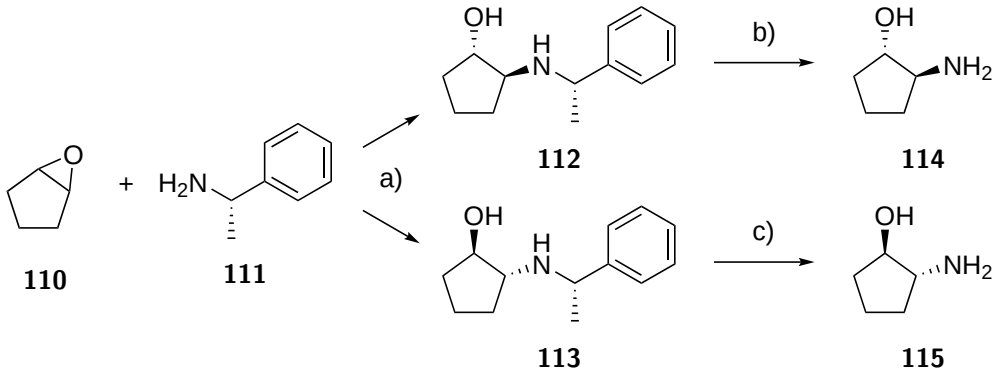
0.1 Cyclopentyl alcohol derivatives

0.1.1 Synthesis of the cyclopentyl alcohol head groups

Synthesis of the cyclopentyl alcohol derivatives began with the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1), using a procedure reported by Overman and Sugai.[?,?,?] These precursors were synthesised by opening cyclopentene oxide **110** using (*S*)-1-phenylethan-1-amine **111** to give approximately equal amounts of two diastereomers, **112** and **113**, which were separated using column chromatography. The removal of the methylbenzyl groups proved more difficult than expected, with the conditions reported by Overman and Sugai[?] yielding only a salt of the starting material. After several attempts under various conditions (including using the free amine vs. the salt, varying the temperature, ensuring the dryness of the reagents and adding acetic acid), an approach using H_2 gas was attempted (see Table 1). This proceeded smoothly at 5 atm to give the two enantiomers of 2-aminocyclopentan-1-ol, **114** and **115**, both in quantitative yield.



Scheme 1: Synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** a) $AlMe_3$, CH_2Cl_2, 0 °C. **112**: 35.2 %, **113**: 32.1 %. b) See Table 1. c) $Pd(OH)_2$, MeOH, H_2, 5 atm, r.t., 1 d, 100 %.

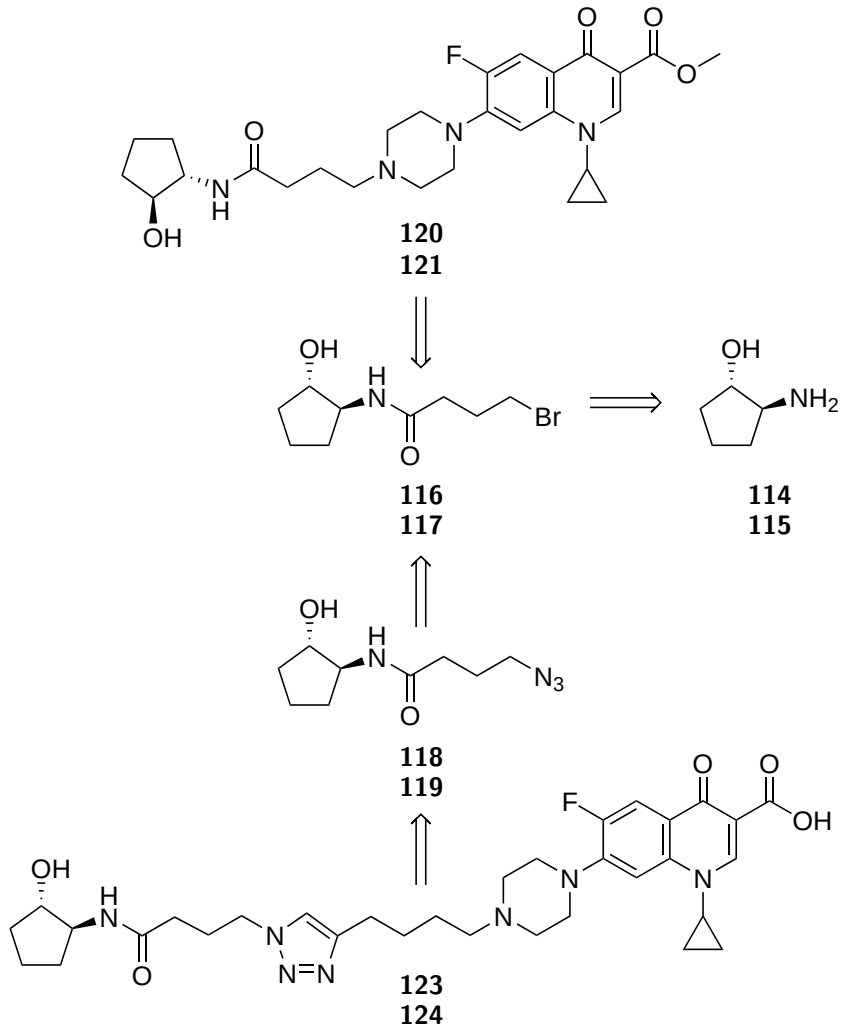
Conditions	Temperature and pressure	Time	Result
112·HCl, ammonium formate, 10 % Pd/C, DMF	r.t., 1 atm	2 d	**112** salt
112, ammonium formate, 10 % Pd/C, DMF	r.t., 1 atm	2 d	**112** salt
112·HCl, ammonium formate, 10 % Pd/C, dry DMF	r.t., 1 atm	2 d	**112** salt
113, ammonium formate, 10 % Pd/C, dry DMF	r.t., 1 atm	2 d	**113** salt
112, ammonium formate, 10 % Pd/C, dry DMF	70 °C, 1 atm	1 d	**112** salt
112, ammonium formate, 10 % Pd/C, dry DMF, AcOH	70 °C, 1 atm	1 d	Complex mixture
112·HCl, dry ammonium formate, 10 % Pd/C, dry DMF	120 °C, 1 atm	7 d	Complex mixture
112·HCl, $Pd(OH)_2$, MeOH, H_2	r.t., 1 atm	1 d	**112** salt
112·HCl, $Pd(OH)_2$, MeOH, H_2	r.t., 3.4 atm	1 d	**114** salt, **112** salt, and an unidentified compound (approx. 7:2:10 by ^{1}H NMR)
112, $Pd(OH)_2$, MeOH, H_2	r.t., 5 atm	1 d	**114**, 100 % yield

Table 1: Conditions attempted for the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1).

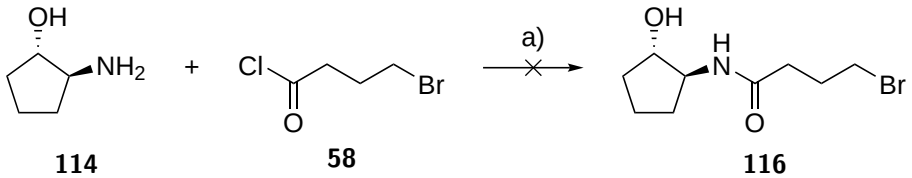
0.1.2 Initial branching strategy

An initial retrosynthesis of the conjugates is shown in Scheme 2, and follows a similar path to previous conjugates.

Synthesis of Br-C_4-cyclopentanol-(*SS*) **116** from (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and 4-bromobutyryl chloride **58** was attempted using Schotten-Baumann conditions (see Scheme 3). However, a large number of impurities were observed by LCMS (see Figure 1), and so three new strategies were attempted: protection of the alcohol (see 0.1.3), installing the linker on methyl ciprofloxacin **92** and then attaching the head group by peptide coupling (see 0.1.4), and using 4-chlorobutyryl chloride **139** as the linker instead of 4-bromobutyryl chloride **58** (see 0.1.5).



Scheme 2: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentyl alcohol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*). *SS* enantiomers are shown, but both will be synthesised.



Scheme 3: Synthesis of Br-C_4-cyclopentanol-(*SS*) **116**. a) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 2 h.

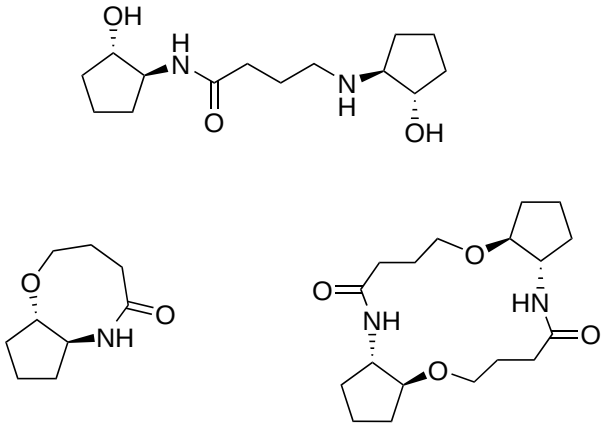
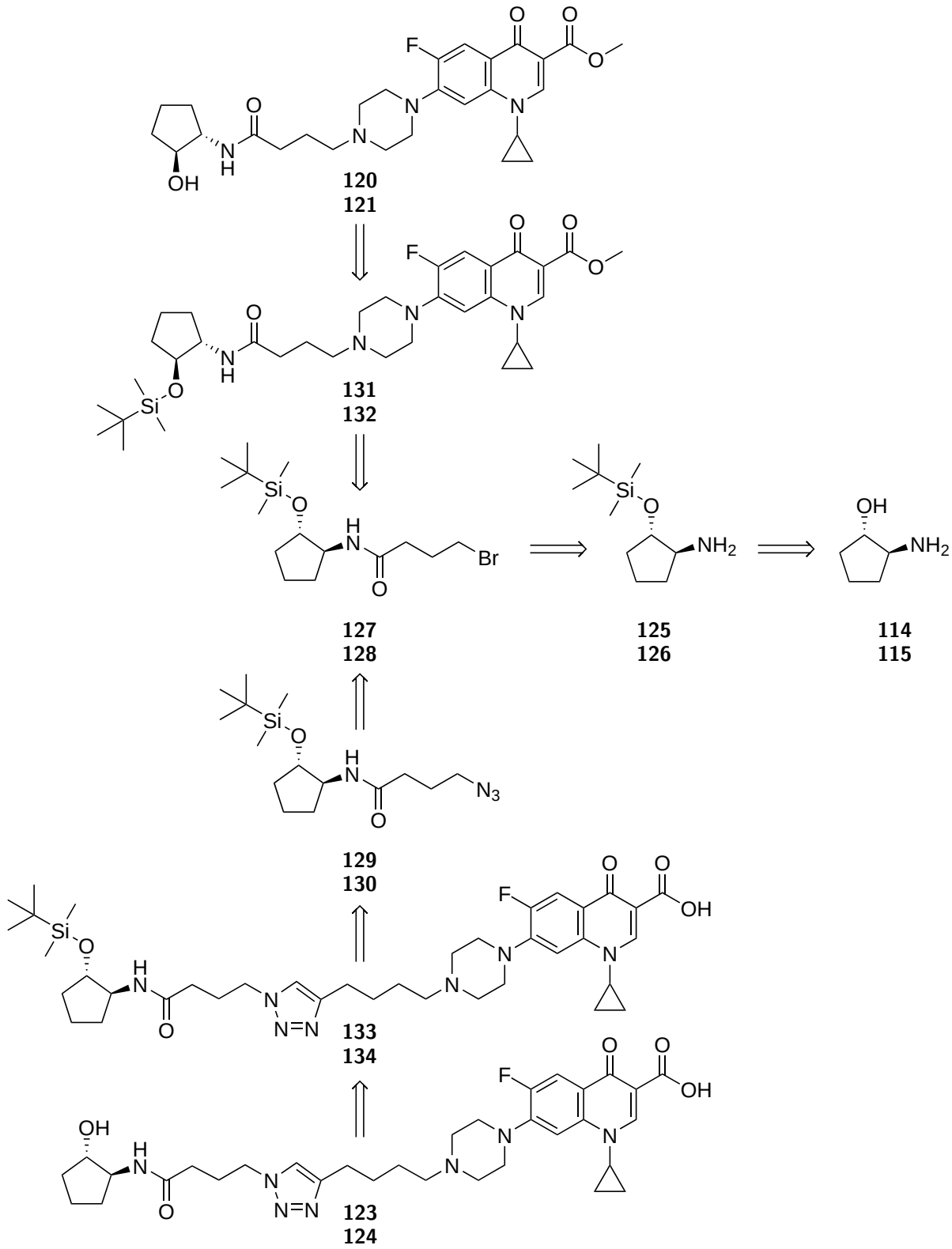


Figure 1: Impurities observed by LCMS during the synthesis of Br-C_4-cyclopentanol-(*SS*) **116**. Regiochemistry is speculative.

0.1.3 TBDMS protection of the alcohol

0.1.3.1 Initial protection strategy

The first attempt at an alternative strategy for the synthesis of the conjugates involved TBDMS protection of the alcohol (see Scheme 4). It was envisaged that protection would eliminate enough of the side reactions with products shown in Figure 1 that intermediates Br-C_4-cyclopentanol-(*SS*) **116** and N_3-C_4-cyclopentanol-(*SS*) **118** could be purified. The TBDMS group could be removed later in the synthesis using TBAF or acid.

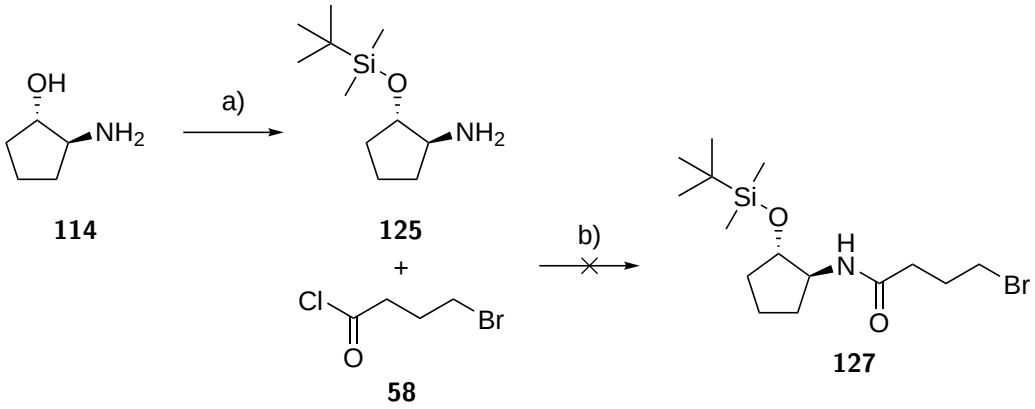


Scheme 4: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentyl alcohol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) using a TBDMS protection strategy. *SS* enantiomers are shown, but both will be synthesised.

The synthesis began with the optimisation of the protection of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** with a TBDMS group on the alcohol (see Scheme 5).

Opt.

OTf[?] Cl[?] DBU[?]



Scheme 5: The attempted synthesis of Br-C_4-cyclopentanol-TBDMS-(*SS*) **127**. a) See Table 2. b) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 2 h.

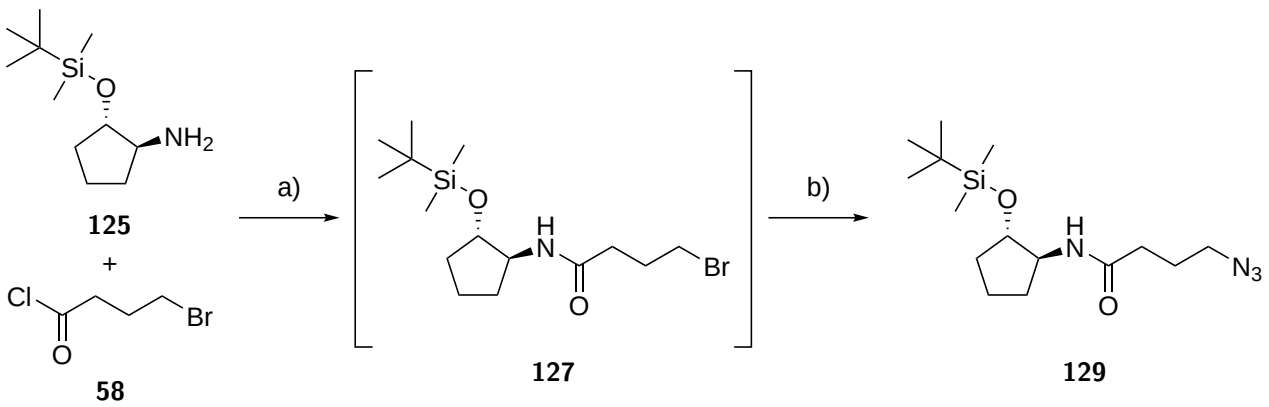
Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	18 h	Trace of **125**, mostly **114**
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	1 d	Didn't go to completion, lost on prep TLC
TBDMSCl, imidazole, CH_2Cl_2	0 °C	1 h	**114**
TBDMSCl, DBU, MeCN	0 °C	1 d	**114**
TBDMSOTf, TEA, CH_2Cl_2	0 °C	4 h	**125** possibly seen but lost in workup
TBDMSOTf in 2 portions, TEA, CH_2Cl_2, NH_4Cl workup	0 °C	6 h	**125** salt
TBDMSOTf in 2 portions, TEA, CH_2Cl_2, aq. workup then column	0 °C	6 h	**125**, 85 % yield

Table 2: Conditions attempted for the synthesis of (1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine **125** (see Scheme 5).

Still get side-reactions when adding tail come back to

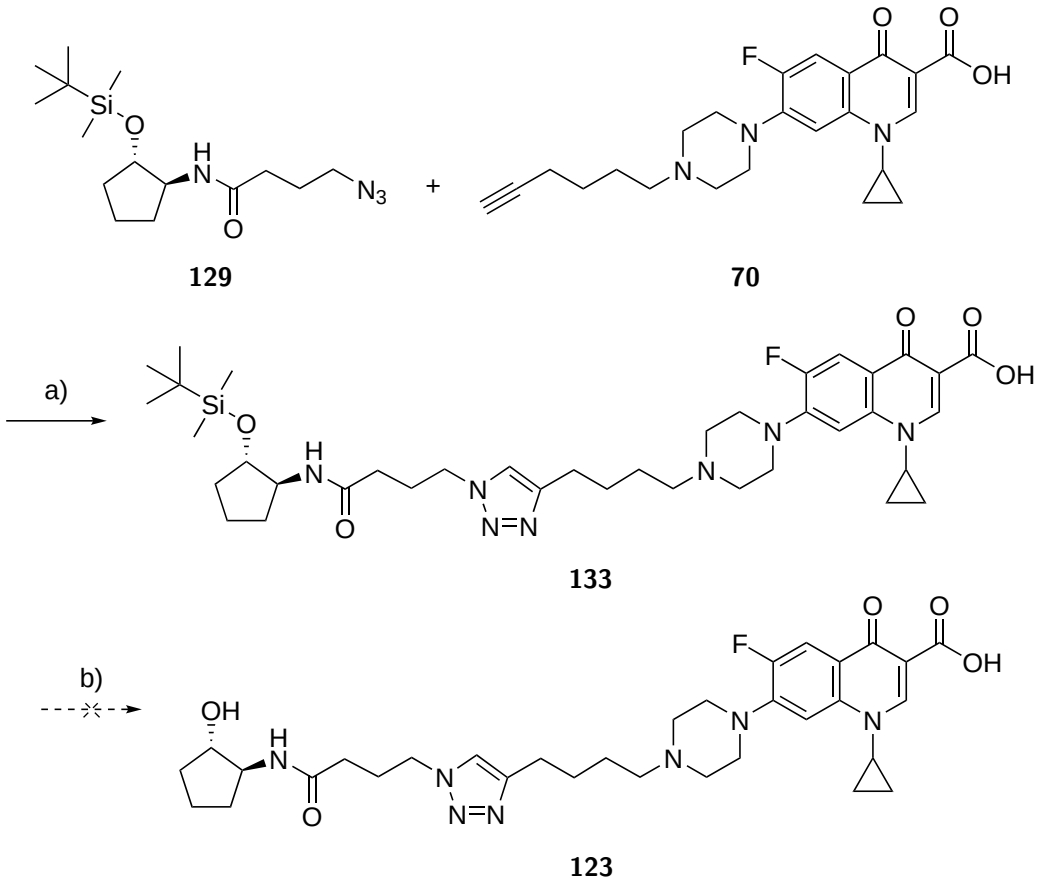
0.1.3.2 Triazoles by two-step reaction

Talk about moving to two-step reaction. come back to



Scheme 6: a) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 3 h. b) NaN_3, DMF, CH_2Cl_2, r.t., 3 h. 99.2 % over 2 steps.

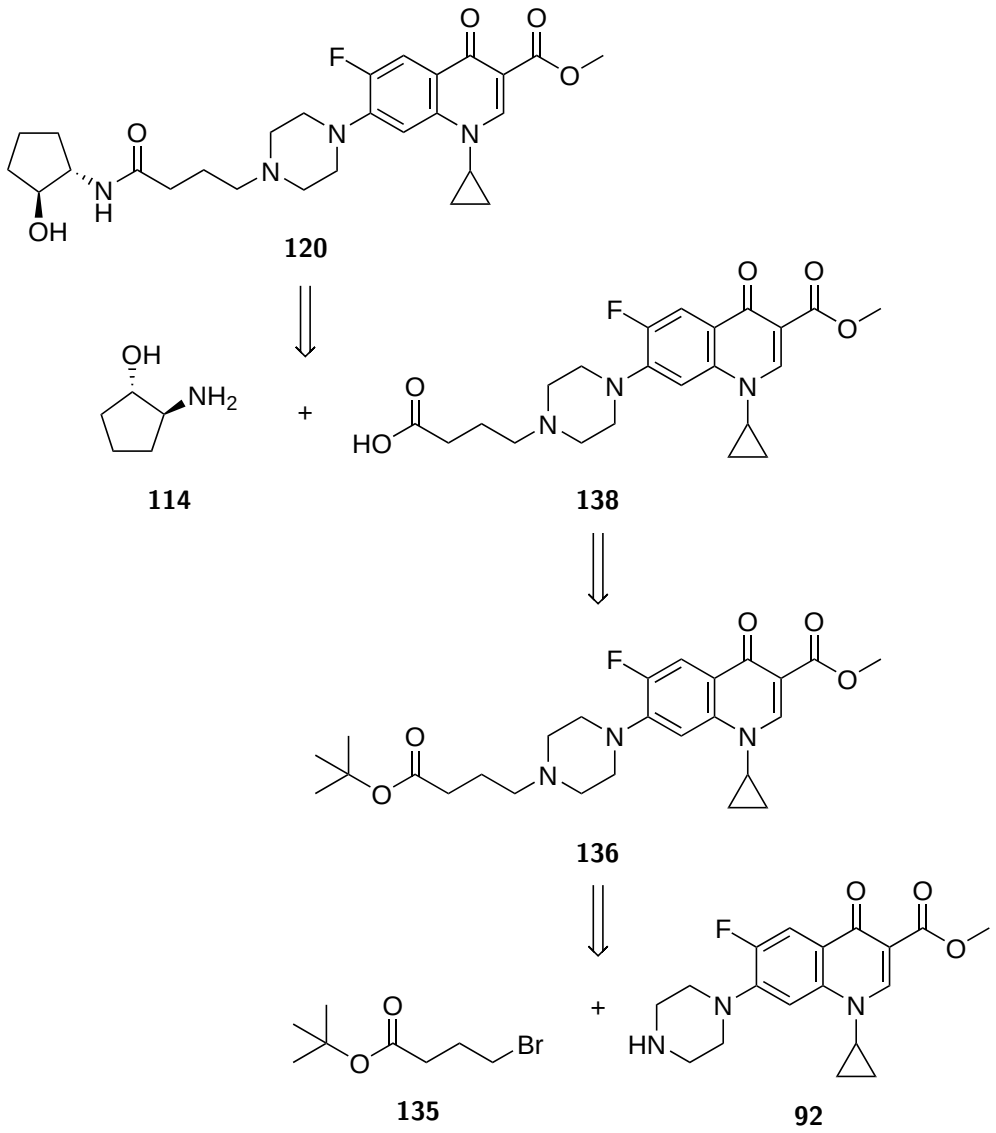
N_3-C_4-cyclopentanol-TBDMS-(*SS*) **129** and the alkynyl ciprofloxacin derivative **70** were subjected to standard click conditions, and the TBDMS-protected (*SS*)-cyclopentyl alcohol-Cip triazole conjugate **133** was synthesised in very good yield. However, removal of the TBDMS group proved difficult. Deprotection using 1.5 eq. TBAF in THF proceeded slowly, reaching completion in 5 d. Increasing the amount of TBAF to 8 eq. allowed the reaction to proceed overnight. Purification of the final conjugate **123** by column chromatography was not successful due to streaking and poor separation. Purification using DOWEX resin and $CaCO_3$ was attempted, but the product could not be recovered from the resin. The purification method could probably be optimised, e.g. by varying the solvent used with the resin, but ultimately this route was abandoned due to the reduction in number of steps afforded by the two methods described below.



Scheme 7: a) $CuSO_4$, sodium ascorbate, THPTA, H_2O, *t*-BuOH, r.t., 87.4 %. b) TBAF, THF, r.t., 16 h.

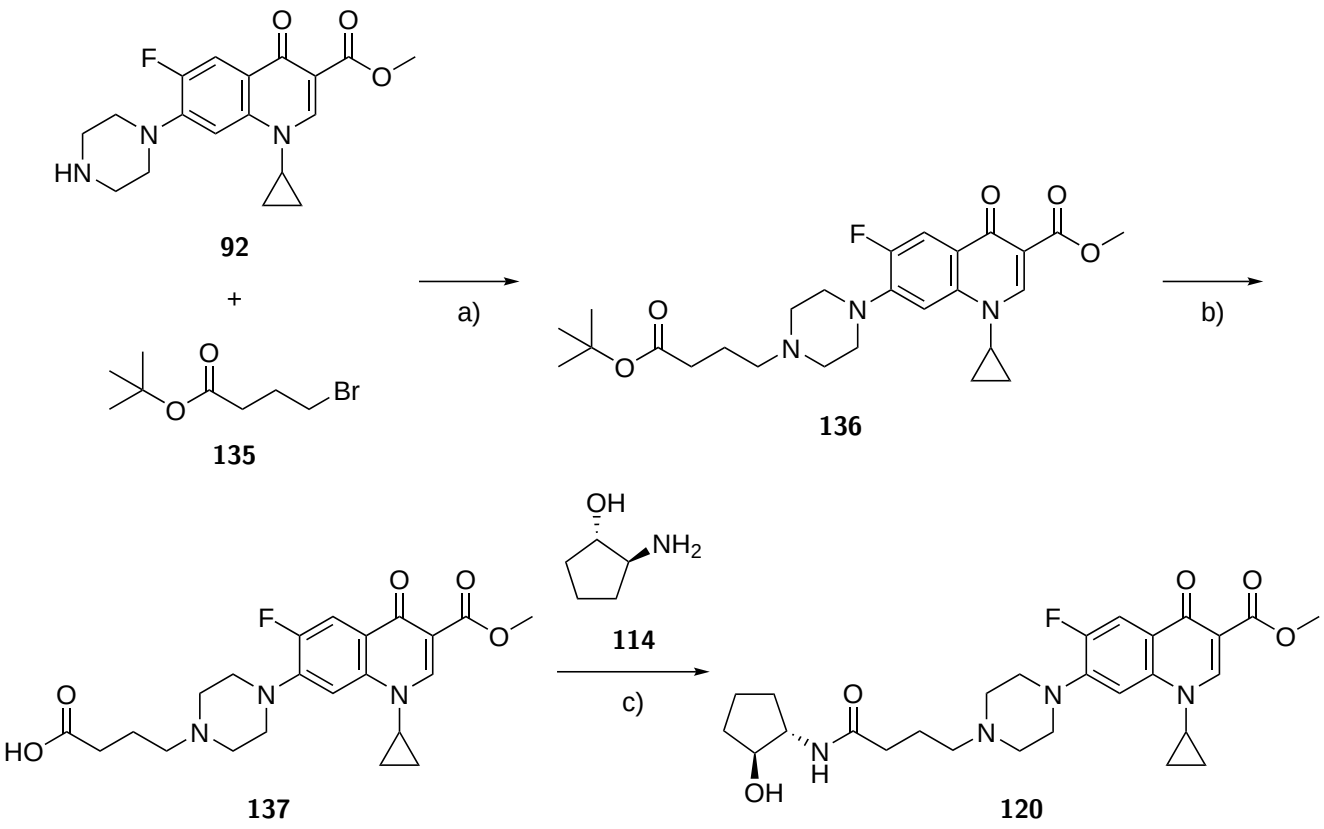
0.1.4 Attaching the linker to ciprofloxacin first

Given the side-reactions and low yields associated with the literate synthesis of the S_N2 conjugates proposed by Ganguly et. al,[?] an alternative synthesis was investigated, involving building up the linker on the ciprofloxacin side before coupling with the head group (see **??**).



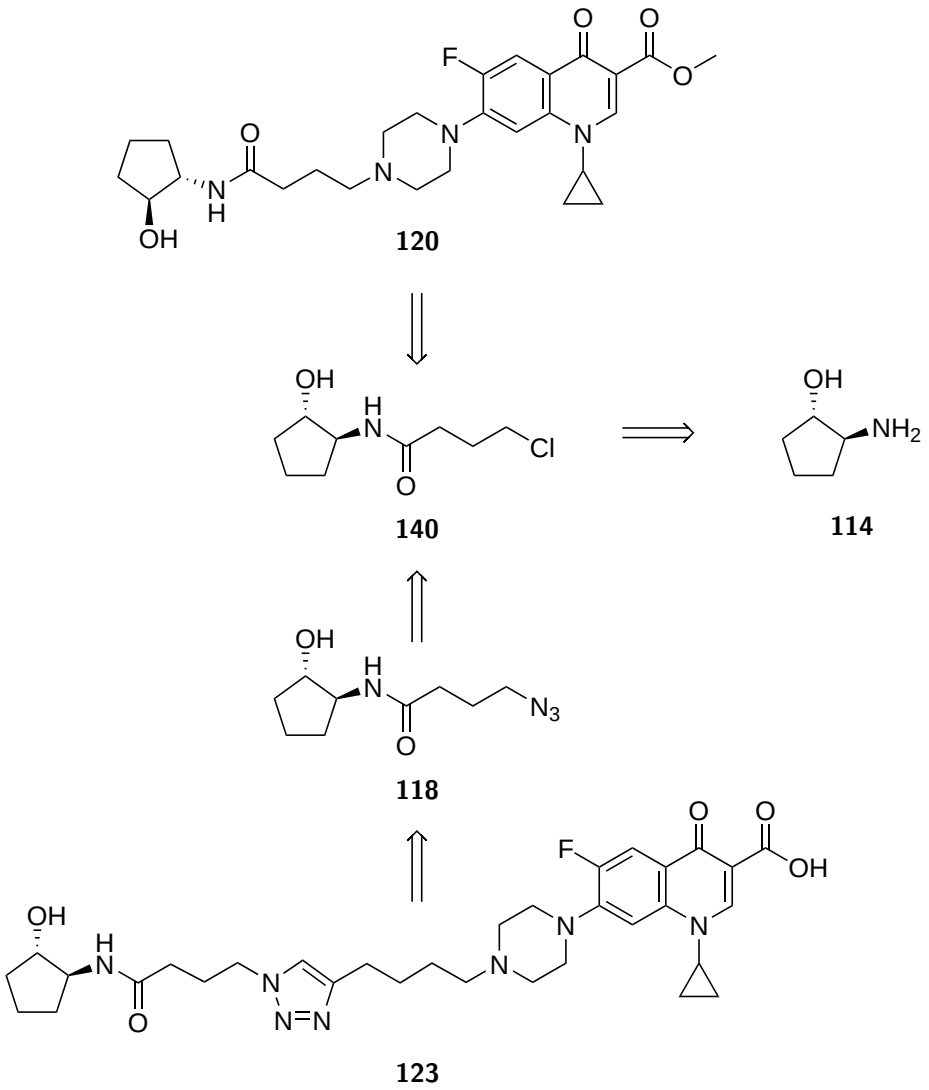
Scheme 8: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates (*RR*) **121** and (*SS*) **120**. *SS* enantiomers are shown, but both will be synthesised.

0.1.4.1 Synthesis of methyl-protected ciprofloxacin with linker with terminal carboxylate

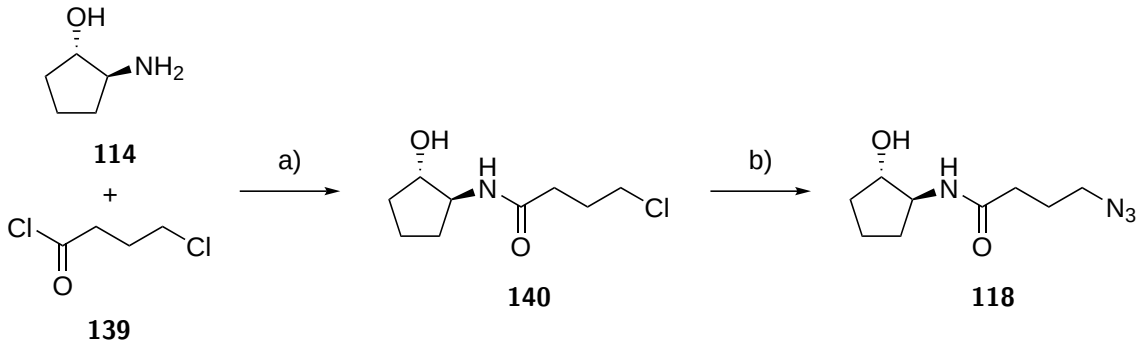


Scheme 9: Synthesis of **120**. a) NaI, TEA, MeCN, 100oC, 16h, 50 %. b) TFA, CH2Cl2, r.t., 18h, 96 %. c) EDC, HOBt, DIPEA, DMF, 35 %.

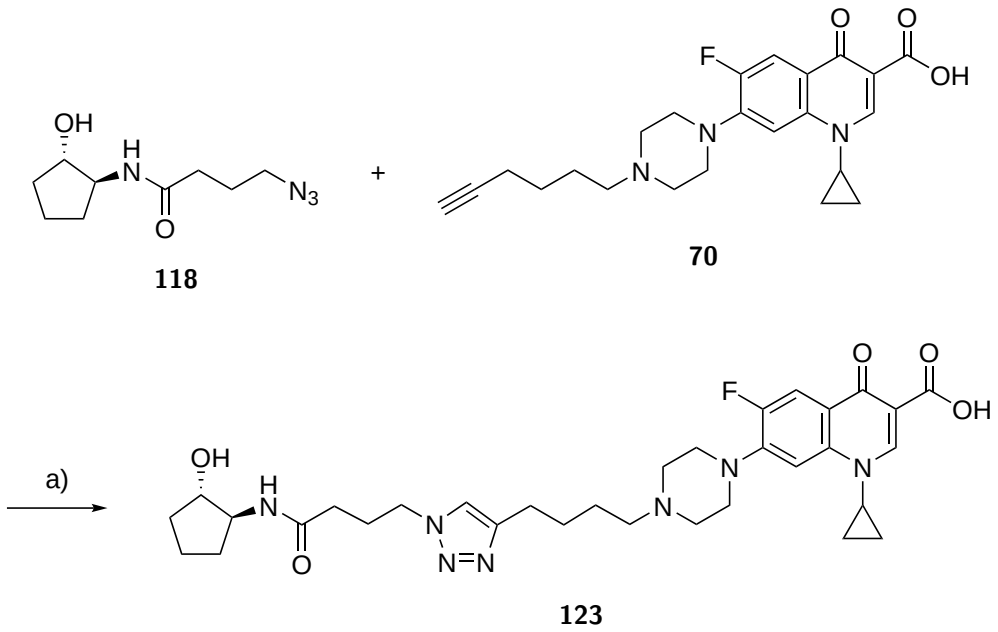
0.1.5 Triazoles from the chloride



Scheme 10: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates (*RR*) **121** and (*SS*) **120**, and the cyclopentyl alcohol-Cip triazole conjugates (*RR*) **124** and (*SS*) **123** using Cl-C_4-cyclopentanol-(*SS*) **140**. *SS* enantiomers are shown, but both will be synthesised.



Scheme 11: Synthesis of N_3-C_4-cyclopentanol-(*SS*) **118**. a) TEA, CH_2Cl_2, 0 °C, 2 h. b) NaN_3, acetonitrile, 50 °C, 24 h, 45.0 %.



Scheme 12: Synthesis of the cyclopentyl alcohol-Cip triazole conjugate **123**. a) $CuSO_4$, THPTA, sodium ascorbate, H_2O, *t*-BuOH, CH_2Cl_2, r.t., 3 d, 22.2 %.

This worked.

Todo list