ARTICLE

OBC
www.rsc.org/obc

Reactive resin facilitated preparation of an enantiopure fluorobicycloketone

Audrey Wong,* Christopher J. Welch,* Jeffrey T. Kuethe, Enrique Vazquez, Mohamed Shaimi, Derek Henderson, Ian W. Davies and David L. Hughes

Department of Process Research, Merck & Co., Inc., PO Box 2000, Rahway, New Jersey 07065, USA. E-mail: audrey_wong@merck.com; christopher_welch@merck.com

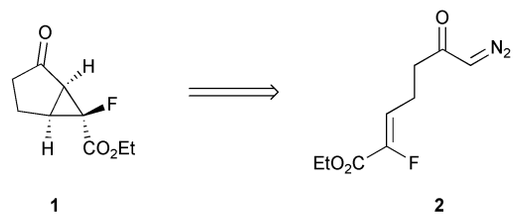
Received 30th September 2003, Accepted 5th November 2003
First published as an Advance Article on the web 20th November 2003

A facile preparation of enantiopure ethyl (1*S*,5*S*,6*S*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate **1** is described. The key feature of the synthesis involves copper-catalyzed enantioselective intramolecular cyclopropanation of a diazoketone to form *endo*-fluorocyclopropane **1** in a single operation. Removal of a problematic chloroketone impurity using a reactive resin treatment enabled a high throughput enantiopurity upgrade by chiral HPLC. The development of a scalable synthesis of **1** is presented, including details of the selection of catalyst and ligand optimization, incorporation of a reactive resin treatment and selection of chiral HPLC media and conditions.

Introduction

Recent increases in the pace of drug discovery necessitate a corresponding increase in the pace of later stage preclinical activities. Oftentimes, the synthetic route used for preparation of the first few milligrams of the lead compound proves unsuitable for providing the larger amounts of material required to fully define pharmacological properties. In such instances, a viable synthetic sequence capable of providing hundreds of grams to kilograms of material is needed. Historically, only a small fraction of all lead compounds survive the increased scrutiny of preclinical evaluation. Consequently, a high value is placed on technologies that facilitate expedited discovery and development. In recent years, enabling technologies such as catalyst and reagent screening, chiral chromatography, and high-throughput process research approaches have become increasingly utilized for the rapid development of processes which supply material for the short term and have some potential for implementation at larger scale. A recent example from these laboratories aptly illustrates this approach.

During the course of biological evaluation of a number of compounds, non-trivial quantities of the enantiopure [3.1.0]-bicyclic ketone **1** which possesses the challenging fluorocyclopropane moiety were required as an intermediate.[1] While several approaches were considered, one attractive retrosynthetic analysis of **1** revealed a potential for an asymmetric intramolecular cyclopropanation of diazoketone **2** (Scheme 1). This approach was appealing since the three contiguous stereocenters in the target are set in a single operation. The discovery and implementation of a scalable process involving enantioselective synthesis of **1** followed by reactive resin treatment and enantiopurity upgrade using preparative chiral HPLC is presented.



1 **2**

Scheme 1 Retrosynthetic analysis.

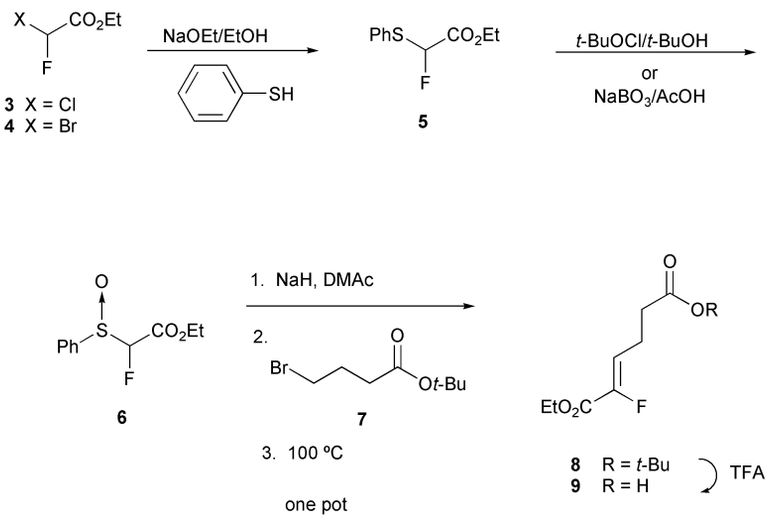
Results and discussion

Reaction of ethyl chlorofluoroacetate **3** or the bromoanalog **4** with benzenethiol in the presence of NaOEt in EtOH provided sulfide **5** in nearly quantitative yield (Scheme 2).[2] Oxidation of sulfide **5** to the corresponding sulfoxide **6** has previously been reported to proceed with sodium periodate or *m*-chloroperbenzoic acid (mCPBA). The major disadvantages with these oxidants were the competing over-oxidation to the sulfone which was observed in up to 20% yield and the need for careful chromatography in order to separate the sulfone from the sulfoxide. After screening a number of oxidative procedures, it was discovered that sulfoxide **6** was obtained as the sole product by reaction with *t*-BuOCl in *t*-BuOH[3] in 85% isolated yield. Alternatively, reaction with sodium perborate in acetic acid[4] also proved acceptable and afforded sulfoxide **6** as the major product in 74% yield with only 2–3% sulfone.

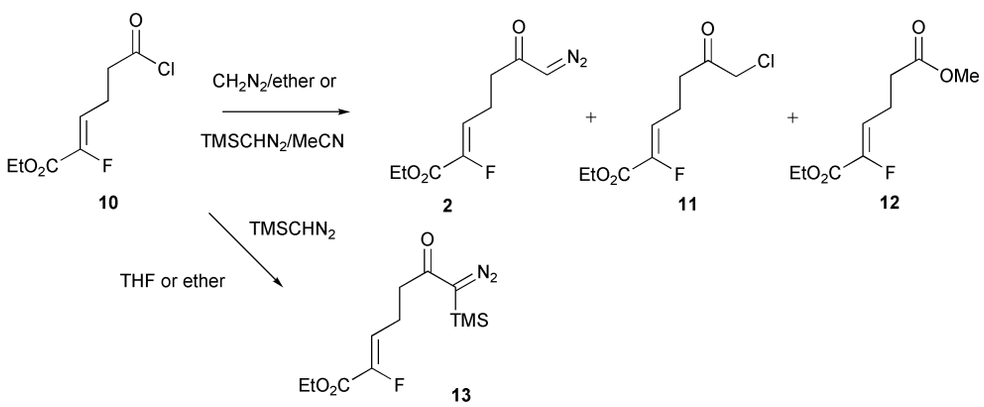
The preparation of acid **9** from sulfoxide **6** involved a series of transformations where acid **9** was the only isolated intermediate. By alkylation with bromide **7**, the acid functionality was installed at the correct oxidation state where the two esters were orthogonally protected and could easily be differentiated from one another. Deprotonation of sulfoxide **6** was achieved using sodium hydride in *N*,*N*-dimethylacetamide (DMAc) followed by treatment with bromide **7**.[5] Aging the reaction mixture at 100 °C (1 h) to effect the thermal *syn*-elimination of the sulfoxide gave crude *t*-butyl ester **8**. The *E* : *Z* double bond ratio of **8** was observed to be greater than 95 : 5 (*E* : *Z*) by ^{1}H NMR analysis of the crude material. Deprotection of **8** with TFA gave the pivotal acid intermediate **9** in 74% overall yield for the three steps.

Preparation of acid chloride **10** was effected with oxalyl chloride in 1,2-dichloroethane at room temperature. Treatment of **10** with diazomethane gave the diazoketone **2** in 78% yield (Scheme 3). Two major impurities formed during the reaction of **10** with diazomethane were identified as α-chloroketone **11** (7%) and methyl ester **12** (< 2%). These impurities were independently synthesized in order to unambiguously establish their presence in the crude sample of diazoketone **2**. Chloride **11** was prepared by treating diazoketone **2** with a solution of HCl in ether, while the methyl ester **12** was formed by reaction of the acid **9** with diazomethane. The use of commercially available trimethylsilyldiazomethane ($TMSCHN_2$), was explored as a safer alternative to diazomethane. Reaction

DOI: 10.1039/b312180c



Scheme 2 Preparation of the acid intermediate **9**.



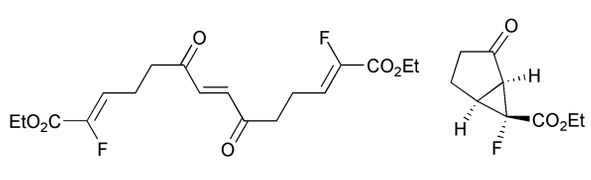
Scheme 3 Preparation of diazoketone **2**.

of acid chloride **10** with $TMSCHN_2$ in either THF or diethyl ether afforded the TMS-diazoketone **13** as the major product. None of the desired diazoketone **2** was detected in the crude reaction mixture when these solvents were utilized. However, when acetonitrile was employed as the reaction solvent,[6] smooth conversion to the diazoketone **2** (74%) was observed. The formation of impurities **11** (6%) and **12** (< 2%) was unavoidable when either diazomethane or $TMSCHN_2$ were used; however, their presence was not detrimental in the subsequent conversion of diazoketone **2** to ketoester **1** (although the presence of chloroketone **11** would later prove to be an impediment to chromatographic resolution).

Stereoselective cyclopropanation reactions of α-diazocarbonyl compounds are catalyzed by many transition metal complexes where complexes of copper and rhodium have emerged as the catalysts of choice.[7,8] A high degree of asymmetric induction has also been achieved in intramolecular cyclopropanations employing various chiral rhodium and copper catalysts.[9,10,11] While the conversion of **2** to **1** has been reported to proceed with catalyst **17**,[12] the major limitation was the formation of **1** as a racemic mixture in low yield.

The dirhodium catalysts introduced by Doyle and Pieters[13] are known to give cyclopropyl compounds with excellent enantioselectivity for intramolecular cyclopropanations of allylic diazoacetates and diazoacetamides. In our case, the use of Doyle's dirhodium catalysts **18** or **19** proved ineffective. The use of **18** resulted in both low yield and ee, and only decomposition for **19** (Table 1). This may be attributed to conformational control of the carbonyl alignment of the metal carbene intermediate.[14] Also, the relatively electron deficient diazoketone carbenes formed may react less selectively compared to those derived from diazoesters and amides, which can be stabilized through resonance interactions between the heteroatoms and the ketone.[14]

The use of chiral complexes of copper was also examined in parallel. When Pfaltz's semicorrin ligand **20** was used in conjunction with $Cu(OTf)_2$ (entry 4, Table 1), modest enantioselectivity was observed. However, the yield was only 56% with the major impurity identified as dimer **14** which was observed in up to 40%.

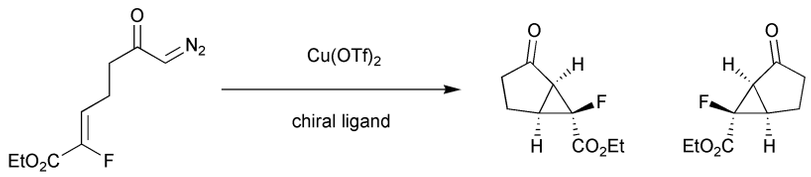


14 **15**

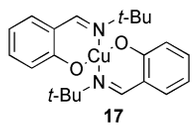
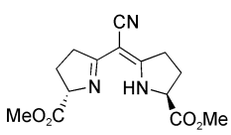
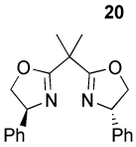
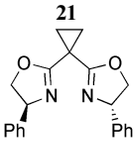
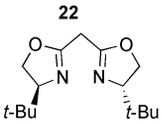
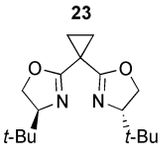
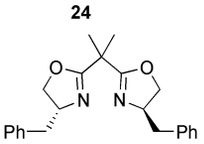
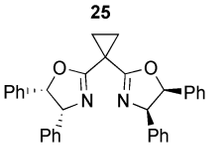
In contrast, the bisoxazoline ligands[15] were the most effective ligands (entries 5–8, 12), giving optimal yields and enantiomeric excess. For example, ligand **21** provided the best ee and yield giving **1** in up to 83% yield and 65% ee (entries 5–7). Other bisoxazoline ligands (entries 9–11) were observed to give **1** in good isolated yield, but with diminished enantioselectivity. The optimal ligand/catalyst loading was 1 mol% $Cu(OTf)_2$: 2 mol% ligand. Increasing the ligand loading did not improve the ee, although decreasing ligand load did decrease ee. In all cases examined, none of the corresponding *exo*-fluorocyclopropane **15** was observed.

Concurrent with the catalyst screening for the asymmetric cyclopropanation, a chiral chromatographic resolution was also being investigated for the preparation of single enantiomers.

Table 1 Intramolecular cyclopropanation catalyst and ligand screen results



2 **1** **16**

Entry	Catalyst	Ligand	% yield **1**	% yield **16**	% ee
1	 **17**		13.5[a]	13.5[a]	0
2	1% Rh_2(5*S*-MEPY)$_4$ **18**		5.4	4.6	7.6
3	1% Rh_2(4*S*-MEOX)$_4$ **19**		0[b]		
4	$Cu(OTf)_2$	 **20**	17.4	38.6	38[c]
5	$Cu(NCCH_3)_4PF_6$	 **21**	65.2	17.8	57
6	5% CuCl/AgOTf	**21**	65.2	13.8	65
7	$Cu(OTf)_2$	**21**	64.4	15.6	61
8	$Cu(OTf)_2$	 **22**	65.6	16.4	60
9	$Cu(OTf)_2$	 **23**	45.0	34.0	14
10	$Cu(OTf)_2$	 **24**	52.7	32.3	24
11	$Cu(OTf)_2$	 **25**	39.0	30	13
12	$Cu(OTf)_2$	 **26**	19.5	65.5	54[c]

[a] Yield from acid **9**. [b] No reaction, decomposition. [c] Denotes the undesired enantiomer **16** in excess.

Standard chiral SFC and HPLC screening of common commercially available chiral stationary phases led to the selection of Chiralpak AD as the stationary phase affording the best separation of the enantiomers of **1**. We initially resolved 26 g of **1** by HPLC on a 5 cm i.d. column using methanol as the eluent, with an overall productivity of about 0.5 kkd (kilograms of purified enantiomer per kilogram of stationary phase per day). Problems with trans-esterification to the methyl ester during solvent removal led to the identification of 15% IPA/heptane as the eluent of choice. Loading studies carried out with enantioenriched **1** (210 mg mL^{-1} in eluent; 60% ee) using a 4.6 × 250 mm column packed with 20 micron preparative Chiralpak AD material afforded a very respectable productivity of 1.2 kkd suggesting a relatively straightforward preparative HPLC resolution at larger scale (Fig. 1).

Despite the indications of facile resolution given by the loading study, attempts at an actual scaled up resolution using crude **1** coming directly from the catalytic cyclopropanation step

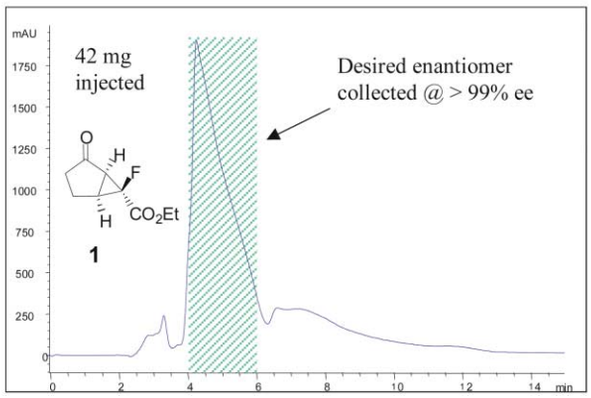


Fig. 1 Preparative injection on analytical HPLC column packed with preparative media allows estimation of productivity. Conditions: Chiralpak AD (4.6 × 250 mm) packed with 20 micron preparative material; 15% IPA in heptane, 1.2 mL min^{-1}; injection of 210 mg mL^{-1} solution of 1 in mobile phase (70% ee). Desired enantiomer collected with > 99% ee, > 90% recovery. Estimated productivity = 1.2 kkd.

proved problematic owing to the presence of a few percent of chloroketone **11**. This impurity eluted just following the peak of interest, and owing to a relatively strong UV absorbance, it obscured the valley region between the two enantiomers, making automated fraction collection problematic (this problem was not observed in the loading study, where material purified by silica chromatography was used as feed). While it is sometimes possible to carry out a preparative separation in the presence of an interfering impurity, for example by employing a chiroptical detector, in this instance we determined that because of potential incompatibility with downstream chemistry and the risk of repeated injection of a potentially reactive alkylating agent onto our HPLC column, the chloroketone impurity would have to be removed prior to preparative HPLC enantioseparation. We were reluctant to incorporate an additional chromatographic step, and therefore turned to the investigation of adsorbents and reactive resins for selective removal of the reactive chloroketone impurity.

When feasible, the use of adsorbents or reactive resins for selective nonchromatographic removal of process impurities offers an attractive option for purification. With the large number of available products, rapid selection of the most appropriate materials and conditions is essential for a timely solution to process impurity problems. We have recently described a microplate-based screening approach that affords expedited selection of adsorbents[16] or reactive resins[17] for use in process purifications, and have successfully applied this approach to the existing separation problem of removing chloroketone **11** from ketoester **1** as a pretreatment of the feed stream for HPLC purification. A survey of commonly used process adsorbents failed to identify a material that selectively adsorbed chloroketone **11** to a useful degree. Assessment of reactivity differences between product and impurity suggested that removal of the potentially reactive chloroketone impurity might be possible using a nucleophilic reactive resin, which would presumably have little effect on the ketoester product. We therefore screened a collection of different commercially available nucleophilic reactive resins, including PS-NH_2, PS thiophenol and PS TsNH-NH_2 (Argonaut Technologies), Piperazine 3, diol, amine, cyclohexyldiol, diamine 3, thiol and trisamine (SiliCycle) and Smopex PEG thiol (Johnson Matthey).

Screening was carried out in microplates containing 1 mL glass insert tubes containing ten to twenty milligrams of the appropriate resins. Addition of 700 µl of a 1 mg mL^{-1} solution of the crude feed mixture in 15% IPA/heptane was added, the tubes capped, then incubated overnight at 35 °C with shaking. Following plate centrifugation, analysis of the supernatant solutions and comparison with a control tube which received feed solution but no resin revealed the extent of depletion of both impurity and product. Three resins were identified that completely removed chloroketone from the feed solution while leaving product levels largely unchanged – Argonaut PS thiophenol, SiliCycle diamine 3 and SiliCycle trisamine. In a follow up comparison, SiliCycle diamine 3 (ethylenediaminopropyl silica) showed the greatest impurity reduction over the course of a three day reaction at room temperature. Subsequent investigations of the effect of temperature showed that stirring a 17.5 mg mL^{-1} solution of crude feed for two hours at 80 °C with 115 wt% of the resin afforded almost complete removal of the impurity with negligible product loss. (Fig. 2). Interestingly, a color change of the resin from white to purple was noted as the reaction proceeded.

Successful implementation of the resin pretreatment of the feed solution followed by preparative HPLC afforded product with excellent recovery, enantiopurity and chemical purity, providing an overall viable process for preparing enantiopure **1** in support of the discovery efforts. While the route is suitable for short term preparation, the need for a chromatographic upgrade of enantiopurity is clearly an impediment to larger scale implementation. Nevertheless, valuable information regarding the catalytic asymmetric cyclopropanation reaction suggests the potential for further optimization of this reaction, should a need for preparation of **1** on a larger scale arise.

Conclusion

In conclusion, an efficient synthesis of ethyl (1*S*,5*S*,6*S*)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate **1** was achieved. The key asymmetric transformation was effected through a copper-mediated intramolecular cyclopropanation, which installed the fluorocyclopropane in up to 65% ee, with excellent diastereocontrol. The development of a reactive resin pretreatment to remove a problematic chloroketone impurity allowed preparative HPLC upgrade of product enantiopurity to be performed.

Experimental

Ethyl 2-phenylsulfenyl-2-fluoroacetate[2] 5

To a solution of 78.3 g (1.15 mol) of NaOEt in 1 L of ethanol was added 110.2 g (1.0 mol) thiophenol. The mixture was stirred at rt for 10 min, and then 140.5 g (1.0 mol) of ethyl chlorofluoroacetate **3** was added dropwise. After stirring for 2 h, 2 L of 1 : 1 MTBE/hexane and 1 L of water were added to the reaction mixture, and the layers were separated. The organic layer was washed with water (2 × 750 mL), then dried over $MgSO_4$. The solvent was removed under reduced pressure to afford 192.7 g (90%) of sulfide **5** as a yellow liquid which was used in the next step without further purification.

Ethyl 2-phenylsulfinyl-2-fluoroacetate[2] 6

Method A. To 10.0 g (0.047 mol) of the sulfide **5** in 90 mL of *t*-BuOH was added dropwise 13.9 g (0.13 mol) of *tert*-butyl hypochlorite over 1 h, while maintaining the temperature below 34 °C. After 1.25 h, the reaction was concentrated under reduced pressure and purified over silica gel, eluting first with hexane and then with 20% EtOAc/hexane to give 9.13 g (85%) of sulfoxide **6** as an inseparable mixture of diastereomers as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (major diastereomer) 1.23 (t, 3H, J = 7.2 Hz), 4.21 (q, 2H, J = 7.2 Hz), 5.71 (d, 1H, J = 49.9 Hz), 7.60 (m, 3H), 7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.03, 62.9, 125.5 (d, J = 41.4 Hz), 129.3, 132.7, 138.0, 162.3 (d, J = 22.3 Hz); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (minor diastereomer) 1.25 (t, 3H, J = 7.2 Hz), 4.23 (q, 2H, J = 7.2 Hz), 5.51 (d, 1H, J = 48.1 Hz), 7.60 (m, 3H), 7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.03, 63.0, 125.2 (d, J = 40.8 Hz), 129.5, 132.6, 138.1 (d, J = 4.8 Hz), 162.5

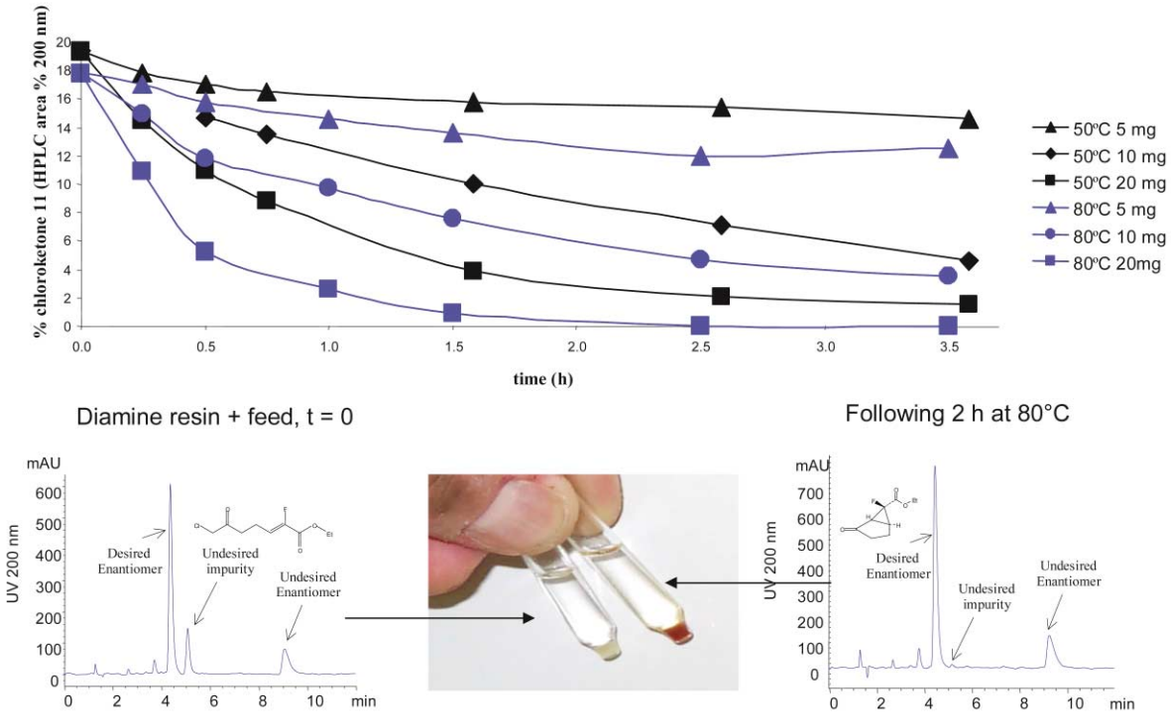


Fig. 2 Effect of resin load and reaction temperature on removal of chloroketone impurity **11** (top). Conditions: 1 mL of 17.5 mg mL^{-1} solution of crude **1** in 15% IPA/heptane treated with varying amounts of Diamine 3 resin (SiliCycle), shaken at 50 °C or 80 °C, then centrifuged, supernatant analyzed by chiral HPLC (Chiralpak AD (4.6 × 250mm) 15% IPA/heptane, 1.0 mL min^{-1}, UV 200 nm). Each data point corresponds to an individual microtube reaction. Treatment of feed solution for 2 h at 80 °C with 20 mg Diamine 3 resin affords effective removal of chloroketone **11**.

(d, J = 23.7 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (major diastereomer) −193.0; δ (minor diastereomer) −192.0.

Method B. To a 50 °C solution of 2.2 kg (10.3 mol) of sulfide **5** in 19 L of acetic acid was added 1.9 kg (12.3 mol) of sodium perborate over 2 h. The reaction was stirred for 1 h and quenched with 19 L of water. The pH was adjusted to 7 by the addition of 21 L of conc. ammonium hydroxide. The aqueous solution was extracted with MTBE (1 × 20 L, 1 × 10 L), and the combined organic layers were dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to yield 1.78 kg (74%) of the sulfoxide **6**.

Preparation of Ethyl (*Z*)-2-fluoro-5-carboxypent-2-enoate[1] 9

To a −5 °C slurry of 18.7 g (0.47 mol) of 60% NaH in 390 mL of dry *N*,*N*-dimethylacetamide (DMAc) was added dropwise a solution of 89.9 g (0.39 mol) of the sulfoxide **6** in 210 mL of DMAc over 45 min. The reaction was warmed to rt, stirred for 20 min, then cooled to 5 °C. To the mixture was added 95.8 g (0.43 mol) of *tert*-butyl-4-bromobutyrate[5] **7** over 10 min. After 1.5 h, the dark brown solution was heated to 100 °C for 1.25 h, cooled to rt, and quenched with 600 mL of sat. NH_4Cl. The mixture was diluted with 100 mL of water and 1 L of 1 : 1 EtOAc/hexane. The layers were separated, and the organic layer was concentrated under reduced pressure to provide crude ester **8** which was used in the next step without further purification.

To a solution of 96.0 g (0.39 mol) of the crude *t*-butyl ester **8** in 680 mL of 1,2-dichloroethane was added 178.1 g (1.56 mol) of TFA. The reaction was heated to reflux for 2 h, cooled to rt, and concentrated under reduced pressure. The pH was adjusted to 7–8 using solid $NaHCO_3$ and 1.1 L of sat. $NaHCO_3$. The resulting aqueous layer was washed with MTBE (1 × 300 mL). The aqueous layer was then acidified to pH 1 with 37 mL of conc. HCl and extracted with MTBE (1 × 1.5 L, 1 × 500 mL). The combined MTBE layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified over a plug of silica gel, eluting first with hexane, then with 30% EtOAc/hexane, which yielded 56.4 g (74%) of the product **9** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J = 7.1 Hz), 2.55 (m, 4H), 4.28 (q, 2H, J = 7.1 Hz), 6.11 (dt, 1H, J = 32.7 and 7.3 Hz), 7.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.5 (d, J = 3.3 Hz), 32.4, 61.8, 147.4 (d, J = 11.1 Hz), 148.7 (d, J = 258.5 Hz), 160.7 (d, J = 35.3 Hz), 178.0; ^{19}F NMR ($CDCl_3$, 376 Hz) δ −129.0.

Ethyl (*Z*)-2-fluoro-5-chlorocarbonylpent-2-enoate 10

To a solution of 5.00 g (26 mmol) of the acid **9** in 50 mL 1,2-dichloroethane was added 1 drop of DMF followed by 5.00 g (39.4 mmol) of oxalyl chloride. The reaction was stirred for 2 h at rt, and the solvent was removed under reduced pressure to afford the crude acid chloride **10** as a yellow oil which was sufficiently pure for the next step.

Ethyl (2*Z*)-7-diazo-2-fluoro-6-oxohept-2-enoate 2

Method A. A solution of 5.48 g (26 mmol) of the acid chloride **10** in 20 mL of ether was added dropwise over 10 min to a 0 °C solution of CH_2N_2 in ether, which was prepared by treatment of a solution of 13.5 g (0.13 mol) of *N*-nitroso-*N*-methylurea in 130 mL of ether with a solution of 36.8 g (0.66 mol) of KOH pellets in 130 mL of water. The mixture was stirred for 1 h at 0 °C, and concentrated under reduced pressure to give 4.42 g (78%) of diazoketone **2** as a yellow oil, which was used without further purification. The product can be purified over silica gel to give **2** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H, J = 7.1 Hz), 2.56 (m, 4H), 4.28 (q, 2H, J = 7.1 Hz), 5.27 (br s, 1H), 6.18 (dt, 1H, J = 32.7 and 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.05, 19.5, 38.6, 54.5, 61.6, 118.5 (d, J = 11 Hz), 148.4 (d, J = 255 Hz), 160.4 (d, J = 36 Hz), 192.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −129.5.

Method B. To a cooled solution of 1.9 mL (3.8 mmol) of $TMSCHN_2$ (2.0 M in hexanes) in 10 mL of acetonitrile at 0 °C was added 0.40 g (1.9 mmol) of the acid chloride **10** in 2 mL of acetonitrile. The mixture was stirred at rt for 1–2 h, and the solvent was removed under reduced pressure to give 0.38 g (74%) of diazoketone **2**.

Ethyl (2*Z*)-7-chloro-2-fluoro-6-oxohept-2-enoate 11

To a solution of 1.0 g (4.68 mmol) of the diazoketone **2** in 10 mL of ether is added 9.36 mL (9.36 mmol) of 1.0 M HCl in ether dropwise over 10 min. The reaction was stirred for 15 min and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel, eluting with 10% EtOAc/hexanes to yield 0.99 g (95%) of the chloride **11** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J = 7.1 Hz), 2.55 (dq, 2H, J = 2.0, 7.3 Hz), 2.81 (t, 2H, J = 7.0 Hz), 4.08 (s, 2H), 4.26 (q, 2H, J = 7.1 Hz), 6.11 (dt, 1H, J = 32.9 and 7.7 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.3 (d, J = 3.3), 37.9 (d, J = 2.2 Hz), 47.8, 61.7, 117.9 (d, J = 11.0 Hz), 148.6 (d, J = 257.8 Hz), 160.3 (d, J = 35.3 Hz), 201.2; ^{19}F NMR ($CDCl_3$, 376 Hz) δ −128.8.

Ethyl 6-methyl (2*Z*)-2-fluorohex-2-enedioate 12

A solution of 1.48 g (7.78 mmol) of the acid **9** in 10 mL of ether was added dropwise over 15 min to a 0 °C solution of CH_2N_2 in ether, which was prepared by treatment of a solution of 4.0 g (38.8 mmol) of *N*-nitroso-*N*-methylurea in 40 mL of ether with a solution of 10.9 g (19 mmol) of KOH pellets in 40 mL water. The mixture was stirred for 1 h at 0 °C, and the solvent was removed under reduced pressure to afford 1.53 g (96%) of the methyl ester **12** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J = 7.22 Hz), 2.47 (m, 2H), 2.55 (m, 2H), 3.70 (s, 3H), 4.27 (q, 2H, J = 7.22 Hz), 6.13 (dt, 1H, J = 7.6, 32.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 19.9 (d, J = 3.39 Hz), 32.7, 52.0, 61.4, 118.4 (d, J = 11.1 Hz), 148.8 (d, J = 258.3 Hz), 160.7 (d, J = 35.2 Hz), 172.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −129.2.

Ethyl (1*S*,5*S*,6*S*)-6-fluoro-2-oxobicycl[3.1.0]hexane-6-carboxylate 1

To a solution of 16.9 mg (0.047 mmol) of $Cu(OTf)_2$ in 39 mL of 1,2-dichloroethane was added 31.2 mg (0.09 mmol) of (*S*)-(−)-2,2′-isopropylidenebis(4-phenyl-4,5-dihydro-1,3-oxazole) **21** and the mixture was stirred for 1 h. The reaction was brought to reflux, and a solution of 500 mg (2.33 mmol) of **2** in 8 mL of 1,2-dichloroethane was added dropwise over 2 h. The reaction was cooled to room temperature, concentrated under reduced pressure, and filtered over a plug of silica to afford 0.34 g (80%) of **1** as a colorless oil: (+**1**) $[\alpha]_D$ +0.104 (*c* 0.0055, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J = 7.2 Hz), 2.22 (m, 3H), 2.43 (m, 1H), 2.59 (d, 1H, J = 6.4 Hz), 2.67 (dt, 1H, J = 6.2 and 2.1 Hz), 4.25 (q, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.6, 34.2 (d, J = 12 Hz), 35.6, 40.2 (d, J = 12 Hz), 62.5, 79.5 (d, J = 246 Hz), 167.1 (d, J = 25 Hz), 208.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −211.4.

(4*S*,4′*S*)-2,2′-Cyclopropane-1,1-diylbis(4-phenyl-4,5-dihydro-1,3-oxazole) 22

To a −65 °C solution of 1.0 g (3.26 mmol) of 2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazoline], 0.76 g (7.52 mmol) of TMEDA and 0.33 g (3.26 mmol) of diisopropylamine in 46 mL THF was added 2.6 mL (6.5 mmol) of 2.5M *n*-BuLi in hexanes. The solution was warmed to −25 °C for 20 min, then cooled to −65 °C and 0.64 g (3.42 mmol) of 1,2-dibromoethane was added dropwise. The mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with 25 mL of sat. NH_4Cl and diluted with 20 mL of MTBE. The layers were separated, and the organic layer was concentrated. The crude residue was purified by silica gel chromatography eluting with 70% EtOAc/hexanes to afford 0.42 g (39%) of **22** as a light brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (m, 4H), 4.17 (t, 2H, J = 8.12 Hz), 4.69 (dd, 2H, J = 8.38, 10.06 Hz), 5.22 (dd, 2H J = 7.63, 10.04 Hz), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 18.6, 69.6, 75.6, 126.8, 127.0, 127.7, 128.9, 128.9, 142.5, 167.1.

(4*R*,5*S*,4′*R*,5′*S*)-2,2′-cyclopropane-1,1-diylbis(4,5-diphenyl-4,5-dihydro-1,3-oxazole) 26

Following the general procedure described for the preparation of **22**, compound **26** was prepared from 2,2′-methylenebis-[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline to give **26** (23%) as a white solid, mp 163–165 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (m, 4H) 5.62 (d, 2H, J = 10.19 Hz), 5.98 (d, 2H, J = 10.24 Hz), 7.01 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 19.02, 73.97, 86.18, 126.67, 126.97,127.42, 127.67, 127.69, 127.94, 128.13, 136.45, 137.79, 167.18. Anal. Calcd for $C_{33}H_{28}N_2O_2.0.5H_2O$: C, 80.30; H, 5.92; N, 5.68. Found: C, 80.12; H, 5.66; N, 5.95%.

Chiral HPLC analysis

Chiral HPLC analysis for %ee determination was performed on an Agilent model 1100 HPLC instrument. Conditions: Chiralpak, AD-RH (Chiral Technologies, Inc., 5μm. 4.6 × 150 mm); 60% H_2O/40% MeCN; 0.8 mL min^{-1} flow rate, 15 min.; 20 °C; UV 200 nm.

Chiral screening and method optimization

Chiral SFC screening was carried out using Berger Instruments analytical supercritical fluid chromatographs fitted with six-position column selection valves and Agilent model 1100 diode array UV-Visible detectors. Chiral HPLC screening was carried out using an Agilent model 1100 HPLC instrument fitted with a well plate autosampler, a circular dichroism detector (Jasco, CD 1595) and a polarimetric detector (PDR Chiral, Advanced Laser Polarimeter). Loading studies were performed with an Agilent 1100 HPLC instrument fitted with a preparative autosampler and a well plate fraction collector.

Screening of adsorbents and reactive resins for selective removal of chloroketone impurity, 11, from ketoester 1

Screening of adsorbents[16] and reactive resins[17] for selective removal of chloroketone impurity, **11**, from ketoester, **1**, was carried out as previously described [16,17] with analysis of treated solutions using by HPLC (Chiralpak AD-H, 4.6 × 150 mm; 5%IPA/heptane @ 1.5 mL min^{-1}; UV @ 200 nm.

Preparative chiral HPLC resolution of 1

Preparative chromatography was performed on a system containing dual Varian SD-1 pumps (800 mL min^{-1}), Varian 215 injector pump 100 mL min^{-1}, Varian 320 variable wavelength UV/VIS detector, R&S Techologies/Varian LC ReSonator liquid handling module and control software, with a Prochrom/Novasep dynamic axial compression (DAC) column (5 cm i.d.) packed with Chiralpak AD (*ca*. 25 cm bed length). Initially, 26 g of **1** was resolved using an eluent of 100% methanol at a flow rate of 240 mL min^{-1} with detection at 220 nm using a typical injection of 10 mL of an 80 mg mL^{-1} solution of **1** in methanol to afford an overall productivity of about 0.5 kkd (kilograms of purified enantiomer per kilogram of stationary phase per day).

Further method optimization studies using a 4.6 × 250 mm column packed with 20 micron preparative Chiralpak AD material led to the selection of 15% 2-propanol (IPA) in heptane as the preferred eluent for preparative separation. Loading studies with enantioenriched **1** (210 mg mL^{-1} in eluent; 60% ee) afforded a productivity of 1.2 kkd.

References

1 A. Nakazato, T. Kumagai, K. Sakagami, R. Yoshikawa, Y. Suzuki, S. Chaki, H. Ito, T. Taguchi, S. Nakanishi and S. Okuyama, *J. Med. Chem.*, 2000, **43**, 4893.
2 T. Allmendinger, *Tetrahedron*, 1991, **47**, 4905.
3 L. Skattebol, B. Boulette and S. Soloman, *J. Org. Chem.*, 1967, **32**, 3111.
4 A. McKillop and J. A. Tarbin, *Tetrahedron Lett.*, 1983, **24**, 1505.

5 C. Morin and M. Vidal, *Tetrahedron*, 1992, **42**, 9277.
6 It has been observed that using acetonitrile as a solvent gives the diazoketone. N. L. Subasinghe, C. Illig, J. Hoffman, M. J. Rudolph, K. J. Wilson, R. Soll, T. Randle, D. Green, F. Lewandowski, M. Zhang, R. Bone, J. Spurlino, R. DesJarlais, I. Deckman, C. J. Molloy, C. Manthey, Z. Zhou, C. Sharp, D. Maguire, C. Crysler and B. Grasberger, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1379 (*Chem. Abstr.*, 2000, **133**, 177162).
7 For a review on asymmetric cyclopropanation using Rh-catalysts, see: (*a*) K. M. Lydon and M. A. McKervey, in *Comprehensive Asymmetric Catalysis II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, Germany, 1999; chapter 16.2, pp. 539–580; (*b*) For a review on asymmetric cyclopropanation using Cu-catalysts see: A. Pfaltz, in *Comprehensive Asymmetric Catalysis II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, Germany 1999, chapter 16.1, pp. 518–538; (*c*) For a review on asymmetric catalytic metal carbene transformation, see: M. P Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
8 For reviews on asymmetric synthesis using diazo compounds, see: (*a*) M. A. Calter, *Curr. Org. Chem.*, 1997, **1**, 37; (*b*) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; (*c*) J. Adams and D. Spero, *Tetrahedron*, 1991, **47**, 1765.
9 A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339.
10 D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **11**, 726.
11 I. Collado, C. Pedregal, A. Mazon, J. F. Espinosa, J. Blanco-Urgoiti, D. D. Schoepp, R. A. Wright, B. G. Johnson and A. E. Kingston, *J. Med. Chem.*, 2002, **45**, 3619.
12 R. G. Charles, *J. Org. Chem.*, 1957, **22**, 677; R. Pellicciari, M. Marinozzi, B. Natalini, G. Costantino, R. Luneia, G. Giorgi, F. Moroni and C. Thomsen, *J. Med. Chem.*, 1996, **39**, 2259.
13 M. P. Doyle and T. J. Pieters, *J. Am. Chem. Soc.*, 1991, **113**, 1423.
14 (*a*) M. Barberis, J. Perez-Prieto, S.-E. Stiriba and P. Lahuerta, *Org. Lett.*, 2001, **3**, 3317; (*b*) M. P. Doyle, M. Y. Eismont and Q. L. Zhou, *Russ. Chem. Bull.*, 1997, **46**, 955; (*c*) P. Muller and E. Maitrejean, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1807.
15 S. E. Denmark and C. M. Stiff, *J. Org. Chem.*, 2000, **65**, 5875.
16 C. J. Welch, M. Shaimi, M. Biba, J. R. Chilenski, R. H. Szumigala, U. Dolling, D. J. Mathre and P. J. Reider, *Sep. Sci.*, 2002, **25**, 847.
17 C. J. Welch, M. Biba, A. Drahus, D. A. Conlon, H. T. Hsien and P. J. Collins, *Liq. Chromatogr.*, 2003, **26**, 1949.