phase column (5 μm $SiO_2$, 250 × 4.6 mm, 1 $cm^3$ $min^{-1}$, cyclohexane, 3% THF, UV detection at 220 nm) afforded, in order of elution, the diastereoisomers derived from (*R*)-(−)-**1** (7.4 min) and (*S*)-(+)-**1** (9.6 min), respectively.

*Molecular Modelling Calculations*.—All molecular modelling calculations were conducted using the CHEMX modelling package (January 1992) on a Vaxstation 3520. Within the CHEMX package, the van der Waals energy ($E_{vdW}$) calculation only considers contributions from the torsion ($V_{tor}$), electrostatic ($V_{el}$), and non-bonded or polarisation ($V_{nb}$) terms, as defined below:

$$E_{vdW} = V_{tor} + V_{el} + V_{nb}$$

Because of inadequate parameterisation for iron within the CHEMX package, the torsion barrier associated with $V_{tor}$ is zero by default. The electrostatic contribution ($V_{el}$) is computed by default using Coulomb's law. The van der Waals interaction potential ($V_{nb}$) within the software package is that of Del Re *et al.*,[11] and takes the form:

$$V_{nb} = \frac{A \exp(-Br)}{r^D} - \frac{C}{r^6}$$

Rotational conformations were generated by driving the designated bond through 0–360°, in 2° increments. The van der Waals energy was minimised for each conformation by independent rotation (maximum of 20 cycles) about all designated bonds, until the default energy convergence limit had been achieved. The cyclopentadienyl ligand was treated as a rigid body and rotated about the axis from the centroid of the $C_5H_5$ ring to the Fe atom.

## Acknowledgements

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* 1 $mm^3$ = 1 μl.