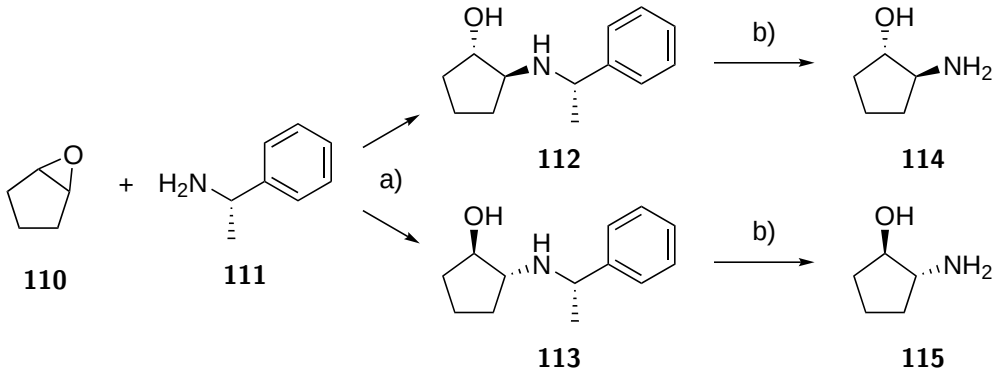
0.1 Cyclopentyl alcohol derivatives

0.1.1 Synthesis of the cyclopentyl alcohol head groups

Synthesis of the cyclopentyl alcohol derivatives began with the synthesis of (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** and (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** (see **??**). These were synthesised by opening cyclopentene **110** oxide using (*S*)-1-phenylethan-1-amine **111** to give approximately equal amounts of two diastereomers, **113** and **112**, which were separated using column chromatography.[1–3] The methylbenzyl group was then removed by hydrogenation to give the two enantiomers of 2-aminocyclopentan-1-ol, **115** and **114**, both in quantitative yield.

this was optimised, maybe add that?



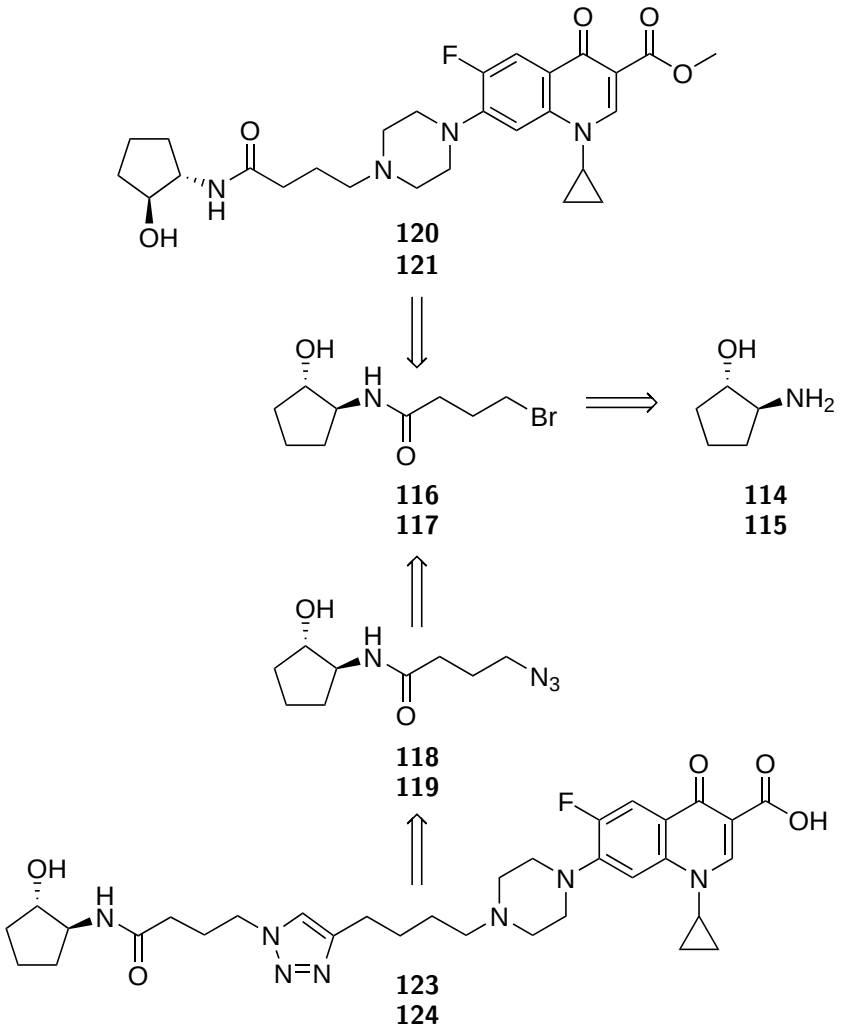
Scheme 1: Synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** a) $AlMe_3$, CH_2Cl_2, 0 °C. **112** : 35.2 %, **113** : 32.1 %. b) $Pd(OH)_2$, MeOH, H_2, 5 atm, r.t., 1 d, **114** : 100 %, **115** : 100 %.

Conditions	Temperature/pressure	Time	Result
HCl salt, ammonium formate, 10 % Pd/C, DMF	r.t.	2 d	S.M. salt
Free amine, ammonium formate, 10 % Pd/C, DMF	r.t.	2 d	S.M. salt
HCl salt, ammonium formate, 10 % Pd/C, dry DMF	r.t.	2 d	S.M. salt
Free amine, ammonium formate, 10 % Pd/C, dry DMF	r.t.	2 d	S.M. salt
Free amine, ammonium formate, 10 % Pd/C, dry DMF	70 °C	1 d	S.M. salt
Free amine, ammonium formate, 10 % Pd/C, dry DMF, AcOH	70 °C	1 d	Mess
HCl salt, dry ammonium formate, 10 % Pd/C, dry DMF	120 °C	7 d	Unidentified but probably not product
HCl salt, $Pd(OH)_2$, MeOH, H2	1 atm	1 d	S.M. salt
HCl salt, $Pd(OH)_2$, MeOH, H2	3.4 atm	1 d	Possible conversion but lost in work-up
Free amine, $Pd(OH)_2$, MeOH, H2	5 atm	1 d	PRODUCT!!!

Table 1: Conditions attempted for the synthesis ofthe two enantiomers of 2-aminocyclopentan-1-ol, **115** and **114**.

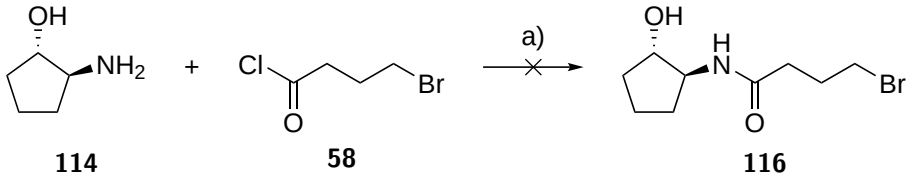
0.1.2 Initial branching strategy

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



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

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

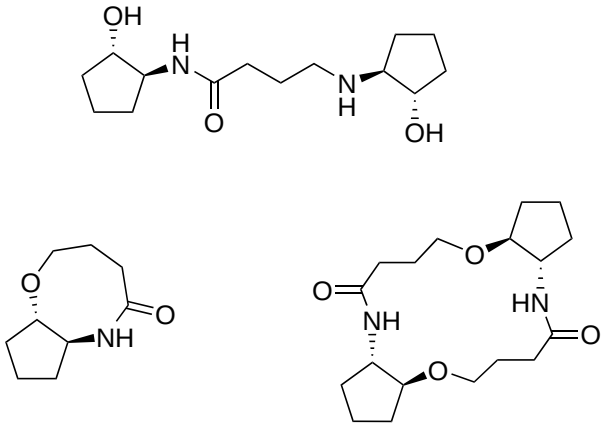
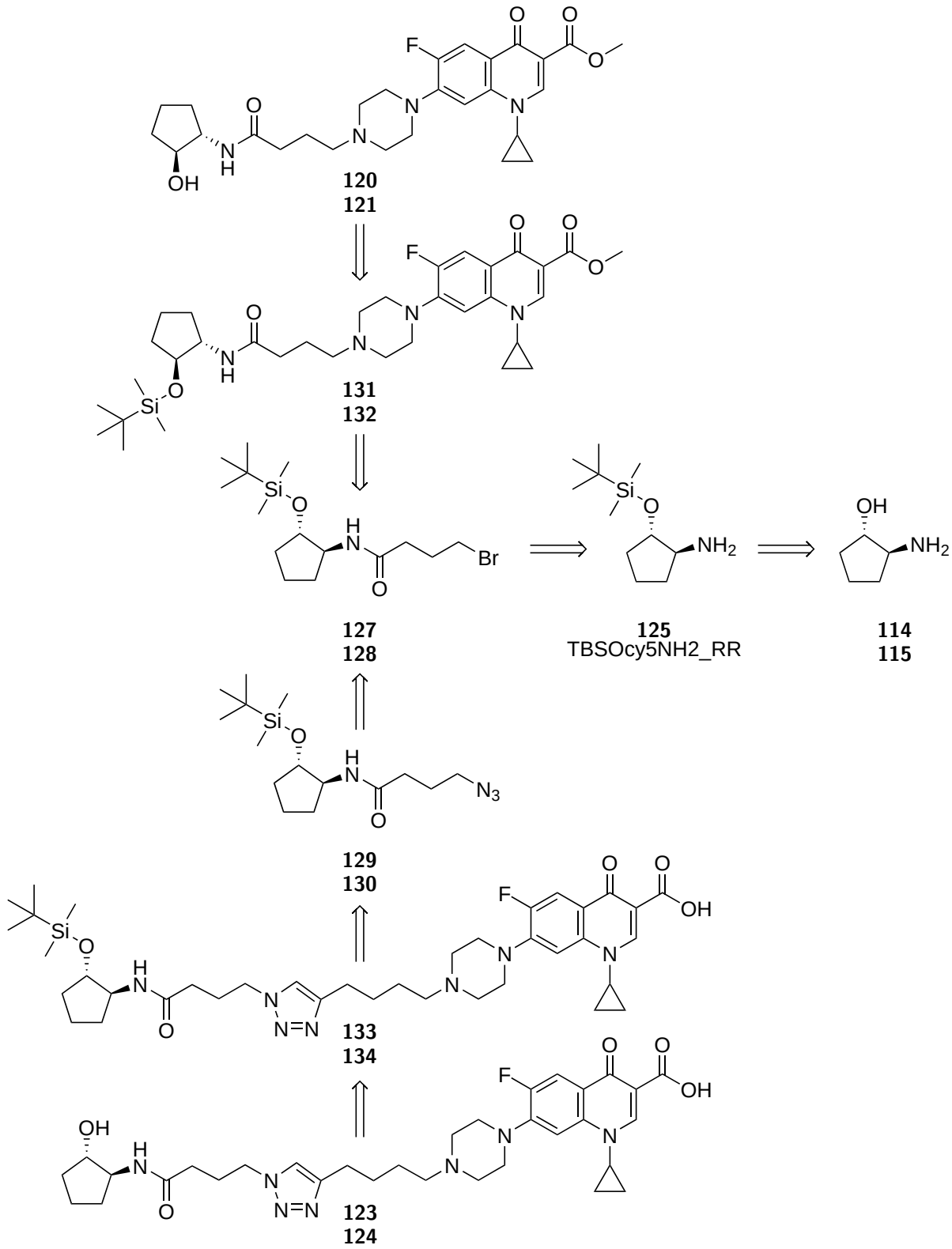


Figure 1: Impurities observed by LCMS during the synthesis of Br-C_4-cyclopentanol-(*SS*) **116**. Regiochemistry is speculative.

0.1.3 TBDMS protection of the alcohol

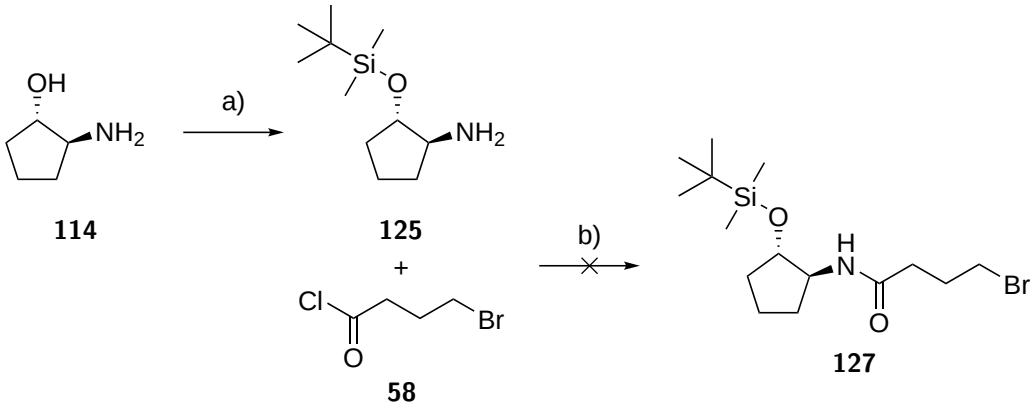
0.1.3.1 Initial

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 (*RR*) **121** and (*SS*) **120**, and the cyclopentyl alcohol-Cip triazole conjugates (*RR*) **124** and (*SS*) **123** 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.



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.

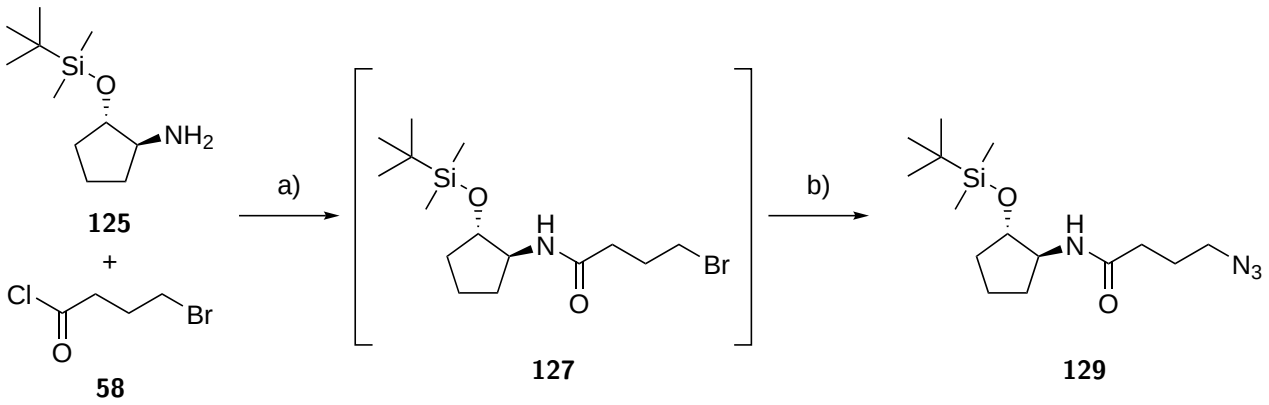
Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	18 h	Trace of product?
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	1 d	Didn't go to completion, lost on prep TLC
TBDMSCl, imidazole, CH_2Cl_2	0 °C	1 h	S.M. salt in aq layer?
TBDMSCl, DBU, MeCN	0 °C	1 d	S.M.
TBDMSOTf, TEA	0 °C	4 h	Product possibly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

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

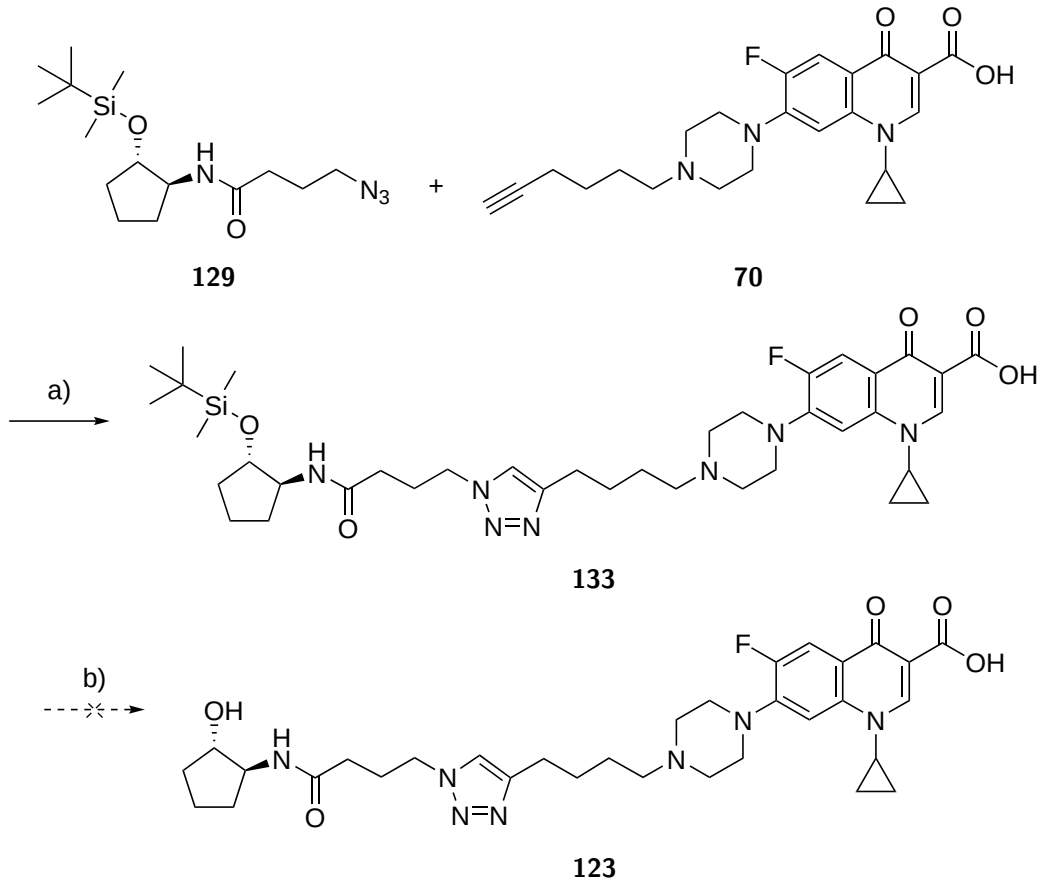
Protection optimisation
Still get side-reactions when adding tail

0.1.3.2 Triazoles by two-step reaction

Talk about moving to two-step reaction.



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.

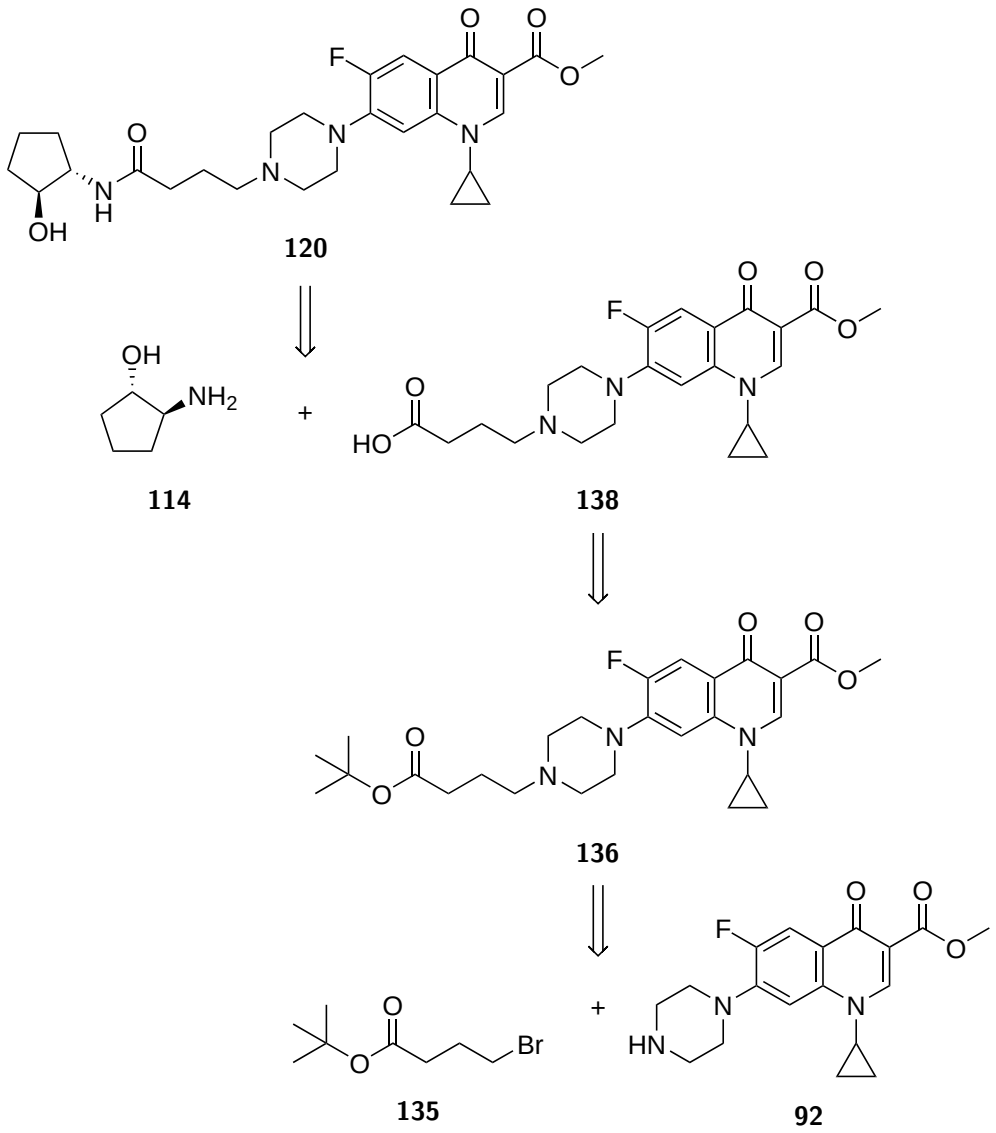


Scheme 7: a) $CuSO_4$, sodium ascorbate, THPTA, H_2O, *t*-BuOH, r.t., 87.4 %. b) TBAF, THF, r.t., 5 d.

Did click, then failed to deprotect.

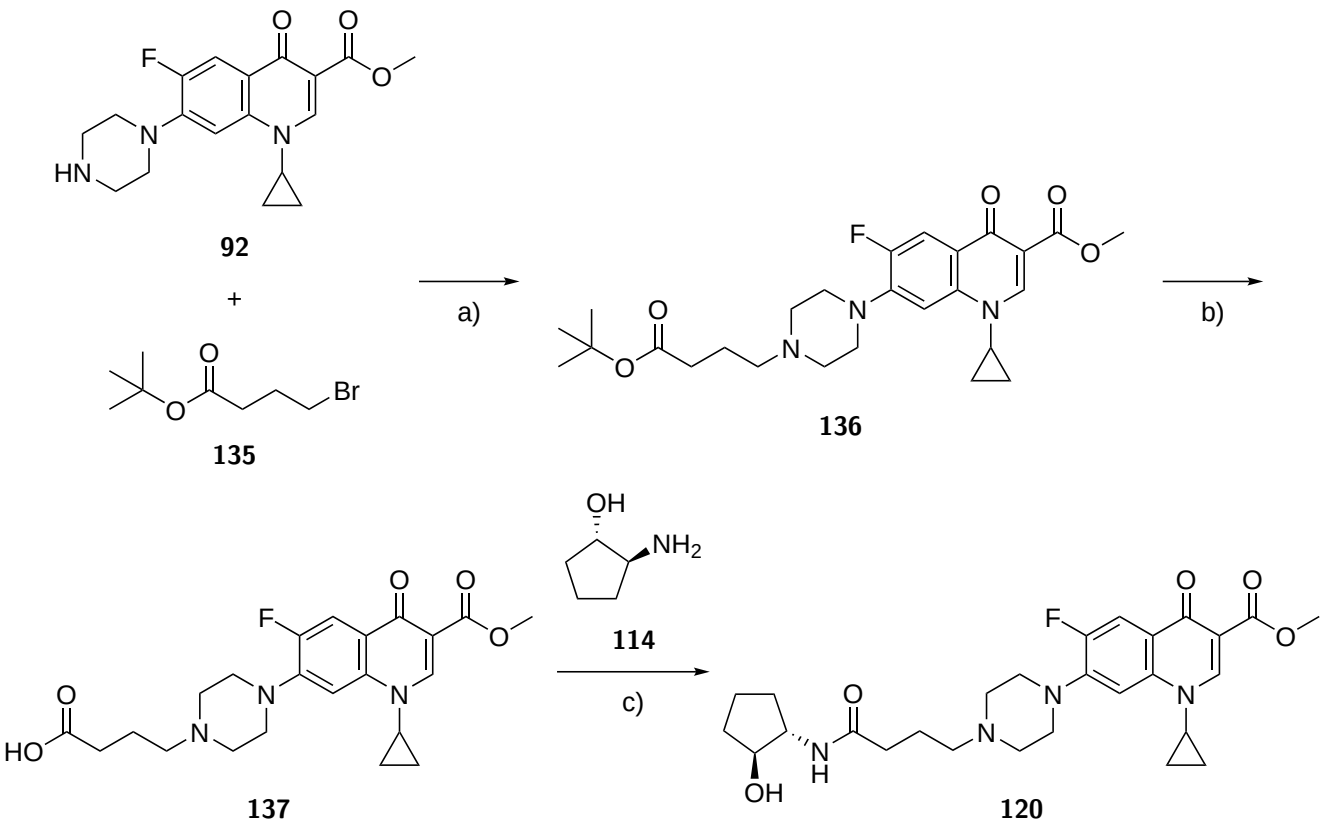
0.1.4 Attaching the linker to ciprofloxacin first

Given the side-reactions and low yields associated with the literate synthesis of the S_N2 conjugates proposed by Ganguly et. al,[4] we investigated a second synthesis, building up the linker on the ciprofloxacin side before coupling with the head group (see **??**).



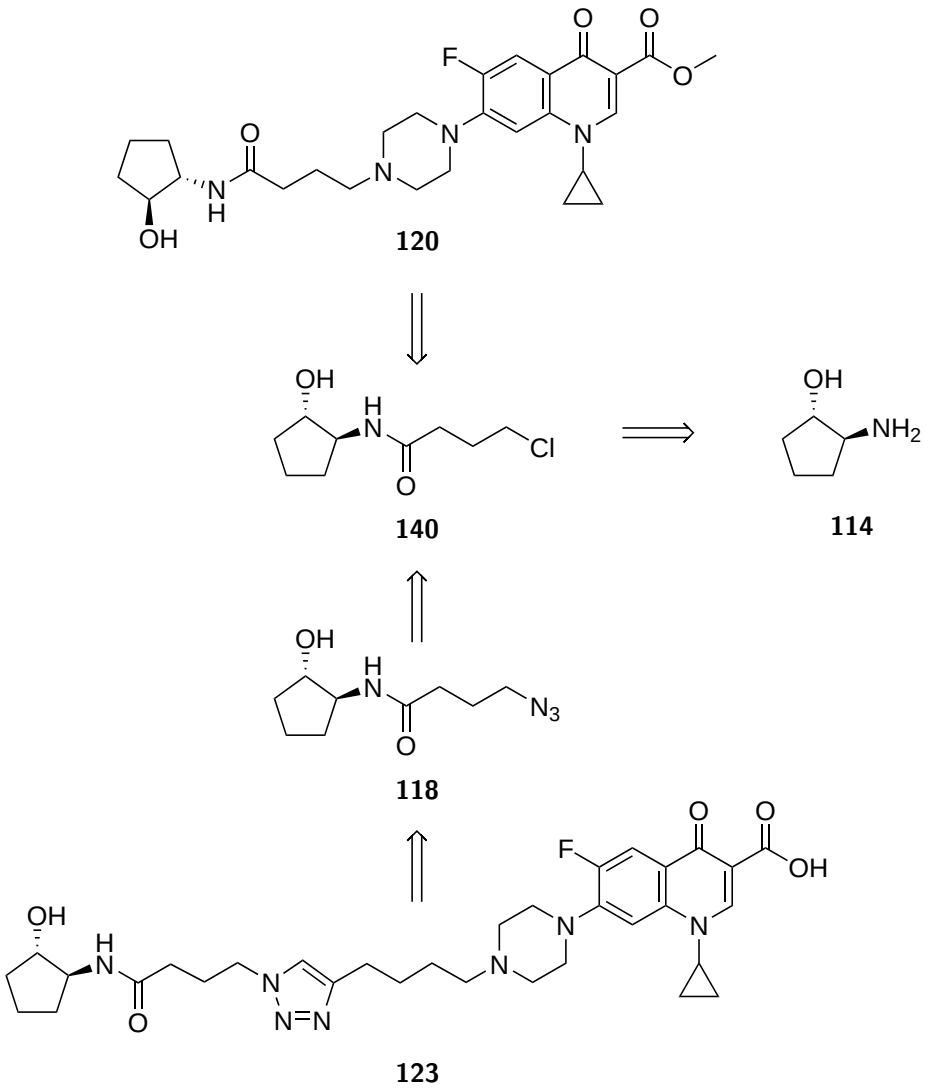
Scheme 8: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates (*RR*) **121** and (*SS*) **120**. *SS* enantiomers are shown, but both will be synthesised.

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

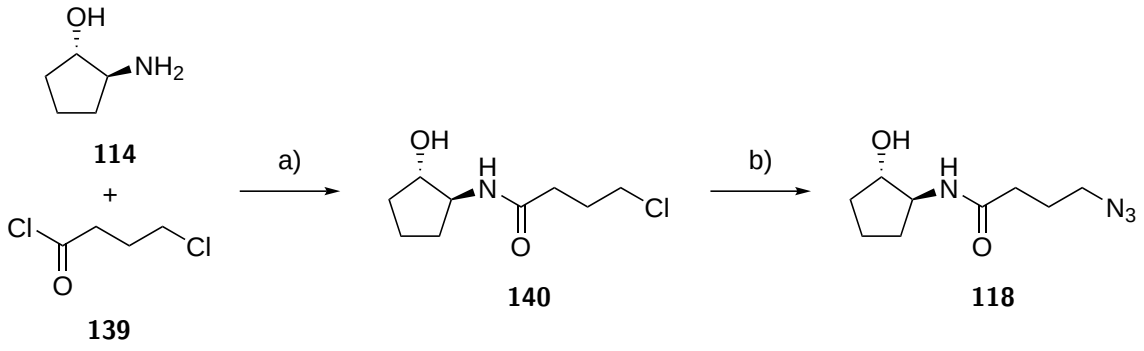


Scheme 9: Synthesis of **120**. a) NaI, TEA, MeCN, 100oC, 16h, 50 %. b) TFA, CH2Cl2, r.t., 18h, 96 %. c) EDC, HOBt, DIPEA, DMF, 35 %.

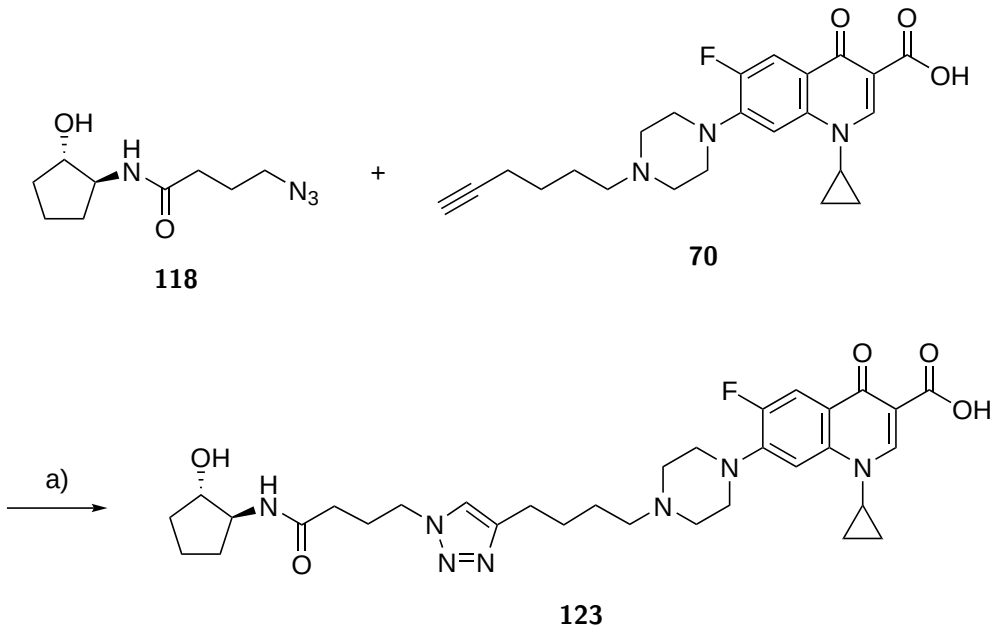
0.1.5 Triazoles from the chloride



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.

1 References

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Todo list