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New Route to 4-Aminocyclopent-2-en-1-ols: Synthesis and Enantioselective Rearrangement of 4-Amino-substituted Cyclopentene Oxides

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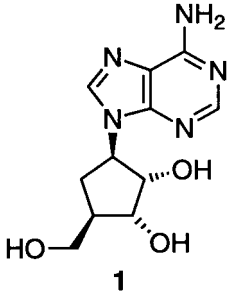
Abstract—A new route for the asymmetric synthesis of 4-aminocyclopent-2-en-1-ols (90% ee) for carbocyclic nucleoside analogue synthesis is described. The approach involves the stereoselective preparation of *cis* 4-amino-substituted cyclopentene oxides and subsequent chiral base-mediated rearrangement to the corresponding allylic alcohols. Full details on the synthesis and stereoselectivity of epoxidation of 4-amino-substituted cyclopentenes are presented.

Introduction

Carbocyclic nucleosides such as the naturally occurring aristeromycin **1** and neoplanacin A **2** exhibit potent anti-viral activity and these compounds as well as analogues such as **3** and **4** have attracted considerable synthetic interest in recent times.[1,2] Unfortunately, the anti-viral potential of aristeromycin **1** has been limited due to its toxicity.



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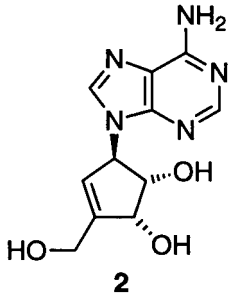

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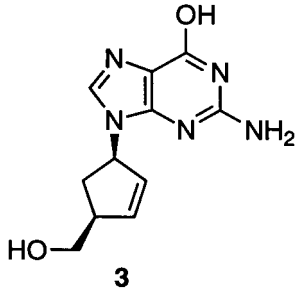

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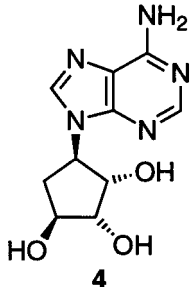

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Some time ago, Schneller and co-workers reported that 5′-noraristeromycin **4** possessed anti-viral activity but had reduced toxicity.[3] Because of the biological interest in carbocylic nucleoside analogues, we decided to develop a novel, general strategy for the asymmetric construction of the 4-aminocyclopent-2-en-1-ol core of these molecules.

Our approach to carbocyclic nucleoside analogues involved a novel synthesis of 4-aminocyclopent-2-en-1-ols **7** as outlined in Scheme 1. Trost[4] and Miller[5] have independently shown the synthetic usefulness of amino alcohols like **7** in the carbocyclic nucleoside arena and Zwanenburg et al.[2] have developed a cycloaddition route to such compounds. Our route to amino alcohols **7** makes use of the chiral base-mediated rearrangement of epoxides *cis*-**6** to allylic alcohols **7** as the key step. The stereoselective synthesis of epoxides **6** and the preparation of the alkenes **5** were also of significant interest as little was known about the preparation of these types of compounds when we started our endeavours in this area.[6]

Results and Discussion

Initially, we required access to a wide range of mono and diprotected amino cyclopentenes **5** and three approaches were used (Scheme 2; Table 1): (i) monoprotection of known[7–11] hydrochloride salt **9** to give alkenes **5a–d** and **5f–g**; (ii) Mitsunobu substitution of cyclopenten-3-ol **8** with an appropriately chosen amine derivative **10a–c** or phthalimide to give alkenes **5h–k** and (iii) deprotection of a diprotected alkene **5h** to give the monoprotected alkene **5e**. For the monoprotection route, full details of the preparation of amides **5a**[12] and **5b**[9] and carbamate **5f**[8] have been previously reported. In addition, the dibenzoylation of

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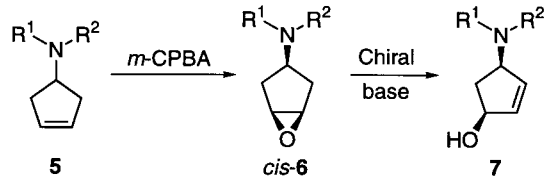
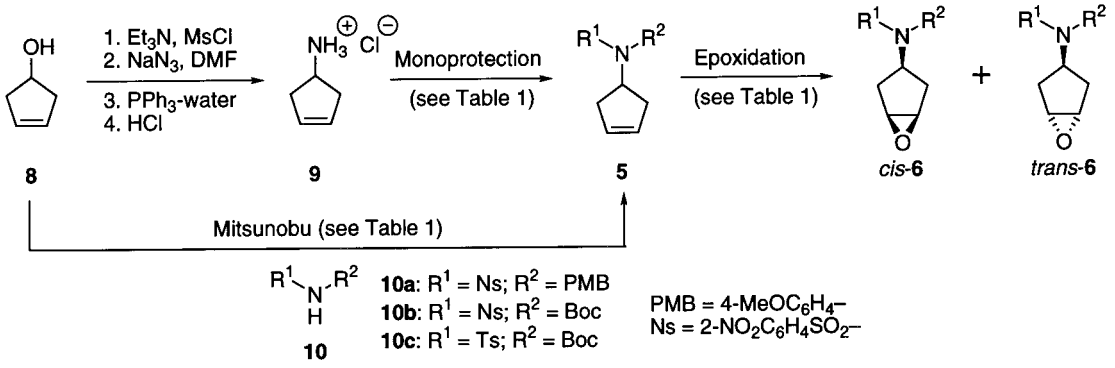


Scheme 1.

hydrochloride salt **9** has been described.[13] The Mitsunobu route is more novel with the only previously reported examples involving Mitsunobu reactions of cyclopenten-3-ol **8** with heterocyclic bases (e.g. 3-benzoylthymine).[14–16]

The synthesis of hydrochloride salt **9** has been reported a number of times before using three different approaches.[7–11] However, each route was either many steps or low yielding or both. Therefore, a new synthesis of salt **9** was developed. Our synthesis (Scheme 2) starts with easily prepared[17] cyclopenten-3-ol **8** which was mesylated and subsequently reacted with sodium azide in DMF (80°C, 16 h) to furnish the corresponding azido cyclopentene. Then, triphenylphosphine-mediated reduction in aqueous THF was used to generate the amine which was isolated as hydrochloride salt **9** in 65% yield over the three steps without purification of any of the intermediates. A range of amides, sulfonamides and carbamates (**5a–d** and **5f–g**) were prepared from salt **9** via standard *N*-monoprotection reactions (Scheme 2, Table 1, entries 1–4 and 6–7).

We have prepared diprotected alkenes **5h–k** by Mitsunobu reactions of cyclopenten-3-ol **8** (Scheme 2, Table 1, entries 8–11). Of the wide range of Mitsunobu reagents[18] available for the introduction of nitrogen,[19] we chose phthalimide (because of its commercial availability), Weinreb's TsNHBoc reagent **10c**[20] and Fukuyama's NsNHPMB reagent **10a**.[21] Weinreb's and Fukuyama's reagents were selected because their use in Mitsunobu reactions was well documented and they had relatively easily removable *N*-protecting groups. In addition, a novel Weinreb–Fukuyama hybrid reagent NsNHBoc **10b** was prepared in which the tosyl group is replaced by the more readily cleaved nosyl group. Sulfonamide **10a** was prepared in 89% yield by simple nosylation of 4-methoxybenzylamine and the product conveniently crystallised from methanol.[21] *N*-Boc protected sulfonamides **10b** (89% yield) and **10c** (93% yield) were prepared by reaction of the corresponding



Scheme 2.

Table 1. Synthesis and stereoselective epoxidation of 4-aminocylopentenes **5**

Entry	SM[a]	Conditions for alkene synthesis	R^1	R^2	Alkene	Yield (%)[b]	Epoxide	*m*-CPBA[c] *cis*:*trans*	TFDO[d] *cis*:*trans*
1	**9**	Et_3N, BzCl, DMAP, CH_2Cl_2	Bz	H	**5a**	83	**6a**	97:3	70:30
2	**9**	Et_3N, TFAA, pyridine, CH_2Cl_2	CF_3CO	H	**5b**	64	**6b**	98:2	38:62
3	**9**	Et_3N, MsCl, DMAP, CH_2Cl_2	Ms	H	**5c**	100	**6c**	98:2	–
4	**9**	Et_3N, TsCl, DMAP, CH_2Cl_2	Ts	H	**5d**	94	**6d**	84:16	40:60
5	**5h**	CAN, water, MeCN	Ns[e]	H	**5e**	74	**6e**	84:16	–
6	**9**	Et_3N, BnOCOCl, DMAP, CH_2Cl_2	Cbz	H	**5f**	78	**6f**	82:18	–
7	**9**	Et_3N, Boc_2O, DMAP, CH_2Cl_2	Boc	H	**5g**	77	**6g**	75:25	52:48
8	**8**	**10a**, PPh_3, DEAD, CH_2Cl_2	Ns	PMB	**5h**	52	**6h**	26:74	–
9	**8**	**10b**, PPh_3, DEAD, THF	Ns	Boc	**5i**	64	**6i**	2:98	2:98
10	**8**	**10c**, PPh_3, DEAD, THF	Ts	Boc	**5j**	76	**6j**	2:98	2:98
11	**8**	Phthalimide, PPh_3, DEAD, THF	Phthalimido		**5k**	71	**6k**	2:98	–

[a] Starting material for monoprotection or Mitsunobu reactions.
[b] Isolated yield of alkenes **5** after chromatography.
[c] Epoxidation conditions: *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 16 h, ratio of diastereoisomers determined by ^1H NMR spectroscopy on the crude product mixture.
[d] Trifluoroacetone, $Na_2EDTA_{(aq)}$, $NaHCO_3$, Oxone®, MeCN–water, 0°C, 4 h, ratio of diastereoisomers determined by ^1H NMR spectroscopy on the crude product mixture.
[e] Ns=2-$NO_2C_6H_4SO_2$–.

sulfonamide with Boc_2O according to a literature protocol.[22] With the sulfonamides **10a–c** in hand, the Mitsunobu reactions with cyclopenten-3-ol **8** proceeded smoothly in moderate to good yields (Scheme 2, Table 1, entries 8–11) and it was especially pleasing to note that the Weinreb–Fukuyama reagent **10b** performed well (64% yield of alkene **5h**, Table 1, entry 8).

There have been sporadic reports on the stereoselective epoxidation of 4-aminocyclopentenes **5**. For example, highly stereoselective amide-directed[23,24] epoxidation of alkenes **5a** and **5b** has been reported as a good method for preparing epoxides *cis*-**6a** and *cis*-**6b**.[9,12] Reduced *cis* selectivity has been observed with carbamate protecting groups (such as Boc and Cbz).[8,25] In a similar fashion, *cis*-selectivity has been observed when the nitrogen is part of a heterocyclic base.[15,16] In contrast, when the nitrogen possessed two benzamide groups, a completely *trans* selective epoxidation was observed presumably as a result of steric factors.[13]

Initially, the epoxidations of alkenes **5a–j** were carried out using standard *m*-CPBA conditions (*m*-CPBA, $NaHCO_3$, CH_2Cl_2, room temperature, 16 h) and the crude products were analysed by ^1H NMR spectroscopy to determine the degree of stereoselectivity (Scheme 2, Table 1). The major products of epoxidation of monoprotected alkenes **5a–g** (Table 1, entries 1–7) were assigned as having *cis* stereochemistry by analogy with the known epoxidations of **5a** and **5b**.[9,12] These assignments were consistent with a ^1H NMR spectroscopy correlation: δ_H(CHO) signal for *cis* monoprotected epoxides is more downfield than that for *trans* epoxides—examples: 3.57 ppm for *cis*-**5a**, 3.54 ppm for *trans*-**5a**; 3.49 ppm for *cis*-**5d**, 3.40 ppm for *trans*-**5d**; 3.53 ppm for *cis*-**5e**, 3.44 ppm for *trans*-**5e**; 3.47 ppm for *cis*-**5f**, 3.40 ppm for *trans*-**5f**; 3.58 ppm for *cis*-**5g**, 3.54 ppm for *trans*-**5g**.

In contrast, *m*-CPBA epoxidations of diprotected alkenes **5h–k** were *trans* selective (Table 1, entries 8–11). In these cases, the major products were assigned as *trans* epoxides by comparison with the known epoxidation of the dibenzamide **5** (R^1=R^2=Bz).[13] Additional support for all of the assignments of stereochemistry came from the following two reactions (with ^1H NMR spectra comparison): (i) *N*-diprotected epoxide *cis*-**6j** was the major product obtained by Boc protection of the 84:16 mixture of *N*-monoprotected epoxides *cis*- and *trans*-**6d** and (ii) *N*-monoprotected epoxide *trans*-**6e** was the major product obtained from the CAN-mediated deprotection of the 74:26 mixture of *N*-diprotected epoxides *trans*- and *cis*-**6h**.

Since there was literature precedent to suggest that directed epoxidation could occur with amides and carbamates,[9,12,23,24] the epoxidations were repeated with in situ generated methyl(trifluoromethyl)dioxirane,[26,27] a reagent that does not hydrogen bond (Table 1). Epoxidation of diprotected alkenes **5i** and **5j** are still completely *trans* selective even with methyl(trifluoromethyl)dioxirane (Table 1, entries 9 and 10) but there is a significant lowering of *cis* selectivity with a range of monoprotected alkenes (Table 1, entries 1, 2, 4 and 7). In all of the monoprotected alkene examples, synthetically useless mixtures of diastereomeric epoxides **6** are generated with methyl(trifluoromethyl)dioxirane.

The following conclusions may be drawn about the epoxidation results. With *m*-CPBA, monoprotected alkenes **5a–g** are epoxidised with *cis* selectivity and diprotected alkenes **5h–k** are epoxidised with *trans* selectivity. This is presumably a consequence of hydrogen bonded directed attack with monoprotected alkenes and steric control with diprotected alkenes in line with the literature precedent discussed previously. In terms of the hydrogen bonded directed epoxidation, amides (e.g. **5a** and **5b**) and sterically small sulfonamides (e.g. **5c**) give the highest levels of *cis* selectivity. Sterically large sulfonamides (e.g. **5d** and **5e**) and carbamates (e.g. **5f** and **5g**) are worse *cis* directors of epoxidations.

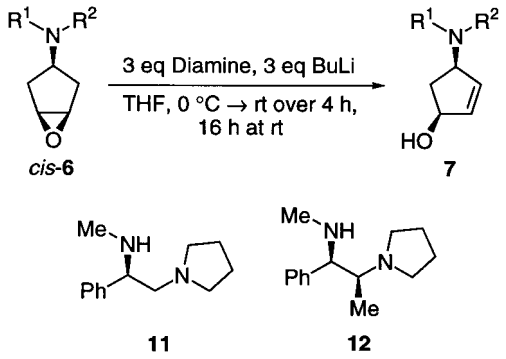
The *trans* selectivity of epoxidation with diprotected alkenes is highest when two large groups are attached (e.g. **5i–k**) and the *trans* selectivity observed with alkenes **5i** and **5j** is insensitive to changes in epoxidising reagent. However, the *cis* selectivity of monoprotected alkenes with *m*-CPBA is lost when methyl(trifluoromethyl)dioxirane is used due to interference with the hydrogen bonding. Only approximately 50:50 mixtures of *cis* and *trans* epoxides are produced from the methyl(trifluoromethyl)dioxirane-mediated epoxidation of monoprotected alkenes **5a**, **5b**, **5d** and **5g** reflecting the fact that one of the substituents on nitrogen is a sterically insignificant proton.

From a synthetic viewpoint, the easiest *cis* monoprotected epoxides to obtain as single diastereoisomers after purification by chromatography were epoxides *cis*-**6a** (79% isolated yield) and *cis*-**6b** (73% isolated yield). For the *trans* epoxides, we isolated diprotected epoxide *trans*-**6i** in 84% yield and epoxide *trans*-**6j** in 88% yield after chromatography.

The chiral base-mediated rearrangement of epoxides to allylic alcohols[28] was the first reaction to be rendered asymmetric using chiral lithium amide bases.[29] Since then, it has proved to be a versatile and useful reaction for asymmetric synthesis.[30] Indeed, Asami used the enantioselective rearrangement of a *meso* 4-substituted cyclopentene oxide as a pivotal step in an asymmetric synthesis of carbovir.[31] Also, Hodgson has used a similar process for the production of cyclopentenol building blocks for carbocyclic nucleoside analogue synthesis.[32] Most of the previous work in our group has focused on the rearrangement of *meso* cyclohexene oxides.[33]

Reaction of *N*-diprotected epoxides *trans*-**6i** and **6j** with two equivalents of the chiral base derived from Singh's diamine **11**[34] (our usual conditions[33]) failed to generate any allylic alcohol. In the case of epoxide *trans*-**6i**, a 65% yield of the starting epoxide was recovered after chromatography.

Next, the enantioselective rearrangement of monoprotected epoxide *cis*-**6a** (Scheme 3, Table 2, entry 1) was attempted using three equivalents of the chiral base derived from Singh's diamine **11** due to the presence of the acidic NH proton on the amide. Allylic alcohol **7a** was generated in 73% yield and had 60% ee (as shown by chiral HPLC). The



Scheme 3.

Table 2. Enantioselective rearrangements of 4-aminocyclopentene oxides

Entry	Epoxide	R^1	R^2	Diamine	Alcohol	Yield (%)[a]	ee (%)[b]
1	**6a**	Bz	H	**11**	**7a**	73	60
2	**6a**	Bz	H	**12**	**7a**	51	92
3	**6b**	CF_3CO	H	**11**	**7b**	52	46
4	**6b**	CF_3CO	H	**12**	**7b**	73	88

[a] Isolated yield after chromatography.
[b] Enantiomeric excess determined by chiral HPLC and/or by formation of Mosher's esters.

absolute stereochemistry was established by formation of the Mosher's esters[35] and analysis of the ^{1}H NMR spectrum of the diastereomeric mixture (Kakisawa's method[36]). The sense of induction was consistent with our expectations for diamine **11**.[33,34]

The scope of the reaction was investigated by rearranging epoxides *cis*-**6a** and *cis*-**6b** with the chiral base derived from Singh's diamine **11** and from diamine **12** developed in our laboratory (Scheme 3, Table 2).[33] With each epoxide, we found that the highest enantioselectivity was obtained with our improved diamine **12** (Table 2, entries 2 and 4) and this enabled synthetically useful 4-aminocyclopent-2-en-1-ols **7a** and **7b** to be prepared in high enantiomeric excess (approx. 90% ee). Our results suggest that the presence of a deprotonated amide *cis* to the epoxide is crucial for facilitating such rearrangement reactions. Similarly high enantioselectivity has been obtained by Asami but those reactions require the preparation of a structurally complex diamine.[25]

Conclusion

In summary, we have described a novel route for the preparation of 4-aminocyclopent-2-en-1-ol **7a** (92% ee), a key building block for carbocyclic nucleoside analogue synthesis. Along the way, we have developed a new synthesis of hydrochloride salt **9** and some new methods for the synthesis of diastereomerically pure 4-amino-substituted cyclopentene oxides **6**. In addition, we have highlighted the importance of a deprotonated amide *cis* to the epoxide in chiral base-mediated rearrangement reactions of such epoxides.

Experimental

General methods

Water is distilled water. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. *n*-Butyllithium was titrated against diphenylacetic acid before use. *m*-CPBA (approx. 70% pure) was used as supplied by Aldrich Chemical Company Ltd. Petrol refers to the fraction of petroleum ether boiling in the range 40–60°C and was redistilled in Winchester quantities before use. Proton (270 MHz) and carbon (67.9 MHz) NMR spectra were recorded on a Jeol EX-270 spectrometer using an internal deuterium lock.

4-Aminocyclopentene Hydrochloride 9. Et_3N (8.0 mL, 57.3 mmol) and MsCl (3.6 mL, 45.8 mmol) were added dropwise to a stirred solution of cyclopenten-3-ol **8** (3.2 g, 38.2 mmol) in CH_2Cl_2 (80 mL) at 0°C under N_2. After 30 min, water (80 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×80 mL) and the combined organic extracts were washed with 2 M $HCl_{(aq)}$ (2×80 mL) and then water (80 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. The crude product was dissolved in DMF (150 mL) and NaN_3 (4.5 g, 68.7 mmol) was added. The mixture was heated at 80°C for 16 h and after cooling, Et_2O (300 mL) was added and the mixture was washed with brine (5×100 mL). The solvent was evaporated by atmospheric distillation through a Vigreux column. The residue was dissolved in THF (140 mL), PPh_3 (14.4 g, 55.0 mmol) was added and the solution was stirred at rt for 1.5 h. Water (8.0 mL) was added and the mixture was heated at reflux for 16 h. After cooling, CH_2Cl_2 (40 mL) and 1 M $HCl_{(aq)}$ (80 mL) were added and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3×40 mL) and evaporated under reduced pressure to give the crude product. Trituration with EtOH and repeated evaporation gave known[9] hydrochloride salt **9** (3.6 g, 65%) as light brown crystals, mp 217–218°C (lit.[9] 219–221°C).

4-Benzamidocyclopentene 5a. Benzoyl chloride (0.98 mL, 12.6 mmol) was added dropwise to a stirred solution of hydrochloride salt **9** (502 mg, 4.2 mmol), Et_3N (1.7 mL, 12.6 mmol) and DMAP (52 mg, 0.43 mmol) in CH_2Cl_2 (20 mL) at 0°C under N_2. After 16 h at rt, the solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (50 mL). The organic layer was washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by chromatography (25:1 $CHCl_3$–MeOH) gave known[12] alkene **5a** (652 mg, 83%) as white crystals, mp 119–121°C (lit.[12] 126°C).

4-Trifluoroacetamidocyclopentene 5b. A solution of trifluoroacetic anhydride (0.52 mL, 3.86 mmol) in CH_2Cl_2 (3.5 mL) was added dropwise to a stirred solution of hydrochloride salt **9** (400 mg, 3.54 mmol) and Et_3N (0.54 mL, 3.84 mmol) in pyridine (4.8 mL) at 0°C under N_2. After 4.5 h, CH_2Cl_2 (15 mL) was added and the organic layer was washed with 1 M $HCl_{(aq)}$ (4×15 mL), dried (Na_2SO_4)

and evaporated under reduced pressure to give known[9] alkene **5b** (389 mg, 64%) as light brown crystals, mp 60–61°C (lit.[9] 62°C).

4-Methanesulfonamidocyclopentene 5c. MsCl (0.04 mL, 0.44 mmol) was added dropwise to a stirred solution of hydrochloride salt **9** (50 mg, 0.42 mmol), Et_3N (0.18 mL, 1.26 mmol) and DMAP (6 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at 0°C under N_2. After 16 h at rt, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (25:1 $CHCl_3$–MeOH) to give alkene **5c** (67 mg, 100%) as white crystals, mp 55–57°C; R_f (25:1 $CHCl_3$–MeOH) 0.6; IR ($CDCl_3$) 3381, 1333, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.69 (s, 2H), 4.67 (d, 1H, J=8 Hz), 4.15 (tq, 1H, J=4, 8 Hz), 2.98 (s, 3H), 2.77 (dd, 2H, J=8, 15 Hz), 2.33 (dd, 2H, J=4, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 128.5, 53.2, 41.2, 40.5; MS (CI, NH_3) m/z 179 $(M+NH_4)^+$, 82; HRMS (CI, NH_3) m/z calcd for $C_6H_{10}NO_2S$ $(M+NH_4)^+$ 179.0854, found 179.0855.

4-*tert*-Butoxycarbonamidocyclopentene 5g. Using the procedure described above, Boc_2O (42 mg, 0.19 mmol), hydrochloride salt **9** (20 mg, 0.17 mmol), Et_3N (0.07 mL, 0.50 mmol) and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) gave the crude product which was purified by chromatography (25:1 $CHCl_3$–MeOH) to give known[8] alkene **5g** (24 mg, 77%) as white crystals, mp 71–73°C (lit.[8] 70–72°C).

4-(4-Methylbenzenesulfonamido)cyclopentene 5d. TsCl (287 mg, 1.51 mmol) was added in one portion to a stirred solution of hydrochloride salt **9** (150 mg, 1.26 mmol), Et_3N (0.53 mL, 3.77 mmol) and DMAP (15 mg, 0.13 mmol) in CH_2Cl_2 (8 mL) at rt under N_2. After 16 h at rt, water (20 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were washed with water (2×20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by chromatography (EtOAc) gave alkene **5d** (278 mg, 94%) as white crystals, mp 79–81°C; R_f (EtOAc) 0.7; IR ($CDCl_3$) 1340, 1159 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.77 (d, 2H, J=8 Hz), 7.32 (d, 2H, J=8 Hz), 5.61 (s, 2H), 4.73 (d, 1H, J=8 Hz), 3.96–3.89 (m, 1H), 2.54 (dd, 2H, J=8, 15 Hz), 2.44 (s, 3H), 2.12 (dd, 2H, J=5, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 143.2, 137.4, 129.4, 128.2, 126.5, 52.8, 40.0, 21.2; MS (EI) m/z 237 M^+, 172, 155, 91, 82; HRMS (EI) m/z calcd for $C_{12}H_{15}NO_2S$ M^+ 237.0824, found 237.0821.

4-Benzyloxycarbonamidocyclopentene 5f. Using the procedure described above, benzyl chloroformate (0.07 mL, 0.47 mmol), hydrochloride salt **9** (51 mg, 0.42 mmol), Et_3N (0.13 mL, 0.93 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) gave the crude product which was purified by chromatography (4:1 hexane–EtOAc) to give alkene **5f** (72 mg, 78%) as white crystals, mp 56–58°C; R_f (4:1 hexane–EtOAc) 0.3; IR ($CDCl_3$) 1712 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–7.27 (m, 5H), 5.69 (s, 2H), 5.09 (s, 2H), 4.90 (br s, 1H), 4.41–4.30 (m, 1H), 2.74 (dd, 2H, J=7, 15 Hz), 2.20 (dd, 2H, J=4, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 155.9, 136.4, 128.7, 128.5, 128.0, 66.5, 50.5, 40.3; MS (EI) m/z 217 M^+, 156, 126, 91; HRMS (EI) m/z calcd for $C_{13}H_{15}NO_2$ M^+ 217.1103, found 217.1103.

***N*-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide 10a.** 4-Methoxybenzylamine (2.5 mL, 19.0 mmol) was added dropwise to a stirred solution of 2-nitrobenzenesulfonyl chloride (4.63 g, 21.0 mmol) and Et_3N (2.9 mL, 21.0 mmol) in CH_2Cl_2 (100 mL) at rt under N_2. After 24 h at rt, water (50 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Trituration of the residue with MeOH gave sulfonamide **10a** (5.44 g, 89%) as needles, mp 117–119°C; R_f (1:1 EtOAc–petrol) 0.6; IR (Nujol) 3307, 1367, 1334, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.01 (dd, 1H, J=2, 8 Hz), 7.83 (dd, 1H, J=2, 8 Hz), 7.72–7.62 (m, 2H), 7.13 (d, 2H, J=9 Hz), 6.75 (d, 2H, J=9 Hz), 5.60 (br s, 1H), 4.24 (br s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4, 147.8, 133.7, 133.3, 132.7, 131.1, 129.3, 127.4, 125.2, 114.0, 55.3, 47.4.

***N*-(*tert*-Butoxycarbonyl)-2-nitrobenzenesulfonamide 10b.** Boc_2O (1.78 g, 8.16 mmol) was added in one portion to a stirred solution of 2-nitrobenzenesulfonamide (1.49 g, 7.42 mmol), Et_3N (1.14 mL, 8.16 mmol) and DMAP (92 mg, 0.75 mmol) in CH_2Cl_2 (15 mL) at rt under N_2. After 2 h at rt, the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by recrystallisation from EtOAc–petrol gave sulfonamide **10b** (1.72 g, 77%) as white crystals, mp 194–196°C; IR ($CHCl_3$) 3382, 1751, 1545, 1415, 1363, 1148 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.37–8.34 (m, 1H), 7.87–7.78 (m, 3H), 7.41 (s, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 149.4, 147.5, 135.0, 132.5, 132.3, 131.2, 124.4, 85.5, 27.4; MS (CI, NH_3) m/z 320 $M+NH_4^+$; HRMS (CI, NH_3) m/z calcd for $C_{11}H_{14}N_2O_6S$ $M+NH_4^+$ 320.0916, found 320.0911; Anal. calcd for $C_{11}H_{14}N_2O_6S$: C, 43.7; H, 4.7; N, 9.3. Found: C, 43.6; H, 4.4; N, 9.1.

***N*-(*tert*-Butoxycarbonyl)-4-methylbenzenesulfonamide 10c.** Using the procedure described above, Boc_2O (5.61 g, 25.70 mmol), *p*-toluenesulfonamide (4.00 g, 23.36 mmol), Et_3N (3.58 mL, 25.70 mmol) and DMAP (285 mg, 2.34 mmol) in CH_2Cl_2 (30 mL) gave the crude product which was purified by recrystallisation from Et_2O–petrol to give known[20] sulfonamide **10c** (5.90 g, 93%) as white crystals, mp 117–119°C (lit.[20] 117–119°C); IR ($CHCl_3$) 3389, 1746, 1348, 1148 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (d, 2H J=8 Hz), 7.35 (d, 2H, J=8 Hz), 2.45 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 149.2, 144.7, 135.9, 129.4, 128.2, 84.0, 27.8, 21.6; MS (CI, NH_3) m/z 289 $M+NH_4^+$; HRMS (CI, NH_3) m/z calcd for $C_{12}H_{17}NO_4S$ $M+NH_4^+$ 289.1222, found 289.1224.

***N*-(*tert*-Butoxycarbonyl)-4-(2-nitrobenzenesulfonamido)-cyclopentene 5i.** Cyclopenten-3-ol **8** (100 mg, 1.19 mmol) was added in one portion to a stirred solution of PPh_3 (936 mg, 3.57 mmol) and sulfonamide **10b** (539 mg, 1.78 mmol) in THF (18 mL) at rt under N_2. Then, DEAD (0.47 mL, 2.97 mmol) was added and the solution stirred at rt for 48 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography (20:1 CH_2Cl_2–petrol) to give alkene **5i** (279 mg, 64%) as

white crystals, mp 100–103°C; R_f (20:1 CH_2Cl_2–petrol) 0.4; IR ($CHCl_3$) 1731, 1545, 1367, 1151 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.36–8.31 (m, 1H), 7.81–7.71 (m, 3H), 5.69 (s, 2H), 5.17–5.05 (m, 1H), 2.89 (dd, 2H, J=10, 15 Hz), 2.65 (dd, 2H, J=2, 15 Hz), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.3, 146.0, 134.1, 133.9, 133.2, 131.9, 128.7, 124.3, 85.0, 56.0, 37.9, 27.9; MS (CI, NH_3) m/z 386 $M+NH_4^+$, 286; HRMS (CI, NH_3) m/z calcd for $C_{16}H_{20}N_2O_6S$ $M+NH_4^+$ 386.1386, found 386.1391; Anal. calcd for $C_{16}H_{20}N_2O_6S$: C, 52.2; H, 5.5; N, 7.6. Found: C, 52.1; H, 5.5; N, 7.5.

***N*-(*tert*-Butoxycarbonyl)-4-(4-methylbenzenesulfonamido)cyclopentene 5j.** Using the procedure described above, cyclopenten-3-ol **8** (100 mg, 1.19 mmol), PPh_3 (936 mg, 3.57 mmol), sulfonamide **10c** (480 mg, 1.78 mmol) and DEAD (0.47 mL, 2.97 mmol) in THF (18 mL) gave the crude product which was purified by chromatography (20:1 CH_2Cl_2–petrol) to give alkene **5j** (305 mg, 76%) as white crystals, mp 95–98°C; R_f (20:1 CH_2Cl_2–petrol) 0.4; IR ($CHCl_3$) 1724, 1354, 1154 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.79–7.75 (m, 2H), 7.32–7.29 (m, 2H), 5.68 (s, 2H), 5.28 (quin, 1H, J=9 Hz), 2.73 (d, 4H, J=9 Hz), 2.44 (s, 3H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.5, 143.9, 137.7, 129.3, 128.8, 127.5, 84.2, 55.6, 37.7, 27.9, 21.6; MS (CI, NH_3) m/z 355 $M+NH_4^+$, 299; HRMS (CI, NH_3) m/z calcd for $C_{17}H_{23}NO_4S$ $M+NH_4^+$ 355.1692, found 355.1695; Anal. calcd for $C_{17}H_{23}NO_4S$: C, 60.5; H, 6.9; N, 4.2. Found: C, 60.2; H, 7.2; N, 4.0.

***N*-(4-Methoxybenzyl)-4-(2-nitrobenzenesulfonamido)cyclopentene 5h.** Using the procedure described above, cyclopenten-3-ol **8** (680 mg, 8.1 mmol), PPh_3 (2.1 g, 8.1 mmol), sulfonamide **10a** (2.0 g, 6.2 mmol) and DEAD (1.27 mL, 8.1 mmol) in CH_2Cl_2 (50 mL) gave the crude product which was purified by chromatography (20:1 CH_2Cl_2–petrol) to give alkene **5h** (1.25 g, 52%) as a thick yellow oil, R_f (CH_2Cl_2) 0.5; IR (Nujol) 1544, 1372, 1346, 1162 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80–7.46 (m, 4H), 7.21 (d, 2H, J=9 Hz), 6.73 (d, 2H, J=9 Hz), 5.62 (br s, 1H), 4.81 (tt, 1H, J=5, 9 Hz), 4.39 (s, 2H), 3.76 (s, 3H), 2.57 (dd, 2H, J=9, 16 Hz), 2.28 (dd, 2H, J=5, 16 Hz); ^{13}C NMR ($CDCl_3$): δ 158.9, 147.7, 134.4, 133.1, 131.4, 131.2, 129.3, 129.2, 129.1, 124.0, 113.6, 57.1, 55.3, 47.4, 37.0.

4-Phthalimidocyclopentene 5k. Using the procedure described above, cyclopenten-3-ol **8** (50 mg, 0.59 mmol), PPh_3 (203 mg, 0.77 mmol), phthalimide (113 mg, 0.77 mmol) and DEAD (0.12 mL, 0.77 mmol) in THF (5 mL) gave the crude product which was purified by chromatography (2:1 Et_2O–petrol) to give alkene **5k** (90 mg, 71%) as white crystals, mp 128–134°C; R_f (2:1 Et_2O–petrol) 0.2; IR ($CHCl_3$) 1709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85–7.68 (m, 4H), 5.08 (s, 2H), 5.01 (tt, 1H, J=8, 10 Hz), 2.86 (dd, 2H, J=8, 15 Hz), 2.68 (dd, 2H, J=10, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 168.3, 133.8, 132.1, 129.0, 123.1, 48.5, 36.5; MS (CI, NH_3) m/z 231 $M+NH_4^+$, 214; HRMS (CI, NH_3) m/z calcd for $C_{13}H_{11}NO_2$ $M+NH_4^+$ 214.0868, found 214.0868.

4-(2-Nitrobenzenesulfonamido)cyclopentene 5e. A solution of CAN (840 mg, 1.53 mmol) in water (3.3 mL) was added dropwise to a stirred solution of alkene **5h** (200 mg, 0.51 mmol) in MeCN (13 mL) at 0°C. After 3 h at rt, water (25 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3×25 mL) and the combined organic extracts were washed with 20% $Na_2SO_{3(aq)}$ (25 mL) and water (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Trituration of the residue with 1:1 EtOAc–petrol gave alkene **5e** (100 mg, 74%) as a pale yellow solid, R_f (1:1 EtOAc–petrol) 0.6; IR (Nujol) 3327, 1542, 1372, 1344, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.19–8.12 (m, 1H), 7.88–7.71 (m, 3H), 5.64 (br s, 2H), 5.50 (d, 1H, J=8 Hz), 4.15–4.05 (m, 1H), 2.58 (dd, 2H, J=8, 15 Hz), 2.12 (dd, 2H, J=5, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 147.8, 134.4, 133.6, 132.9, 130.8, 128.4, 125.3, 53.9, 39.9; MS (CI, NH_3) m/z 286 $M+NH_4^+$, 82.

General procedure for *m*-CPBA epoxidation

Solid $NaHCO_3$ (3.8 mmol) and *m*-CPBA (approx. 70% pure material, 2.9 mmol) were added in portions to a stirred solution of the alkene **5** (2.1 mmol) in CH_2Cl_2 (20 mL) at rt under N_2. After 16 h at rt, 20% Na_2SO_3 (30 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were washed with 20% $Na_2SO_{3(aq)}$ (30 mL), 5% $NaHCO_{3(aq)}$ (30 mL), water (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ^1H NMR spectroscopy revealed the ratio of diastereoisomers (see Table 1) and where the major epoxide was required for further reaction, the crude product was purified by chromatography.

***N*-(*tert*-Butoxycarbonyl)-4-(2-nitrobenzenesulfonamido)-cyclopentene oxide *trans*-6i.** Using the general procedure for *m*-CPBA epoxidation, $NaHCO_3$ (320 mg, 3.8 mmol), *m*-CPBA (492 mg, 2.9 mmol) and alkene **5i** (700 mg, 2.1 mmol) in CH_2Cl_2 (20 mL) gave a crude product which contained a 98:2 mixture of epoxides *trans*- and *cis*-**6i**. Purification by chromatography (9:1 CH_2Cl_2–petrol) gave epoxide *trans*-**6i** (617 mg, 84%) as white crystals, mp 119–123°C; R_f (9:1 CH_2Cl_2–petrol) 0.2; IR ($CDCl_3$) 1735, 1545, 1367, 1152 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20–8.16 (m, 1H), 7.71–7.63 (m, 3H), 4.63–4.50 (m, 1H), 3.51 (s, 2H), 2.43 (dd, 2H, J=8, 16 Hz), 2.20 (dd, 2H, J=8, 16 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.0, 147.4, 134.0, 133.8, 132.5, 131.9, 124.3, 85.5, 56.4, 54.4, 31.4, 27.8; MS (CI, NH_3) m/z 402 $M+NH_4^+$, 346; HRMS (CI, NH_3) m/z calcd for $C_{16}H_{20}N_2O_7S$ $M+H^+$ 385.1069, found 385.1070; Anal. calcd for $C_{16}H_{20}N_2O_7S$: C, 50.0; H, 5.2; N, 7.3. Found: C, 50.1; H, 5.2; N, 7.2.

4-(4-Methylbenzenesulfonamido)cyclopentene oxide *trans*- and *cis*-6d. Using the general procedure for *m*-CPBA epoxidation, $NaHCO_3$ (71 mg, 0.84 mmol), *m*-CPBA (109 mg, 0.63 mmol) and alkene **5d** (100 mg, 0.42 mmol) in CH_2Cl_2 (2 mL) gave a crude product (98 mg, 92%) as a white solid which contained a 16:84 mixture of epoxides *trans*- and *cis*-**6d**. Diagnostic signals for epoxide *trans*-**6d**: ^1H NMR ($CDCl_3$): δ 4.56 (d, 1H, J=9 Hz), 3.45–3.38 (m, 1H), 3.39 (s, 2H), 2.31 (dd, 2H, J=8, 14 Hz), 1.37 (dd, 2H, J=8, 14 Hz); diagnostic signals for epoxide *cis*-**6d**: ^1H NMR ($CDCl_3$): δ 4.95 (d, 1H, J=9 Hz), 3.87–3.78 (m, 1H), 3.49 (s, 2H), 1.89–1.85 (m, 4H).

4-Benzamidocyclopentene oxide *cis*-6a. Using the general procedure for *m*-CPBA epoxidation, $NaHCO_3$ (619 mg, 7.3 mmol), *m*-CPBA (862 mg, 5.0 mmol) and alkene **5a** (620 mg, 3.3 mmol) in CH_2Cl_2 (20 mL) gave a crude product which contained a 97:3 mixture of epoxides *cis*- and *trans*-**6a**. Purification by chromatography (3:1 EtOAc–petrol) gave known[12] epoxide *cis*-**6a** (534 mg, 79%) as white crystals, mp 90–92°C (lit.[12] 84°C).

4-Trifluoroacetamidocyclopentene oxide *cis*-6b. *m*-CPBA (664 mg, 2.70 mmol) was added in one portion to a stirred solution of alkene **5b** (481 mg, 2.69 mmol) in CH_2Cl_2 (27 mL) at 0°C under N_2. After 30 min at 0°C, the mixture was stirred at rt for 1.5 h. Cyclopentene (0.1 mL) was added and after 15 min most of the solvent was evaporated under reduced pressure. The slurry was filtered, the precipitate washed with CH_2Cl_2 and the filtrate evaporated under reduced pressure. This process was repeated a further two times. Then, Et_3N (0.5 mL) was added to the filtrate and the solid removed by filtration. The solvent was evaporated under reduced pressure to give the crude product which was purified by chromatography (CH_2Cl_2) to give known[9] epoxide *cis*-**6b** (383 mg, 73%) as off-white crystals, mp 60–61°C (lit.[9] 62°C).

General procedure for methyl(trifluoromethyl)-dioxirane epoxidation

Chilled trifluoroacetone (0.2 mL) was added dropwise to a stirred solution of Na_2EDTA (1.0 mL of a 4×10^{-4} M aqueous solution) and alkene **5** (0.2 mmol) in MeCN (1.5 mL) at 0°C. Solid $NaHCO_3$ (1.6 mmol) and Oxone® (1.0 mmol) were crushed together and added in portions over 1–2 h at 0°C. After 2 h at 0°C, water (20 mL) and CH_2Cl_2 (20 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were washed with water (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the ratio of diastereoisomers (see Table 1).

(1*S*,2*R*)-4-Benzamidocyclopent-2-en-1-ol 7a. *n*-Butyllithium (1.22 mL of a 1.5 M solution in hexane, 1.77 mmol) was added dropwise to a stirred solution of diamine **12** (386 mg, 1.77 mmol) in THF (2 mL) at 0°C under N_2. After 30 min at 0°C, a solution of epoxide *cis*-**6a** (120 mg, 0.59 mmol) in THF (3 mL) was added dropwise via a cannula and the mixture was warmed to rt over 4 h. After 16 h at rt, saturated $NH_4Cl_{(aq)}$ (5 mL) was added followed by Et_2O (20 mL) and the two layers separated. The aqueous layer was extracted with Et_2O (2×20 mL) and the combined organic extracts were washed with 2% $HCl_{(aq)}$ (3×20 mL), saturated $NaHCO_{3(aq)}$ (3×20 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by chromatography (23:2 CH_2Cl_2–MeOH) gave allylic alcohol (1*S*,2*R*)-**7a** (62 mg, 51, 92% ee) as white crystals, mp 63–64°C; $[\alpha]_D$=+116 (*c* 1.1 in $CHCl_3$); R_f (23:2 CH_2Cl_2–MeOH) 0.3; IR ($CHCl_3$) 3441, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.71 (dd, 2H, *J*=2, 7 Hz), 7.47–7.29 (m, 3H), 5.99 (td, 1H, *J*=2, 5 Hz), 5.84 (dd, 1H, *J*=2, 5 Hz), 4.94–4.91 (m, 1H), 4.70–4.67 (m, 1H), 3.89 (br s, 1H), 3.40 (s, 1H), 2.70 (td, 1H, *J*=8, 15 Hz), 1.62 (dt, 1H, *J*=3, 15 Hz); ^{13}C NMR ($CDCl_3$): δ 167.2, 136.6, 134.2, 133.7, 131.5, 128.4, 126.9, 75.2, 54.0, 40.9; MS (EI) *m/z* 203 M^+, 105; HRMS (EI) *m/z* calcd for $C_{12}H_{13}NO_2$ M^+ 203.0346, found 203.0940; HPLC: Chiralcel OJ, 5% EtOH in heptane, 1.0 mL min^{-1}, 215 nm, 14.6 min [(1*S*,2*R*)-**7a**], 16.8 min [(1*R*,2*S*)-**7a**].

(1*S*,2*R*)-4-Trifluoroacetamidocyclopent-2-en-1-ol 7b. Using the procedure described above, *n*-butyllithium (1.54 mL of a 1.5 M solution in hexane, 2.3 mmol), diamine **12** (505 mg, 2.3 mmol) and epoxide *cis*-**6b** (150 mg, 0.77 mmol) in THF (5 mL) gave the crude product which was purified by chromatography (23:2 CH_2Cl_2–MeOH) to give allylic alcohol (1*S*,2*R*)-**7b** (110 mg, 73, 88% ee) as a pale yellow syrup, $[\alpha]_D$=+55 (*c* 2.8 in $CHCl_3$); R_f (23:2 CH_2Cl_2–MeOH) 0.3; IR ($CHCl_3$) 3604, 3426, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.12 (td, 1H, *J*=2, 6 Hz), 5.88 (ddd, 1H, *J*=1, 2, 6 Hz), 4.88–4.85 (m, 2H), 3.89 (br s, 1H), 2.79 (ddd, 1H, *J*=7, 8, 15 Hz), 2.64 (s, 1H), 1.65 (dt, 1H, *J*=3, 15 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.5 (q, *J*=37 Hz), 137.9, 132.4, 115.7 (q, *J*=288 Hz), 75.1, 54.1, 40.5; MS (CI, NH_3) *m/z* 213 M+NH_4^+, 178; HRMS (CI, NH_3) *m/z* calcd for $C_7H_8F_3NO_2$ M+NH_4^+ 213.0851, found 213.0850.

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