A convenient chemo-enzymatic synthesis and ^{18}F-labelling of both enantiomers of *trans*-1-toluenesulfonyloxymethyl-2-fluoromethyl-cyclopropane†
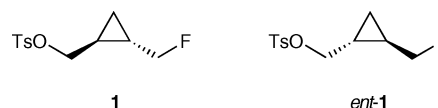
Patrick Johannes Riss* and Frank Rösch

The present report is concerned with a stereoselective, reliable route to *trans*-1,2-disubstituted cyclopropanes and in particular to (*S*,*S*)-1-tosyloxymethyl-2-fluoromethyl-cyclopropane (**1**) and (*R*,*R*)-1-tosyloxymethyl-2-fluoromethyl-cyclopropane (*ent*-**1**) as conformationally restricted, terminally fluorinated C$_4$-building blocks for medicinal chemistry. The enzymatic kinetic resolution based synthesis of **1** and *ent*-**1** utilises inexpensive, commercially available starting materials. It is based on enantiomeric resolution of *rac*-cyclopropane carboxylic esters using esterase from *Streptomyces diastatochromogenes*. Both enantiomers of **1** were prepared selectively in high overall yield over nine steps, starting from ethyl acrylate. The successful radiosynthesis of [^{18}F]-**1** and [^{18}F]-*ent*-**1** is also reported.

Introduction

Fluorine is increasingly included in substitution patterns during the systematic development of potential pharmaceuticals. The C–F bond is an isosteric substitution for C–H and an isoelectronic substitution for the hydroxyl group (van der Waals radii: H: 1.2 Å, F: 1.35 Å, OH: 1,43 Å). Therefore, carbon-bound fluorine can be introduced as a hydrogen mimic or a hydroxyl replacement. Its introduction can affect adsorption, distribution and metabolic properties of a pharmaceutically relevant lead structure.[1] Recent studies have elucidated specific contributions of fluorine in ligand–protein binding interactions.[2] In addition, fluorine-18 provides unique properties as a radiolabel for positron emission tomography (PET), a mode of non-invasive imaging and quantification of biochemical conversions and metabolic rates in living systems. Among the best suited and most frequently used PET-radionuclides, fluorine-18 presents outstanding nuclear and chemical properties.[3] For these reasons, fluorinated building blocks remain of significant interest for the incorporation of fluorine in defined positions of potential radioligands.

We were interested in (*S*,*S*)-**1** and (*R*,*R*)-*ent*-**1** as C$_4$-synthons for the introduction of a terminally fluorinated, conformationally restricted cyclopropane ring constraint in suitable (radio-)pharmaceutical precursors (Scheme 1).[4a] In addition, *trans*-1,2-disubstituted cyclopropanes are versatile (*E*)-alkene mimics, which can be employed as isosteric double bond replacements.[4] They are less sensitive to cytochrome p450 affected metabolism in general and to epoxidation in particular, thus eliminating a potential source of toxic metabolites.[5a,b]

The synthesis of **1** and *ent*-**1** required an inexpensive, preparative scale access to a de-symmetrised cyclopropane precursor in high enantiomeric excess. Considerable effort has been spent on the

Institute of Nuclear Chemistry, Johannes Gutenberg-University Mainz, Fritz Strassmann-Weg 2, 55128, Mainz, Germany. E-mail: riss@uni-mainz.de; Fax: +49 6131 3924692; Tel: +49 6131 3925302

† Electronic supplementary information (ESI) available: Spectra of compounds **1**, **8** and **9a**. CCDC reference number 691513. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812777h

Scheme 1 (*S*,*S*)-(+)-Toluene-4-sulfonic acid 2-fluoromethyl-cyclopropylmethyl ester **1** and (*R*,*R*)-(−)-toluene-4-sulfonic acid 2-fluoromethyl-cyclopropylmethyl ester *ent*-**1**.

development and optimisation of (stereoselective) cyclopropanation methods, as cyclopropane units can be found in various natural products and pharmaceuticals.[6] Previously published techniques for the resolution and synthesis of (*S*,*S*)- or (*R*,*R*)-1,2-disubstituted cyclopropanes have included: (a) fractional crystallisation of the corresponding *trans*-1,2-cyclopropane dicarboxylates followed by reduction, (b) chiral auxiliary-mediated,[7] stereoselective Simmons–Smith-cyclopropanation of olefins (Charette–Denmark method),[8] (c) the former combined with enzymes,[9a] (d) transition metal-complex catalysed carbenoid additions,[6d–f,9b] and (e) multi-step synthesis from enantiomerically enriched starting materials.[10] However, yields and enantiomeric excess vary widely. In addition, the Simmons–Smith-reaction provides only limited access to cyclopropanes from α,β-unsaturated carbonyl compounds.[6g]
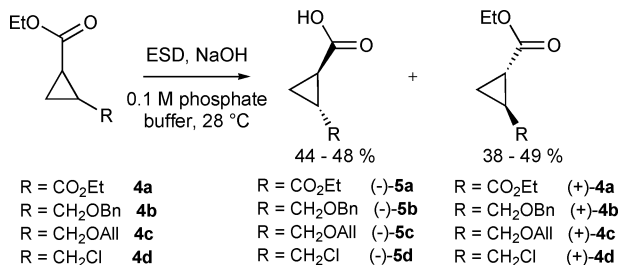
Herein we would like to report a convenient route to 2-substituted cyclopropanecarboxylic acid esters as well as an enzymatic method for the synthesis of diethyl (*S*,*S*)-(+)-cyclopropanedicarboxylate ((+)-**4a**) and ethyl (*R*,*R*)-(−)-cyclopropanedicarboxylate ((−)-**5a**) in high enantiomeric excess. ee-values of 99% for the (*S*,*S*)-(+)-enantiomer and 97% for the corresponding (*R*,*R*)-(−)-analogue were achieved, respectively, after half conversion (*E* > 200).[11] As a complement to the previously published chemical and enzymatic methods for the synthesis of 1,2-disubstituted cyclopropanes, the route presented herein readily affords versatile cyclopropane building blocks **7a** and **7b** in very high enantiomeric excess, avoiding sensitive or expensive reagents. **7a** was subsequently employed in the synthesis of **1** and *ent*-**1**. Both labelling synthons [^{18}F]-**1** and [^{18}F]-*ent*-**1** were successfully synthesised from [^{18}F]F$^-$ and precursors **11a** and *ent*-**11a** in a radiochemical yield of about 50%.
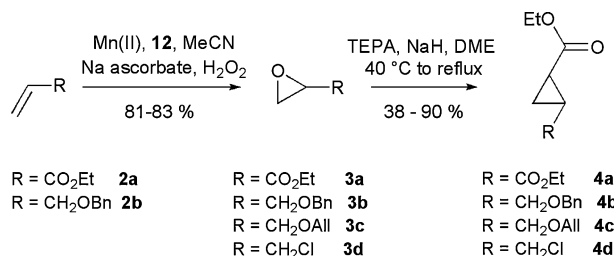
Results and discussion

Our approach is based on the enantiomeric resolution of racemic mixtures of esters **4a–d** (Scheme 2) employing an esterase from *Streptomyces diastatochromogenes* (ESD; E.C.3.1.1.1.), which we have found to show useful selectivity for the hydrolysis of cyclopropane carboxylic esters in the past.[12]

R = CO$_2$Et   **4a**   R = CO$_2$Et   (−)-**5a**   R = CO$_2$Et   (+)-**4a**
R = CH$_2$OBn **4b**   R = CH$_2$OBn (−)-**5b**   R = CH$_2$OBn (+)-**4b**
R = CH$_2$OAll **4c**   R = CH$_2$OAll (−)-**5c**   R = CH$_2$OAll (+)-**4c**
R = CH$_2$Cl   **4d**   R = CH$_2$Cl   (−)-**5d**   R = CH$_2$Cl   (+)-**4d**

Scheme 2 Enantiomeric resolution of substrate esters **4a–d**.

The Wadsworth–Emmons cyclopropanation was chosen for the preparation of racemic mixtures **4a–d** (Scheme 3), as it provides straightforward access to the desired *trans*-configured 1,2-disubstituted cyclopropanes in good yields at low cost.[13,15] Therefore, triethyl phosphonoacetate (TEPA) was converted into the P-ylide with potassium *tert*-butoxide and subsequently reacted with epoxides **3a–d**. The substrate epoxides **3a–d** were either prepared from parent olefins in >85% yield or obtained from commercial suppliers. Starting from olefinic precursors, *trans*-cyclopropanes were isolated in 56 to 75% yield employing a two-step procedure *via* Mn(II) catalysed epoxidation to afford compounds **3a–b** followed by *trans*-selective cyclopropanation under Horner–Wadsworth–Emmons conditions (Scheme 3).[13,14] In contrast to most copper/rhodium catalysed or non-catalysed additions of carbenoids which were examined by us, this route afforded the desired *trans*-configured cyclopropanes as single products. Thereby, the elaborate separation of (*Z*)- or open chain by-products was made obsolete.[16] During initial screening, racemates **4a–d** were hydrolysed employing ESD in phosphate buffer at pH 7.0. The pH was maintained *via* the controlled addition of 2 M NaOH solution. In the case of substrate **4a**, ESD showed a remarkably high selectivity. Only the (*R,R*)-configured enantiomer was recognised by the biocatalyst and both the remaining diester (+)-**4a** and the acid (−)-**5a** were isolated in high yield (49% and 46%, 99% and 97% ee, respectively). Unfortunately, only low enantioselectivity was observed after half conversion in all other cases. Neither esters **4b–d** nor acids **5b–**

R = CO$_2$Et   **2a**   R = CO$_2$Et   **3a**   R = CO$_2$Et   **4a**
R = CH$_2$OBn **2b**   R = CH$_2$OBn **3b**   R = CH$_2$OBn **4b**
                     R = CH$_2$OAll **3c**   R = CH$_2$OAll **4c**
                     R = CH$_2$Cl   **3d**   R = CH$_2$Cl   **4d**

Scheme 3 Epoxidation of terminal olefins using the 1,4,7-trimethyl-1,4,7-triazacyclononane (**12**) (TMTACN) Mn(II) ascorbate system,[14] followed by cyclopropane synthesis *via* Wadsworth–Emmons cyclopropanation on **3a–d**.

d were obtained in good enantiomeric excess. The addition of water miscible solvents, *e.g.* dioxane, decreased selectivity. In a multigram scale-up run (15.0 g substrate), ester **4a** was isolated in 49% (99% ee) yield, employing an enzyme concentration of 400 mg l$^{−1}$. Using diethyl ether for extraction of the non-hydrolysed (*S,S*)-ester, the residual enzyme in the buffer solution (containing acid **5a**) remained active for further hydrolysis of substrate **4a**. The latter facilitates fast, multi-batch syntheses of optically active ester (+)-**4a** without wasting the biocatalyst. In addition, the enzyme showed sufficient stability in solution at 28 °C to employ even lower concentrations in exchange for prolonged reaction times, without any significant loss in hydrolytic activity and yield.

In contrast to the racemic mixture **4a** which remains liquid at r.t., neat (+)-**4a** crystallised in colourless platelets (mp = 38 °C) displaying an optical purity of 99% ee. Acid (−)-**5a** was obtained *via* lyophilisation of the residual buffer solution, followed by acidic work-up to give carboxylic acid (−)-**5a** in 46% yield (97% ee). The relative configuration of compound **4a** was verified using X-ray crystallography (Fig. 1). The absolute configuration of (+)-**4a** and (−)-**5a** was assigned by comparison of the rotational directions with literature references. Therefore, a reference sample of ester (+)-**4a** and acid (−)-**5a** was hydrolysed to the diacid and the optical rotations were measured.[27b] Compound (+)-**4a** was assigned diethyl (+)-(*S,S*)-*trans*-cyclopropane-1,2-dicarboxylate, after the hydrolysed product showed the same angle of rotation as (+)-(*S,S*)-*trans*-cyclopropane-1,2- dicarboxylic acid. The (*R,R*)-configuration was analogously assigned to (−)-**5a**.[7,26]
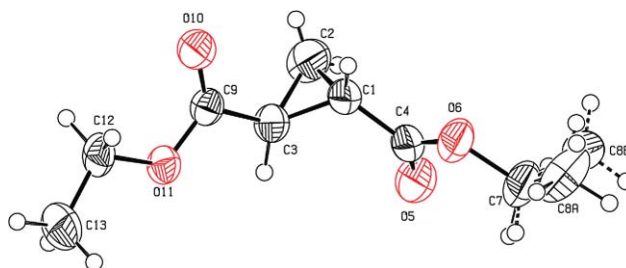
Fig. 1 X-Ray diffraction crystal structure of enantiopure (+)-**4a**.[27,28] A probability of 50% was chosen for the ellipsoids. One ethyl group (C7 and C8) is disordered unequally over two sites (C8A and C8B).

Diols **6a** and *ent*-**6a** were conveniently obtained in 82 to 88% yield *via* LiAlH$_4$ (LAH) reduction of **4** and **5** in THF using a modified procedure involving equimolar aqueous hydrolysis and quick short-path distillation in a Kugelrohr apparatus (Scheme 4).[7,17] The optical rotations of both product diols were in accordance with the assigned absolute configurations.[7]

(+)-**4a**   (+)-**6a**   (−)-**5a**   (−)-*ent*-**6a**
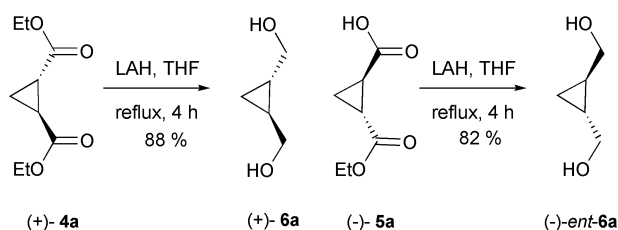
Scheme 4 Reductions of diester (*S,S*)-(+)-**4a** or acid (*R,R*)-(−)-**5a** to diol (+)-**6a** and (−)-*ent*-**6a**.

Compounds (+)-**6a** and (−)-*ent*-**6a** were desymmetrised using NaH in DMF followed by addition of benzyl chloride and catalytic amounts of TBAI (Scheme 5). A two-step procedure involving diacetylation followed by selective removal of one acetyl group using porcine pancreatic lipase (PPL) in phosphate buffer–dioxane at pH 7 resulted in de-symmetrised diols **7b** in even higher yield.[11,18,21] In addition, this double-enzymatic approach avoided preparative column chromatography as the products were substantially pure after complete hydrolysis to the monoacetate (Scheme 5).
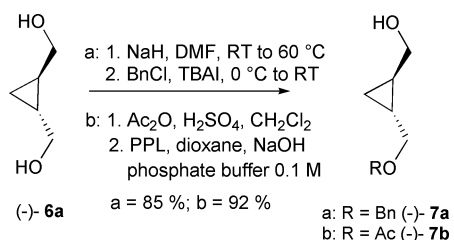

Scheme 5 De-symmetrisation of diol (−)-**6a**, *via* benzylation of the anion (a) or selective hydrolysis of the diacetate (b).

Product alcohols **7a** and *ent*-**7a** were preferably fluorinated *via* sulfonylation followed by a Finkelstein-analogue nucleophilic exchange using CsF in 2-propanol to obtain fluorides **9a** and *ent*-**9a** (Scheme 6). CsF displays a remarkable solubility (12.6 mole in 1000 g MeOH), while CsBr is the least soluble in alcohols among all caesium halogenides. Nevertheless, as leaving group, the mesylate gave even better results.[19] Fluoro-dehydroxylation employing diethylamino sulfur trifluoride (DAST) in dichloromethane at −80 °C to r.t. was also examined.[20] Although freshly obtained DAST produced fluorides **9a** and *ent*-**9a** in good yields (>90%), reagent stability issues led to poor reproducibility of fluorination outcomes after a few weeks.
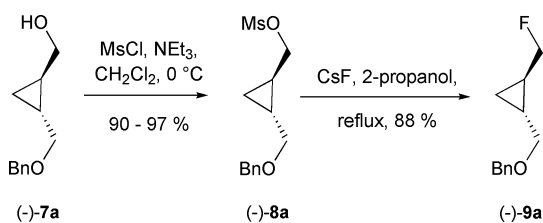

Scheme 6 Two-step fluorination *via* mesylation and Finkelstein exchange with CsF dissolved in 2-propanol.

Hydrogenolytic cleavage of the fluorides in 2-methoxy-2-methyl-propane (MTBE) followed by concentration and tosylation in one pot finally afforded target compounds (*S,S*)-(+)-**1** and (*R,R*)-(−)-*ent*-**1** in 87% yield over two steps (Scheme 7).[25]
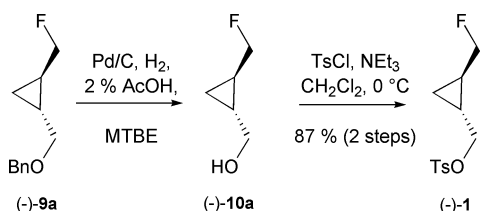
Scheme 7 Debenzylation of ether (−)-**9a** and subsequent tosylation to final product (−)-**1**.[24]

The radiosynthesis of [18F]-**1** and [18F]-*ent*-**1** was performed as illustrated for [18F]-*ent*-**1** in Scheme 8. **6a** and *ent*-**6a** were converted to the labelling precursors **11a**[26] and *ent*-**11a**, respectively, followed by exposure to pre-dried, cyclotron produced, no carrier added (n.c.a) [18F]fluoride. The labelling synthons [18F]-**1** and [18F]-*ent*-**1**, were obtained in a non-decay-corrected radiochemical yield of 52 ± 8% and 50 ± 3%, respectively, after a reaction time of 3 min in MeCN at 90 °C followed by HPLC-purification and solid phase extraction. Although the convenient half-life of fluorine-18 facilitates multi-step procedures and the production of 18F-fluorinated **1** can be automated, direct nucleophilic labelling of a suitable precursor is even more efficient in some cases. In this regard, **7a** and **7b** can serve as versatile building-blocks for precursor synthesis.
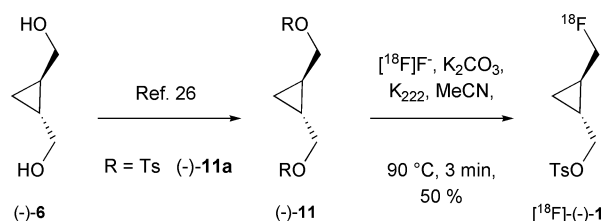
Scheme 8 Preparation of labelling precursors, exemplified for (−)-**11a** and subsequent radio-fluorination.

Conclusions

In conclusion, both enantiomers of **1** were prepared selectively in 18.7% and 16.4% overall yield, respectively, over eight to ten steps, starting from ethyl acrylate. The more versatile intermediates (*S,S*)-(+)-**7a** and (*S,S*)-(+)-**7b** were obtained in 20.5% and 22.2% yield, respectively, over 5 steps. Again, cyclopropanation using epoxide precursors and TEPA-anion in DME proved to be a useful route to 2-substituted cyclopropane-1-carboxylic acid esters in *trans*-configuration. Although enzymatic resolution of substrates **4b–d** failed due to the lack of selectivity in the hydrolytic cleavage of the ethyl esters, both (+)-**4a** and (−)-**5a** were separated and isolated in high yields and high enantiomeric excess. Furthermore, [18F]-**1** and [18F]-*ent*-**1** were successfully synthesised for the first time and isolated in a non-decay corrected radiochemical yield of 52 ± 8% and 50 ± 3%.

Compounds (+)-**4a**, (−)-**5a**, along with de-symmetrised diols **7a**, *ent*-**7a**, **7b** and *ent*-**7b** provide broad access to enantiomerically enriched 1,2-disubstituted *trans*-cyclopropanes. Utilising the route presented herein, these can be prepared in a synthetically useful multigram scale, thereby providing the means for the synthesis of a broad range of 1,2-disubstituted cyclopropane building blocks.

Experimental

NMR-spectra were recorded with a Bruker AC 200 FT-NMR-spectrometer, *J* values are given in Hertz, chemical shifts are reported downfield from TMS ($\delta = 0$ ppm) referred to the solvent residual signal ^{1}H NMR (300 MHz, CHCl$_3$ 7.224 ppm) and ^{13}C NMR (100 MHz, CDCl$_3$ 77.0 ppm). Field desorption (FD) mass spectra were recorded on a Finnigan MAT90 FD spectrometer. HRMS-spectra were measured on a Micromass QTOF Ultima

This journal is © The Royal Society of Chemistry 2008

Org. Biomol. Chem., 2008, **6**, 4567–4574 | **4569**

3 spectrometer. IR-spectra were obtained from a Nicolet 6700 FTIR spectrometer. Boiling points are uncorrected. Enantiomeric excesses of volatile cyclopropanes were determined by gas-chromatography using hydrogen as carrier gas on a Macherey-Nagel Lipodex E capillary column. All chemicals were obtained in commercial quality from Acros Organics, Sigma Aldrich, VWR, TCI or STREM and used without further purification. Enzymes were obtained from Julich Chiral Solutions (Codexis®) (ESD, recombinant from *E. coli*) and Sigma-Aldrich (PPL, from hog pancreas). Optical rotations were determined using a Perkin-Elmer polarimeter 241 running at 546 and 578 nm (Hg-lamp) at 17 to 25 °C and were extrapolated to the sodium D line. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. TLC was conducted on self-cut Merck silica gel 60 covered aluminium plates. Detection and staining was performed either using iodine on silica gel, potassium permanganate solution, UV fluorescence, vanillin–sulfuric acid, Seebach-reagent (phosphomolybdic acid, cerium sulfate, H$_2$SO$_4$) or Dragendorff-reagent (basic bismuth nitrate, potassium iodide and tartaric acid). Column chromatography was performed on Acros silica gel 60, 0.063-0.200 mesh, p. a. solvents for chromatography were washed with aqueous acid and base and distilled once, prior to use. Anhydrous solvents were used for reactions.

General procedure for the synthesis of epoxides 3a–b:

To a solution of olefin (1 mol) in MeCN (50 ml) were added 1 ml of an 0.4 M TMTACN stock solution in MeCN, 2 ml of an 150 mM stock solution of Mn(II)acetate-tetrahydrate in water and 30 ml of a 80 mM stock solution of sodium ascorbate in water. The mixture was cooled to 0 °C, and approximately 1.8 equiv. of 30% H$_2$O$_2$-solution (stabilised with 1 ppm of Sn) was added in portions until all olefin had been consumed (monitored by TLC). The organic phase was separated and the aqueous layer was extracted with EtOAc (75 ml). The combined organic layers were dried, concentrated and distilled *in vacuo* to afford epoxides **3** in >80% yield.

Ethyl 2,3-epoxypropanoate, compound 3a:[14]

From ethyl acrylate (1 mol) 94.3 g (812 mmol, 81%), distilled at 4 mbar, bp = 42–44 °C (lit.,[22a] 60–62 °C (17 mm)). Found: C, 51.78; H, 6.95 C$_5$H$_8$O$_3$ requires C, 51.72; H, 6.94%. v_{max}/cm^{-1} (neat) 2986(CH), 1735(CO), 1468(CH$_2$), 1387(CH$_3$), 1291(C(O)–O–C), 1251(epoxide), 1200(C(O)–O–C), 1029(C(O)–O–C), 915(epoxide), 819(epoxide), 720(CH$_2$). (lit.,[22b] 1750) δ_H (300 MHz, CDCl$_3$): 1.25 (t, $J = 7.0$ Hz, 3 H, CH$_3$), 2.90 (dd, $J = 4$ Hz, $J = 6$ Hz, 1 H, =CH–), 2.93 (dd, $J = 2.5$ Hz, $J = 6$ Hz, 1 H, =CH–) 3.39 (dd, $J = 2.5$ Hz, $J = 4$ Hz, 1 H, =CH$_2$), 4.20 (q, $J = 7.0$ Hz, 2 H, –OCH$_2$–), 4.21 (q, $J = 7.4$ Hz, 1 H, –OCH$_2$–). δ_C (100 MHz, CDCl$_3$): 14.07, 46.18, 47.33, 61.75, 169.45. *m/z* (FD) 117.05 ([M + H]$^+$ C$_5$H$_8$O$_3$ requires 116.0473).

3-Benzyloxymethylene-1,2-epoxypropane, compound 3b:[23]

From allyl benzyl ether (0.1 mol), yield: 13.6 g (83 mmol, 83%). Found: C, 73.45; H, 7.7 C$_{10}$H$_{12}$O$_2$ requires C, 73.15; H, 7.4%. v_{max}/cm^{-1} (neat) 3071(CH), 3057(CH), 3030(ArH), 2859(CH), 1496, 1453(CH$_2$), 1383(CH$_3$), 1252(epoxide), 1200(C(O)–O–C), 1029(C(O)–O–C), 898(epoxide), 845(epoxide), 736(ArH),

697(ArH). δ_H (300 MHz, CDCl$_3$): 2.20 (dd, $J = 2.6$ Hz, $J = 4.8$ Hz, 1 H, O–CH$_2$–), 2.79 (t, $J = 4.4$ Hz, 1 H, O–CH$_2$–), 3.14–3.21 (m, 1 H,–CH–O), 3.42 (dd, $J = 5.9$, $J = 11.4$ Hz, 1 H,–OCH$_2$–), 3.75 (dd, $J = 3.0$ Hz, $J = 11.4$ Hz, 1 H, –OCH$_2$–), 4.54 (d, $J = 12.1$ Hz, 1 H, ArCH$_2$–), 4.60 (d, $J = 11.8$ Hz, 1 H, ArCH$_2$–), 7.28–7.38 (m, 5 H, ArH). δ_C (100 MHz, CDCl$_3$): 44.3, 50.9, 70.8, 73.3, 127.8, 128.4, 137.9. *m/z* (FD) 164.1 (100) [M + H]$^+$ C$_{10}$H$_{12}$O$_2$ requires 164.0837.

General procedure for cyclopropane synthesis, compounds 4a–d:

At 0 °C, potassium *tert*-butoxide (11.22 g, 0.1 mol) was dissolved in 1,2-dimethoxyethane (100 ml) under nitrogen. To this solution, triethyl phosphonoacetate (29.27 g, 0.13 mol) was added dropwise over 30 min. After effervescence ceased the slightly turbid solution was slowly heated to 40 °C while epoxide **3a–d** (75 mmol) was added dropwise. The temperature was raised to 60 °C until all of the epoxide had been consumed (monitored by TLC), followed by reflux for 8 to 12 h to complete the cyclopropane formation. The reaction was quenched using saturated ammonium chloride solution (25 ml). In all cases except **3b**, prolonged reaction times lead to product degradation. Ethyl acetate (50 ml) was added and phases were separated. The aqueous phase was extracted once with ethyl acetate (50 ml), the combined organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel to afford 38 to 90% of **4a–d** as colourless oils.

***trans*-Cyclopropane-1,2-dicarboxylic acid diethyl ester, compound 4a[6g,9c,d,16b,16c,26a].** From ethyl 2,3-epoxypropanoate **3a** yield 9.63 g (52 mmol, 69%). Found: C, 57.95; H 7.6 C$_9$H$_{14}$O$_4$ requires C, 58.05; H, 7.6%. v_{max}/cm^{-1} (neat): 2993(CH), 1716(CO), 1447(CH$_2$), 1407, 1367(CH$_3$), 1322, 1172(C(O)–O–C), 1033, 743. δ_H (300 MHz, CDCl$_3$): 1.22 (t, $J = 7$ Hz, 3 H, CH$_3$), 1.38 (p, $J = 1.5$ Hz, $J = 7.4$ Hz, 2 H, –CH$_2$–), 2.11 (p, $J = 1.5$ Hz, $J = 7.4$ Hz, 2 H, –CH–), 4.10 (q, $J = 7$ Hz, 2 H, –OCH$_2$–). δ_C (100 MHz, CDCl$_3$): 14.2, 15.2, 22.4, 31.0, 171.7. *m/z* (FD) 186.1 (100) [M + H] C$_9$H$_{15}$O$_4$ requires 186.0892.

***trans*-2-Benzyloxymethylenecyclopropane-1-carboxylic acid ethyl ester, compound 4b[15a].** From 3-benzyloxymethylene-1,2-epoxypropane **3b**, yield: 15.7 g (68 mmol, 90%), chromatographed on silica gel, $R_f = 0.6$ (light petroleum–Et$_2$O, 7 : 3). Found: C, 71.8; H, 7.75 C$_{14}$H$_{18}$O$_3$ requires C, 71.8; H, 7.7. v_{max}/cm^{-1} (neat): 3028(ArH), 2977(CH), 2859(CH), 1720(CO), 1647, 1496, 1453(CH$_2$), 1367(CH$_3$), 1202(C(O)–O–C), 1177(C(O)–O–C), 1085(OCH$_2$), 735(ArH), 697(ArH). δ_H (300 MHz, CDCl$_3$): 0.80–0.89 (m, 1 H, –CH$_2$–), 1.22 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.23 (t, $J = 7$ Hz, 3 H, CH$_3$), 1.54 (p, $J = 4.4$ Hz, 1 H, –CH–C(O)), 1.67–1.78 (m, 1 H, –CH–), 3.38 (dq, $J = 10.3$ Hz, $J = 14.0$ Hz, 2 H, –CH$_2$–O), 4.10 (q, $J = 7$ Hz, 2 H, –OCH$_2$–), 4.50 (s, 2 H, ArCH$_2$–), 7.31 (m, 5 H, ArH). δ_C (100 MHz, CDCl$_3$): 12.9, 14.2, 18.6, 21.6, 60.6, 71.6, 72.7, 127.7, 128.4, 138.8, 173.8. *m/z* (FD) 234.2 (100) [M + H]$^+$ C$_{14}$H$_{18}$O$_3$ requires 234.1256.

***trans*-2-Allyloxymethylenecyclopropane-1-carboxylic acid ethyl ester, compound 4c[16e].** From allyl-glycidyl ether **3c**, yield 9.8 g (53 mmol, 71%), chromatographed on silica gel, $R_f = 0.55$ (light petroleum–Et$_2$O, 3 : 2). Found C, 65.0 H, 8.9. C$_{10}$H$_{16}$O$_3$ requires C, 65.2; H, 8.8%; v_{max}/cm^{-1} (neat): 2983(CH), 1720(CO), 1448(CH$_2$), 1366(CH$_3$), 1269(C(O)–O–C), 1175(C(O)–O–C), 1085(OCH$_2$),

4570 | *Org. Biomol. Chem.*, 2008, **6**, 4567–4574

This journal is © The Royal Society of Chemistry 2008

996(C=C), 943(C=C). δ_H (300 MHz, CDCl$_3$): 0.81–0.93 (m, 1 H, –CH$_2$–), 1.24 (t, $J = 7$ Hz, 3 H, CH$_3$), 1.26–1.34 (m, 1 H, –CH$_2$–), 1.58 (p, $J = 4$ Hz, 1 H, –CH–), 1.74–1.84 (m, 1 H, –CH–C(O)), 3.46 (dd, $J = 8.5$ Hz, $J = 9.9$ Hz, 1 H, O–CH$_2$–), 3.72 (dd, $J = 5.8$ Hz, $J = 10.3$ Hz, 1 H, O–CH$_2$–), 3.92 (dq, $J = 1.5$ Hz, $J = 5.5$ Hz, 2 H, –CH$_2$–O), 4.12 (q, $J = 7.0$ Hz, 2 H, –OCH$_2$–), 5.17 (d, $J = 10.3$ Hz, 1 H, =CH$_2$), 5.26 (d, $J = 17.3$ Hz, 1 H, =CH$_2$), 5.80–5.93 (m, 1 H). δ_C (100 MHz, CDCl$_3$): 13.1, 14.2, 18.5, 22.0, 71.2, 71.7, 117.2, 134.4, 173.0. m/z (FD) 185.2 (100) [M + H]$^+$ C$_{10}$H$_{16}$O$_3$ requires 184.1099.

trans-2-Chloromethylenecyclopropane-1-carboxylic acid ethyl ester, compound 4d[16c,d,f]**.** From epichlorohydrine **3d**, yield 3.72 g (28.5 mmol, 38%), chromatographed on silica gel, $R_f = 0.7$ (light petroleum–Et$_2$O, 4 : 1). As a neat compound, **4d** will decompose albeit slowly at 4 °C. Found: C, 51.8; H, 6.85. C$_7$H$_{11}$ClO$_2$ requires C, 51.7; H, 6.8; Cl, 21.80%; δ_H (300 MHz, CDCl$_3$): 0.87–0.98 (m, 1 H), 1.23 (t, $J = 7$ Hz, 3 H, CH$_3$), 1.29 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.62 (p, $J = 4.4$ Hz, 1 H, –CH–), 1.77–1.87 (m, 1 H, –CH–C(O)), 3.46 (dd, $J = 1.1$ Hz, $J = 7.0$ Hz, 2 H, Cl–CH$_2$–), 4.10 (q, $J = 7$ Hz, 2 H, –OCH$_2$–). δ_C (100 MHz, CDCl$_3$): 11.4, 14.2, 14.9, 20.5, 46.8, 60.7, 172.9. m/z (FD) 162,1 (100) C$_7$H$_{11}$ClO$_2$ requires 162.0448.

General procedure for enzymatic hydrolysis employing ESD, compounds (S,S)-4 and (R,R)-5:

Racemic esters **4a–d** (5 mmol) were suspended in phosphate buffer (5 ml) at pH 7.0. The temperature was adjusted to 28 °C and the reaction was initiated via the addition of 5 mg of ESD. pH was kept at 7.0 via the automated, controlled addition of 2 M NaOH. After 1.25 ml (2.5 mmol) of NaOH had been added (14–28 h depending on substrate and the ratio of enzyme to substrate), the reaction buffer was extracted with diethyl ether (2 × 10 ml) followed by CH$_2$Cl$_2$ (2 × 10 ml). The organic phases were combined, dried over Na$_2$SO$_4$ and concentrated in vacuo, to afford **4a–d** as colourless oils. The remaining phosphate buffer was lyophilised overnight and **5a–d** were isolated from the residue via acidic work-up. An aliquot of both ester and acid fraction was dissolved in alcohol (1 ml) and the optical rotary power was measured as an indicator for enantioselectivity of the reaction.

(+)-(S,S)-Cyclopropane-1,2-dicarboxylic acid diethyl ester, compound (+)-4a. From trans-cyclopropane-1,2-dicarboxylic acid diethyl ester **4a**, yield: 0.456 g (2.45 mmol, 49%), $[\alpha]_D^{20} = +168.8$; (c 1.15, EtOH) (lit.,[12b–c] $[\alpha]_D^{22} = +150.6$; (c 6.8, EtOH; ee = 100%). See **4a** for spectral data.

(+)-(S,S)-2-Benzyloxymethylenecyclopropane-1-carboxylic acid ethyl ester, compound (+)-4b. From trans-2-benzyloxymethylene-cyclopropane-1-carboxylic acid ethyl ester **4b**, yield: 510 mg (2.2 mmol, 44%), $[\alpha]_D^{20} = +9.8$; (c 1, MeOH). (lit.,[15a] $[\alpha]_D^{22}$ (R,R) = -77 (c 0.44, CHCl$_3$) ee >95%). See **4b** for spectral data.

(+)-(S,S)-2-Allyloxymethylenecyclopropane-1-carboxylic acid ethyl ester, compound (+)-4c. From trans-2-allyloxymethylene-cyclopropane-1-carboxylic acid ethyl ester **4c**, yield: 414 mg (2.25 mmol, 45%), $[\alpha]_D^{20} = +1.7$; (c 1.00, MeOH). See **4c** for spectral data.

(+)-(S,S)-2-Chloromethylenecyclopropane-1-carboxylic acid ethyl ester, compound (+)-4d. From trans-2-chloromethylene-cyclopropane-1-carboxylic acid ethyl ester **4d**, crude yield: 249 mg

(1.9 mmol, 38%), $[\alpha]_D^{20} = +4.1$; (c 1.00, MeOH). See **4d** for spectral data.

(−)-(R,R)-Cyclopropane-1,2-dicarboxylic acid ethyl ester, compound (−)-5a[9b–c]**.** From trans-cyclopropane-1,2-dicarboxylic acid diethyl ester **4a**, yield: 363 mg (2.3 mmol, 46%), $[\alpha]_D^{23} = -203.4$; (c 1.00, EtOH) (lit.,[12b–c] $[\alpha]_D^{20} = +148.5$; (c 6.7, EtOH, ee = 90.4%). Found C, 53.4; H, 6.4. C$_7$H$_{10}$O$_4$ requires C, 53.16; H, 6.4%. $v_{max}/$cm^{-1} (neat): 2985(CH), 1692(CO), 1460(CH$_2$), 1379(CH$_3$), 1180(C(O)–O–C). δ_H (300 MHz, CDCl$_3$): 1.22 (t, $J = 7.0$ Hz, 3 H, CH$_3$), 1.38–1.51 (m, 2 H, –CH$_2$–), 2.08–2.22 (m, 2 H, –CH–C(O)), 4.10 (q, $J = 7.0$ Hz, 2 H, –CH$_2$–), 11.5 (brs, 1H, COOH). δ_C (100 MHz, CDCl$_3$): 14.1, 15.8, 22.0, 23.0, 61.3, 171.4, 178.1. m/z (FD) 159.1 (100) [M + H]$^+$ C$_7$H$_{10}$O$_4$ requires 158.0579.

(−)-(R,R)-2-Benzyloxymethylenecyclopropane-1-carboxylic acid, compound (−)-5b. From ethyl trans-2-benzyloxymethylene-cyclopropane-1-carboxylate **4b** yield: 459 mg (2.25 mmol, 45%), $[\alpha]_D^{23} = -14.6$; (c 1.00, EtOH) (lit.,[15a] $[\alpha]_D^{22} = -152$ (c 0.51, CHCl$_3$) ee >95%). Found C, 69; H, 7.0. C$_{12}$H$_{14}$O$_3$ requires C, 69.9; H, 6.8%. $v_{max}/$cm^{-1} (neat) 3028(Ar–H), 2858(CH), 1690(CO), 1454(CH$_2$), 1075(OCH$_2$), 735(Ar–H), 696(Ar–H). δ_H (300 MHz, CDCl$_3$): 0.9–0.96 (m, 1 H, –CH–), 1.26 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.56 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.75–1.82 (m, 1 H, –CH–C(O)), 3.34 (dd, $J = 6.6$ Hz, $J = 10.3$ Hz, 1H), 3.46 (dd, $J = 5.9$ Hz, $J = 10,3$ Hz, 1 H), 4.51 (s, 2 H), 7.25–7.38 (m, 5 H, ArH), 11.2 (brs, 1H, COOH). δ_C (100 MHz, CDCl$_3$): 13.7, 18.4, 22.5, 71.2, 72.6, 127.7, 128.4, 138.0, 180.2. m/z (FD) 206.2 (100) C$_{12}$H$_{14}$O$_3$ requires 206.0943.

(−)-(R,R)-2-Allyloxymethylenecyclopropane-1-carboxylic acid, compound (−)-5c. From trans-2-allyloxymethylenecyclopropane-1-carboxylic acid ethyl ester **4c**, yield: 343 mg (2.2 mmol, 44%), $[\alpha]_D^{23} = -0.7$; (c 3.33, EtOH). Found C, 61.8; H, 7.9. C$_8$H$_{12}$O$_3$ requires C, 61.5; H, 7.7%. $v_{max}/$cm^{-1} (neat) 2930(CH), 1675(CO), 1464(CH$_2$), 1087(O–CH$_2$), 1007, 928(C=C). δ_H (300 MHz, CDCl$_3$): 0.87–0.97 (m, 1 H, –CH–), 1.24 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.55 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.69–1.81 (m, 1 H, –CH–C(O)), 3.31 (dd, $J = 6.6$ Hz, $J = 10.7$ Hz, 1 H), 3.41 (dd, $J = 6.3$ Hz, $J = 10.7$ Hz, 1H), 3.94 (d, $J = 5.9$ Hz, 2 H), 5.13 (d, $J = 10.3$ Hz, 1H), 5.24 (d, $J = 17.3$ Hz, $J = 1.1$ Hz, 1 H), 5.79–5.95 (m, 1 H), 11.28 (brs, 1 H, COOH). δ_C (100 MHz, CDCl$_3$): 13.6, 18.4, 22.5, 71.2, 71.6, 117.2, 134.5, 180.1. m/z (FD) 156.1 (100) C$_8$H$_{12}$O$_3$ requires 156.0786.

(−)-(R,R)-2-Chloromethylenecyclopropane-1-carboxylic acid, compound (−)-5d[16g]**.** From trans-2-chloromethylenecyclopropane-1-carboxylic acid ethyl ester **4d**, yield: 246 mg (2.4 mmol, 48%), $[\alpha]_D^{23} = -3.8$; (c 1.00, EtOH). $v_{max}/$cm^{-1} (neat) 3001(CH), 2945(CH), 2870(CH), 1675(CO), 1464(CH$_2$), 1190(C(O)–O–C), 928, 705, 659. δ_H (300 MHz, CDCl$_3$): 1.00–1.07 (m, 1 H, –CH–), 1.37 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.65 (p, $J = 4.4$ Hz, 1 H, –CH$_2$–), 1.85–1.92 (m, 1 H, –CH–C(O)), 3.43 (dd, $J = 7.0$ Hz, $J = 11.0$ Hz, 1H), 3.51 (dd, $J = 6.6$ Hz, $J = 11.4$ Hz, 1H), 11.39 (brs, 1 H, COOH). δ_C (100 MHz, CDCl$_3$): 15.7, 20.3, 24.5, 46.4, 179.5 m/z (FD) 134,1 (100) C$_5$H$_7$ClO$_2$ requires 134.0135.

Preparative scale procedure for the enzymatic resolution of compound 4a:

In a setup for reactions at controlled pH, **4a** (15.1 g, 80 mmol) was suspended in phosphate buffer (50 ml) at pH 7.1. After

This journal is © The Royal Society of Chemistry 2008

Org. Biomol. Chem., 2008, **6**, 4567–4574 | **4571**

the addition of 20 mg of ESD the reaction was initiated. The progress of hydrolysis was monitored *via* NaOH consumption of the pH-stat setup. After 18 to 24 hours of continuous stirring at 28 °C the NaOH consumption ended. The reaction was terminated and filtered through a pad of celite®. The non hydrolysed (*S,S*)-ester was extracted with diethyl ether (2 × 50 ml) and methylene chloride (2 × 50 ml). After subsequent combination, drying and concentration of the organic phases, (*S,S*)-**4** was obtained in 49% yield of (+)-**4a** as colourless crystals displaying an optical purity 99% ee (Fig.1, crystal structure). $[\alpha]_D^{24} = 168.8$ (*c* 1.15, EtOH).

The remaining reaction mixture was lyophilised to leave a residue that was re-dissolved in a small amount of ice-cooled HCl (10 ml) with cooling. Subsequent exhaustive extraction with portions of diethyl ether (30 ml) at pH 1.8 afforded acid **5a** in 46% yield and 97% ee.[27]

(*R,R*)-Diol and (*S,S*)-diol, compound 6 and *ent*-6:[7,10,17,26]

A solution of **4a** or **5a** (5.58 g, 30 mmol) in dry THF (10 ml) was added dropwise to a stirred solution of LiAlH$_4$ powder (95%) 1.0 equiv. (1.2 g, 30 mmol) and 1.25 equiv. (1.5 g, 37.5 mmol), respectively, in THF (90 ml) at 0 °C. The reaction mixture was heated to reflux for 4 h. After 4 h, a solution of 4.1 (2.22 ml, 123 mmol) and 5.1 equiv. (2.76 ml, 153 mmol) of water in THF (8 ml) was added dropwise with stirring under reflux, to obtain a fine suspension of LiOH and Al(OH)$_3$ in THF. The reaction mixture was filtered through a pad of celite, and the filter cake was washed twice with warm THF (15 ml) and once with dry acetone (15 ml). The filtrate was dried and concentrated *in vacuo*. Purification *via* bulb-to-bulb distillation in a Kugelrohr apparatus (1 mbar bp = 141 °C) (lit.,[7] bp = 96–98 °C 2 mm) gave products (*R,R*)-**6** and (*S,S*)-**6** in 88% (2.69 g, 26.4 mmol) and 82% (2.51 g, 24.6 mmol) yield, respectively, as colourless, viscous oil (bp 141 °C at 0.79 mbar). $[\alpha]_D^{21} = -22.6$; (*c* 1.31, EtOH) (lit.,[7] $[\alpha]_D^{20} = -26.5'$ (neat) ee >99%). $[\alpha]_D^{24} = +24.5$; (*c* 0.81, EtOH). Found: C, 58.7; H, 9.8. C$_5$H$_{10}$O$_2$ requires C, 58.8; H, 9.9%. ν_{max}/cm^{-1} (neat) 3353(OH), 2870(CH), 1430(CH$_2$), 1266, 1056(OCH$_2$). δ_H (300 MHz, CDCl$_3$): 0.42 (t, *J* = 6.6 Hz, 2 H, –CH$_2$–), 0.95–1.06 (m, 2 H, –CH–), 3.05 (dd, *J* = 2.9 Hz, *J* = 11.4 Hz, 2 H, –CH$_2$–), 3.80 (dd, *J* = 7.0 Hz, *J* = 11.4, 2 H, –CH$_2$–), 4.09 (brs, 2H, OH). δ_C (100 MHz, CDCl$_3$): 7.07, 19.80, 65.87. *m/z* (ESI) C$_5$H$_{10}$O$_2$ requires 102.0681.

Desymmetrisation of diols 6 to 7a benzyloxymethylene-cyclopropylmethanol:[8c,d,10b]

Diol **6** (2.04 g, 20 mmol) was added dropwise to a stirred suspension of 0.75 equiv. NaH 60% dispersion in mineral oil (600 mg, 15 mmol) in dry DMF (25 ml) under N$_2$ and heated to 60 °C. After cooling to 0 °C, 0.75 equiv. benzyl chloride (1.89 g, 15 mmol) and 0.1 mol% of TBAI were added all at once. Stirring was continued for 45 min during which the reaction mixture was allowed to warm to RT. Saturated ammonium chloride solution (5 ml) was added and the resultant mixture was concentrated *in vacuo* to leave a residue that was taken up in water (20 ml) and extracted with dichloromethane (3 × 25 ml). The organic layer was separated, dried and concentrated *in vacuo*. The residual oil was purified *via* column chromatography on silica gel, to afford compounds **7a** and *ent*-**7a** as colourless viscous liquids in 85% (3.45 g, 12.8 mmol) yield. $R_f = 0.7$ (EtOAc–light petroleum, 3 : 7)

$[\alpha]_D^{21} = +17.7$; (*c* 2.15, CHCl$_3$) (lit.,[8c] $[\alpha]_D^{23} = 13.8$ (*c* 2.25, CHCl$_3$ ee = 94%), $[\alpha]_D^{23} = 23.0$; (*c* 1.23, EtOH), $[\alpha]_D^{20} = -21.7$; (*c* 1.31, EtOH). Found: C, 75.35; H, 8.45. C$_{12}$H$_{16}$O$_2$ requires C, 75.0; H, 8.4%. ν_{max}/cm^{-1} (neat) 3379(OH), 3032(Ar–H), 2859(CH), 1453(CH$_2$), 1363(CH$_3$), 1070(OCH$_2$), 1049, 734(Ar–H), 696(Ar–H). δ_H (300 MHz, CDCl$_3$): 0.38–0.47 (m, 2 H, –CH$_2$–), 0.91–1.03 (m, 2 H, –CH–), 3.15–3.32 (m, 2 H, –CH$_2$–O), 3.39–3.51 (m, 2 H, O–CH$_2$–), 4.5 (s, 2 H, ArCH$_2$–O), 7.22–7.37 (m, 5 H, ArH). δ_C (100 MHz, CDCl$_3$): 8.0, 16.8, 19.8, 66.3, 72.6, 73.5, 127.6, 127.7, 128.4, 138.3. *m/z* (FD) 192.2 (100) C$_{12}$H$_{16}$O$_2$ requires 192.1150.

Desymmetrisation of diols 6 to compounds 7b and *ent*-7b:[24,26a,29,30]

Diol **6** (1.53 g, 15 mmol) was dissolved in methylene chloride (30 ml), cooled to 0 °C and acetic anhydride (5 ml) was added. The reaction was initiated *via* the addition of one drop of 97% H$_2$SO$_4$. After stirring at RT for 14 h the reaction mixture was extracted with water (15 ml), dried and concentrated *in vacuo*. The residue was purified *via* bulb-to-bulb distillation in a Kugelrohr apparatus to obtain a colourless liquid. $[\alpha]_D^{21} = +17.5$; (*c* 1.00, EtOH), $[\alpha]_D^{25} = -17.3$; (*c* 1.00, EtOH) (lit.,[29] $[\alpha]_D^{23} = -14.1$; (*c* 2.1, EtOH). Found: C, 58.1 H, 7.3 C$_9$H$_{14}$O$_4$ requires C, 58.05; H, 7.58%; ν_{max}/cm^{-1} (neat) 2915(CH), 1732(CO), 1449(CH$_2$), 1366(CH$_3$), 1225(C(O)–O–C), 1072(OCH$_2$), 1029. δ_H (300 MHz, CDCl$_3$): 0.56 (t, *J* = 6.8 Hz, 2 H, –CH$_2$–), 1.03–1.15 (m, 2 H, –CH–), 2.02 (s, 6 H, CH$_3$), 3.89 (d, *J* = 7.0 Hz, 4 H, –CH$_2$–O).[23] *m/z* (FD) 186.1 (100) C$_9$H$_{14}$O$_4$ requires 186.0892.

The product was added to a suspension of 1 g PPL in 20 ml of 0.1 M phosphate buffer at pH 7.1. The pH was maintained stable during the hydrolytic de-symmetrisation *via* the addition of 1.3 M NaOH when necessary. After 19 h, the reaction mixture was filtered through a pad of celite®. The filter cake was washed with Et$_2$O (2 × 10 ml) and the organic layer was separated. The remaining buffer solution was extracted with diethyl ether (20 ml), followed by dichloromethane (20 ml) and again diethyl ether (20 ml). Subsequent combination, drying and concentration of the organic layers afforded **7b** (1.99 g, 13.8 mmol, 92%) as colourless liquid. $[\alpha]_D^{25} = +21.9$; (*c* 1.00, EtOH) (lit.,[30] $[\alpha]_D^{25} = +7.8$; (*c* 0.35, CH$_2$Cl$_2$, ee ~ 20%). Found: C, 58.5; H, 8.3. C$_7$H$_{12}$O$_3$ requires C, 58.3; H, 8.4%. ν_{max}/cm^{-1} (neat) 3004, 2948(CH), 2876(CH), 1717(CO), 1424(CH$_2$), 1369(CH$_3$), 1232(C(O)–O–C), 1067(OCH$_2$), δ_H (300 MHz, CDCl$_3$): 0.51 (t, *J* = 7.0 Hz, 2 H, –CH$_2$–), 0.96–1.11 (m, 2 H, –CH–), 2.03 (s, 3 H, CH$_3$), 3.40 (dd, *J* = 6.5 Hz, *J* = 11.4 Hz, 1 H, –CH$_2$–OAc), 3.89 (dd, *J* = 6.5 Hz, *J* = 11.4 Hz, 1 H, –CH$_2$–OAc), 3.89 (d, *J* = 6.5, 2 H, O–CH$_2$–). δ_C (100 MHz, CDCl$_3$): 8.4, 15.6, 19.8, 21.0, 65.9, 67.8, 171.3. *m/z* (FD) 144.1 (100) C$_7$H$_{12}$O$_3$ requires 144.0786.

2-Methylsulfonyloxymethylene cyclopropylmethyl benzyl ether, compounds 8a and *ent*-8a:

Alcohols **7a** and *ent*-**7a** (1.92 g, 10 mmol) were added to 1 equiv. of triethylamine dissolved in CH$_2$Cl$_2$ (10 ml) and stirred at 0 °C for 30 min. Subsequently, methanesulfonyl chloride was added dropwise to this mixture. The reaction was quenched *via* the addition of cold water (15 ml) with stirring and the mixture was diluted with CH$_2$Cl$_2$ (10 ml). The organic phase was washed with 5% sodium carbonate solution (10 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford **8a** and ent-**8a**

in 90% (2.4 g, 9 mmol) to 97% (2.62 g, 9.7 mmol) yield. $[\alpha]_D^{24} =$ +19.1; (c 1.08, EtOH). Found: C, 57.5; H, 7.1, S, 11.5. $C_{13}H_{18}O_4S$ requires C, 57.8; H, 6.7; S, 11.86%. v_{max}/cm^{-1} (neat) 3023(Ar–H), 2937(CH), 2860(CH), 1454(CH$_2$), 1347(CH$_3$), 1168(–SO$_2$–), 1075(OCH$_2$), 738(Ar–H), 698(Ar–H). δ_H (300 MHz, CDCl$_3$): 0.6–0.67 (m, 2 H, –CH$_2$–), 1.11–1.24 (m, 2 H, –CH–), 2.99 (s, 3 H, CH$_3$), 3.30 (dd, J = 6.3 Hz, J = 9,9 Hz, 1 H, O–CH$_2$–), 3.42 (dd, J = 5.9 Hz, J = 10.3 Hz, 1 H, O–CH$_2$–), 4.1 (d, J = 6.6 Hz, 2 H, –CH$_2$–O), 4.49 (s, 2 H, ArCH$_2$–O), 7.25–7.37 (m, 5 H, ArH). δ_C (100 MHz, CDCl$_3$): 9.0, 16.0, 17.7, 38.1, 66.3, 72.5, 74.0, 127.7, 128.4, 138.2. m/z (FD) 270,2 (100) $C_{13}H_{18}O_4S$ requires 270.0926.

2-Fluoromethylene cyclopropylmethyl benzyl ether, compounds 9a and ent-9a, two-step procedure:

A solution of mesylate **8a** or *ent*-**8a** (901 mg, 3.3 mmol) was added dropwise to a stirred solution of dry CsF (750 mg, 5 mmol) in 2-propanol (4.5 ml) at reflux in a Supelco reactivial® with stirring. After 90 minutes a colourless caesium methane sulfonate precipitate was observed and all of **8** had been consumed. The slightly-brown reaction mixture was filtered and the filter cake was washed with Et$_2$O (2 × 5 ml). The organic phases were combined, concentrated *in vacuo* and chromatographed on silica gel to obtain **9a** and *ent*-**9a** (560 mg, 2.9 mmol, 88%) as a colourless oil. $[\alpha]_D^{24} = -29.3$; (c 1.00 in EtOH); $[\alpha]_D^{21} = +29.9$; (c 1.00, EtOH), R_f = 0.6 (hexanes–Et$_2$O, 9 : 1). Found: C, 74.2; H, 8.0. $C_{12}H_{15}FO$ requires C, 74.2; H, 7.8%. v_{max}/cm^{-1} (neat) 3065(CH), 3010(ArH) 2922(CH), 2861(CH), 1453(CH$_2$), 1123(C–F), 1091(OCH$_2$), 735(Ar–H), 697(Ar–H), 613(C–F). δ_H (300 MHz, CDCl$_3$): 0.54–0.64 (m, 2 H, –CH$_2$–), 1.06–1.18 (m, 2 H, –CH–), 3.25–3.46 (m, 2 H, O–CH$_2$–), 4.17 (ddd, J = 7 Hz, J = 12.5 Hz, J_{H-F} = 48.6 Hz, 1 H, –CH$_2$–F), 4.52 (s, 2 H, ArCH$_2$–O), 7.25–7.36 (m, 5 H, ArH). δ_C (100 MHz, CDCl$_3$): 8.2 (d, J_{C-F} = 6.8 Hz), 16.6 (d, J_{C-F} = 6.8 Hz), 16.8 (d, J_{C-F} = 22 Hz), 72.5, 72.8, 86.9 (d, J_{C-F} = 161.2 Hz), 127.7, 128.4, 138.4. δ_F (376 MHz, CDCl$_3$) −209.6 (t, J = 48.7 Hz) m/z (FD) 194.2 (100) $C_{12}H_{15}FO$ requires 194.1107.

2-Fluoromethylene cyclopropylmethyl benzyl ether, compounds 9a and ent-9a, one-step procedure:

In an oven dried flask diethylamino sulfur trifluoride (DAST) (421 mg, 2.3 mmol) was added to dry dichloromethane (5 ml) *via* a septum inlet under dry argon. The flask was cooled to −80 °C and dry **7a** and *ent*-**7a** (385 mg, 2 mmol) dissolved in dry dichloromethane (5 ml) was added drop wise *via* a syringe. After several minutes of stirring, the flask was warmed to −43 °C (MeCN–dry ice) and the reaction mixture was stirred for 1 h after which the flask was warmed to 0 °C. Stirring was continued for an additional hour at 0 °C and then for 1 h at room temperature. The flask was cooled back to 0 °C prior to the careful, dropwise addition of 5% sodium carbonate solution (intense foaming), followed by pentane (5 ml). At this point the organic phase was separated, quickly dried and passed through a short silica column to remove the polar DAST-products. The addition of chloroform (15 ml) instead of hexane followed by further extraction of the organic phase using sodium carbonate solution (2 × 10 ml), drying and evaporation of the organic phase gave comparable results. The product was purified *via* flash column chromatography to obtain products **9a** and *ent*-**9a** in up to 92% (360 mg, 18.5 mmol) yield.

It was found that the presence of water during the reaction led to the formation of sulfurous acid dialkyl esters as significant by-products. See above for spectral data.

2-Tosyloxymethylene cyclopropylmethyl fluoride, compounds 1 and ent-1:

Pd (5 mol%) on activated carbon was suspended in MTBE (20 ml), containing **9a** or *ent*-**9a** (388 mg, 2 mmol) and 2% (v/v) of glacial acetic acid. Hydrogen was passed through this suspension until all **9** had been consumed. The reaction mixture was filtered through a pad of celite® to remove the catalyst, and concentrated to approximately 1 M alcohol per litre. 1.3 equivalents of NEt$_3$ were added and the reaction mixture was cooled to 0 °C. After the mixture was stirred for 15 min at 0 °C, 1.25 equiv *p*-toluenesulfonyl chloride (476 mg, 2 mmol) was added in portions. The reaction was quenched after four to eight hours *via* the addition of cold, saturated ammonium chloride solution (15 ml) with stirring. The organic layer was diluted with dichloromethane (15 ml) and the organic phase was washed with 5% sodium carbonate solution (10 ml) followed by water (10 ml). Subsequent drying over anhydrous sodium sulfate and concentration *in vacuo* afforded an oily residue that was purified *via* flash column chromatography (AcOEt–light petroleum, 1 : 4) to obtain (S,S)-(+)-**1** and *ent*-**1** as colourless crystals in 87% (450 mg, 1.74 mmol) yield. $[\alpha]_D^{21} = -18.9$; (c 1.00, EtOH), $[\alpha]_D^{25} = +20.4$; (c 2.10, EtOH). Found: C, 55.7; H, 5.9. $C_{12}H_{15}FO_3S$ requires C, 55.8; H, 5.85%. v_{max}/cm^{-1} (neat) 3025(ArH), 2959(CH), 2915(CH), 2870(CH), 1597, 1495, 1465(CH$_2$), 1380(CH$_3$), 1352(–SO2–), 1307(CH$_2$), 1247(CH$_3$), 1188(–C–F), 1170(–SO$_2$–), 1096, 932(Ar–H), 776(Ar–H), 571(–C–F), 663, 553. δ_H (300 MHz, CDCl$_3$): 0.55–0.68 (m, 2 H, –CH$_2$–), 1.06–1.19 (m, 2 H, –CH–), 2.42 (s, 3 H, CH$_3$), 3.91 (d, J = 7.0 Hz, 2 H, –CH$_2$–OTs), 4.20 (dd, J = 6.6 Hz, J_{H-F} = 48.8 Hz, 1 H, –CH$_2$–F), 7.32 (d, J = 7.7 Hz, 2 H, ArH), 7.76 (d, J = 8.1 Hz, 2 H, ArH). δ_C (100 MHz, CDCl$_3$): 8.5 (d, J_{C-F} = 6.8 Hz), 15.6 (d, J_{C-F} = 6.8 Hz), 17.4 (d, J_{C-F} = 24.9 Hz), 21.6, 73.5, 85.7 (d, J_{C-F} = 167.3 Hz), 127.8, 129.9, 133.2, 144.8. δ_F (376 MHz, CDCl$_3$): −211.92 (1 F, t, J_{H-F} = 48.79 Hz). m/z (FD) 258.1 $C_{12}H_{15}FO_3S$ requires 258.0726. HRMS (ESI) 281.0634 (100) ([M + Na] $C_{12}H_{15}FNaO_3S$ requires 281.0624).

2-[18F]Fluoromethylene cyclopropylmethyl tosylate, compounds [18F]-1 and [18F]-ent-1:

[18F]fluoride was produced by proton bombardment of an iso-topically enriched [18O]H$_2$O-target, using the 18O[p,n]18F nuclear reaction. The [18F]HF containing [18O]H$_2$O was passed through a Waters Accell plus light QMA strong anion exchanger cartridge, preconditioned with 1 M K$_2$CO$_3$-solution (10 ml) followed by water (20 ml). The trapped [18F]fluoride was eluted with a solution of cryptand Kryptofix® K222 (15 mg, 0.04 mmol) and K$_2$CO$_3$ (2 mg, 0.015 mmol) in MeCN (1 ml). The MeCN was evaporated at 88 °C under a stream of nitrogen (300 ml min^{-1}) *in vacuo* (10^2 mbar) to remove the remaining water. Additional MeCN was added (2 × 1 ml) and evaporated. The dried [18F]fluoride complex was redissolved in 1 ml of MeCN containing precursor **11a** (4.5 mg, 11 µmol) or *ent*-**11a**, respectively, and heated to 90 °C for three minutes. The reaction was quenched *via* the addition of HPLC-eluent (MeCN–H$_2$O, 1 : 1; 1 ml) and the reaction

This journal is © The Royal Society of Chemistry 2008

Org. Biomol. Chem., 2008, **6**, 4567–4574 | 4573

mixture was purified by semipreparative HPLC (10 × 250 mm VWR Lichrosorb® RP-18 5 μ). The product fraction was collected after a retention time of 12–15 min. The collected HPLC-solvent was diluted with water (4 : 1) and the obtained solution was passed through a VWR EN cartridge. The resin was washed once with water (3 ml) and dried in a gentle stream of nitrogen (200 ml min⁻¹). [¹⁸F]-**1** and [¹⁸F]-*ent*-**1** were isolated in a radiochemical purity of >98% and a non decay corrected radiochemical yield of 52 ± 8% and 50 ± 3%, respectively, *via* elution of the cartridge with Et₂O followed by careful evaporation of the solvent.

Acknowledgements

Notes and references

1 (*a*) K. L. Kirk, *Curr. Top. Med. Chem.*, 2006, 1445; (*b*) J.-P. Bégué and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992; (*c*) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (*d*) C. Isanbor and D. J. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 297; (*e*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

2 (*a*) H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*c*) E. Schweizer, A. Hoffmann-Roeder, K. Schärer, J. A. Olsen, C. Fäh, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy and F. Diederich, *ChemMedChem*, 2006, **1**, 611.

3 (*a*) M.-C. Lasne, C. Perrio, J. Rouden, L. Barré, D. Roeda, F. Dolle and C. Crouzel, *Top. Curr. Chem.*, 2002, **222**, 201; (*b*) L. Cai, S. Lu and V. W. Pike, *Eur. J. Org. Chem.*, 2008, 2853; (*c*) H. J. Wester, *Handbook of Nuclear Chemistry 4*, Kluwer Academic Publishers, Dordrecht, 2003, pp. 119–202.

4 (*a*) M. Watanabe, Y. Kazuta, H. Hayashi, S. Yamada, A. Matsuda and S. Shuto, *J. Med. Chem.*, 2006, **49**, 5587; (*b*) A. De Meijere, *Angew. Chem.*, 1979, **18**, 909; (*c*) B. Perly, I. C. P. Smith and H. C. Jarrell, *Biochemistry*, 1985, **24**, 1055.

5 (*a*) M. A. Carroll, M. Schwartzman, J. Capdevila, J. R. Falok and J. C. McGiff, *Eur. J. Pharmacol.*, 1987, **138**, 281; (*b*) S. K. Yang, D. W. McCourt, P. P. Roller and H. V. Gelboin, *Proc. Natl. Acad. Sci. U. S. A.*, 1976, **73**, 2594.

6 (*a*) For reviews and collections see: H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*b*) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*c*) J. Pietruszka, *Chem. Rev.*, 2003, **103**, 1051; (*d*) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; (*e*) *Houben–Weyl*, Vol. E17a-c, ed. A. de Meijere, Thieme, Stuttgart, 1996; (*f*) H.-U. Reissig, *Houben–Weyl*, Vol. E 21, ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1995; (*g*) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, C. M. Hoiness, *Organic Reactions*, Wiley, New York, 1973, vol. 20, pp. 3–131.

7 M. Schlosser and G. Fouquet, *Chem. Ber.*, 1974, 1162 and references cited therein.

8 (*a*) A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, 1994, **116**, 2651; (*b*) S. E. Denmark and J. P. Edwards, *Synlett*, 1992, 229; (*c*) A. B. Charette, H. Juteau, H. Lebel and C. Molinaro, *J. Am. Chem. Soc.*, 1998, **120**, 11943; (*d*) J. Balsells and P. J. Walsh, *J. Org. Chem.*, 2000, **65**, 5005; (*e*) S. E. Denmark, S. P. O'Connor and S. R. Wilson, *Angew. Chem., Int. Ed.*, 1998, **37**, 1149; (*f*) A. B. Charette, C. Molinaro and C. Brochu, *J. Am. Chem. Soc.*, 2001, **123**, 12168.

9 (*a*) J. Pietruszka, A. C. M. Rieche, T. Wilhelm and A. Witt, *Adv. Synth. Catal.*, 2003, **345**, 1273; (*b*) J. A. Miller, E. J. Hennessy, W. J. Marshall, M. A. Scialdone and S. T. Nguyen, *J. Org. Chem.*, 2003, **68**, 7884; (*c*) R. Csuk and Y. von Scholz, *Tetrahedron*, 1994, **50**, 10431 and references cited therein; (*d*) V. K. Aggarwal, H. W. Smith, G. Hynd, R. V. H. Jones, R. Fieldhouse and S. E. Spey, *J. Chem. Soc., Perkin Trans. 1*, 2000, **19**, 3267.

10 (*a*) R. E. Taylor, F. C. Engelhardt, M. J. Schmitt and H. Yuan, *J. Am. Chem. Soc.*, 2001, **123**, 2964; (*b*) Y. Kazuta, H. Abe, T. Yamamoto, A. Matsuda and S. Shuto, *J. Org. Chem.*, 2003, **68**, 3511.

11 K. Faber, *Biotransformations in Organic Chemistry*, Springer, Heidelberg 5th edn, 2004.

12 (*a*) C. Tesch, K. Nikoleit, V. Gnau, F. Goetz and C. Bormann, *J. Bacteriol.*, 1996, 178; (*b*) G. E. Jeromin, T. Daussmann, H. Hippchen and P. Riss, *Ger. Offen. DE 102004059469 2006; Chem. Abstr.*, 2006, **143**, 26701; (*c*) G. E. Jeromin, M. Bertau, *Bioorganikum*, Wiley-VCH, Weinheim, 2005.

13 W. S. Whadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **79**, 1733.

14 (*a*) A. Berkessel and C. A. Sklorz, *Tetrahedron Lett.*, 1999, 7965; (*b*) A. Grenz, S. Ceccarelli and C. Bolm, *Chem. Commun.*, 2001, 1726 and references cited therein.

15 (*a*) A. Armstrong and J. N. Scutt, *Org. Lett.*, 2003, **5**, 2331; (*b*) A. K. Singh, M. N. Rao, J. H. Simpson, W.-S. Li, J. E. Thornton, D. E. Kuehner and D. J. Kacsur, *Org. Process Res. Dev.*, 2002, 618.

16 (*a*) T. Rasmussen, J. F. Jensen, N. Èstergaard, D. Tanner, T. Ziegler and P.-O. Norrby, *Chem.–Eur. J.*, 2002, **8**, 177 and references cited therein; (*b*) K. B. Wiberg, R. K. Barnes and J. Albin, *J. Am. Chem. Soc.*, 1975, **79**, 4994; (*c*) M. P. Doyle, W. H. Tamblyn and V. Bagheri, *J. Org. Chem.*, 1981, **46**, 5094; (*d*) I. A. D'yakonov and T. V. Domareva, *Zh. Obshch. Khim.*, 1955, **25**, 934, 1486; (*e*) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and T. Shimizu, *J. Org. Chem.*, 1968, **33**, 544; (*f*) B. T. Golding and S. Mwesigye-Kibende, *J. Chem. Soc., Chem. Commun.*, 1983, 1103; (*g*) I. A. D'yakonov and O. V. Guseva, *Sbornik Statei Obshchei Khim. Akad. Nauk S.S.S.R.*, 1953, **1**, 425.

17 Most published methods make use of continuous liquid–liquid extraction, *e.g.*: K. Ruhland and E. Herdtweck, *Adv. Synth. Catal.*, 2005, **347**, 398.

18 O. Houille, T. Schmittberger and D. Uguen, *Tetrahedron Lett.*, 1996, **37**, 625.

19 *Gmelins Handbuch der Anorganischen Chemie*, Verlag Chemie, Weinheim, 8th edn, 1938, reprint 1955.

20 (*a*) M. Hudlicky, *Organic Reactions*, Wiley, Hoboken, 1988, vol. 35; (*b*) R. P. Singh and J. M. Shreeve, *Synthesis*, 2002, 2561; (*c*) R. P. Singh, D. T. Meshri and J. M. Shreeve, *Adv. Org. Synth.*, 2006, **2**, 291.

21 T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, Hoboken 3rd edn.

22 (*a*) H.-D. Becker and B. Ruge, *J. Org. Chem.*, 1980, **45**, 2189; (*b*) R. W. White and W. D. Emmons, *Tetrahedron*, 1962, **17**, 31.

23 (*a*) S. Krompiec, N. Kuznik, M. Urbala and J. Rzepa, *J. Mol. Catal. A*, 2006, **248**, 198; (*b*) M. Muehlbacher and C. D. Poulter, *J. Org. Chem.*, 1988, **53**, 1026.

24 C. D. Poulter, J. Muscio and R. J. Goodfellow, *J. Org. Chem.*, 1975, **40**, 139.

25 Please note that fluoroalcohols **10** may be strong skin irritants.

26 (*a*) A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, 1959, **81**, 2012; (*b*) Y. Inouye, T. Sugita and H. M. Walborsky, *Tetrahedron*, 1964, **20**, 1695; (*c*) Y. Inouye, S. Sawada, M. Ohno and H. M. Walborsky, *Tetrahedron*, 1967, **23**, 3237; (*d*) V. J. Heintz and T. A. Keiderling, *J. Am. Chem. Soc.*, 1981, **103**, 2395.

27 (*a*) An ether solution of acid **5a** was dried over sodium sulfate and exposed to excess diazomethane in ether in a standard 2 ml screw-cap vial for 20 minutes. The obtained solution can be used for GC-determination of ee-values; (*b*) S. R. Landor, P. D. Landor and M. Kalli, *J. Chem. Soc., Perkin Trans. 1*, 1983, **12**, 2921(mp acid = 172–174 °C; (*R*,*R*): $[\alpha]_D^{20} = -218$ (*c* 1, EtOH); (lit.,[7] $[\alpha]_D^{20} = -238.8$ (*c* 2.036, H₂O). (*S*,*S*) $[\alpha]_D^{20} = +232.4$ (*c* 1, EtOH) (lit.,[26d] $[\alpha]_D^{20} = +228$ (*c* 1.75, EtOH).

28 Deposited at the Cambridge Structural Database: CCDC 691513.

29 (*a*) B. S. J. Blagg, M. B. Jarstfer, D. H. Rogers and C. D. Poulter, *J. Am. Chem. Soc.*, 2002, **124**, 8846; (*b*) A. G. M. Barrett, D. Hamprecht, J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 1997, **119**, 8608.

30 S. Hu and J. S. Dordick, *J. Org. Chem.*, 2002, **67**, 314.