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Synthesis of spirolactams and spiropiperidines as CCR4 receptor antagonists

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Abstract—The synthesis of racemic and non-racemic spirocyclic lactams that display high binding affinity toward CCR4 is described. Two distinct series of spirocycles were prepared from the common intermediate **9**.

CCR4 is a G-protein coupled receptor that binds two chemokines, macrophage derived chemokine (MDC) and thymus and activation regulated chemokine (TARC).[1] CCR4 is expressed primarily by Th2 T cells, and there is considerable evidence that CCR4 regulates the migration of Th2 cells in disease settings.[2] Because CCR4 is preferentially expressed by Th2 cells, and its ligands are induced at sites of allergic inflammation, we and others have pursued CCR4 antagonists as novel agents for the treatment of asthma and atopic dermatitis.[3] Recent reports from these laboratories described a series of 2,3,5-trisubstituted thiazolidinone[4] and 1,3,5-trisubstituted pyrrolidinone[5] CCR4 inhibitors as novel therapeutic agents of allergic inflammation. As a continuation of these series, we have evaluated rigidified analogs such as spirolactam **2** (Fig. 1). Herein, we disclose the synthetic details in which both racemic and enantiomerically pure spirolactams as well as racemic spiropiperidines were constructed.

Taking a cue from our previous work,[5] we envisioned a route to the scaffold (2,8-diaza-spiro[4.5]decane-1,7-dione) via the bicyclic lactam methodology developed by Meyers and Brengel.[6] As outlined in Scheme 1, racemic lactams were attained by the condensation of ethanolamine with ketoacid **4** in refluxing toluene and azeotropic removal of water. The enantiopure lactams,

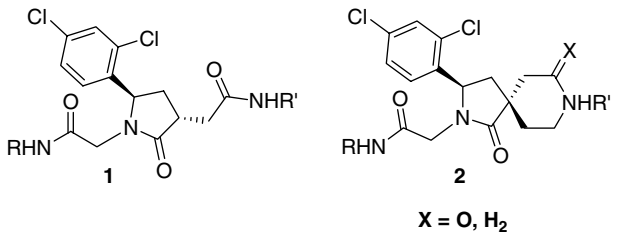

Figure 1. Previously explored lactam (**1**) and proposed spirocyclic template (**2**).

by the same method, were accessed by employment of (*S*)- or (*R*)-phenylglycinol to afford bicyclic lactam **5** (R = Ph) as one diastereomer. In our work, we required the use of (*S*)-phenylglycinol as the (*R*) derived lactam gave analogs much less potent.[5] Titanium(IV)chloride/triethylsilane mediated ring opening and *N*-acyliminium ion reduction[7] provided lactam **6** in 80% yield. When R = Ph for lactam **6**, only one diastereomer was observed by NMR. The alcohol of racemic lactam **6** (R = H) was protected as its silyl ether **9**. To obtain enantiopure lactams, the general synthetic scheme briefly diverges to remove the chiral auxiliary. A modified procedure of auxiliary removal[8] was used that involved conversion of the alcohol bearing moiety of lactam **6** to its corresponding chloride and subsequent treatment with sodium ethoxide in ethanol at 45 °C to provide enamide **7**. Hydrolysis of the enamide was then easily accomplished with HCl to afford lactam **8** in an

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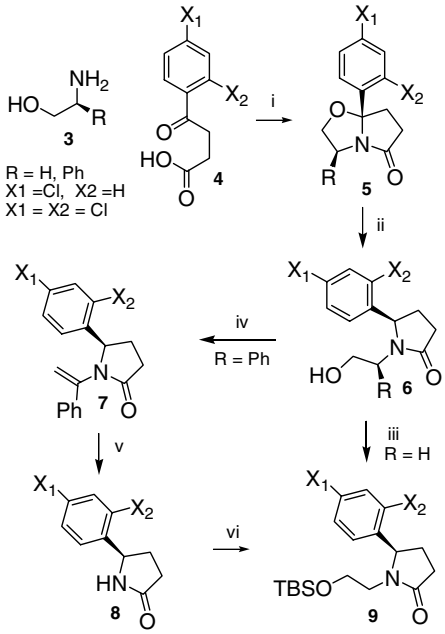
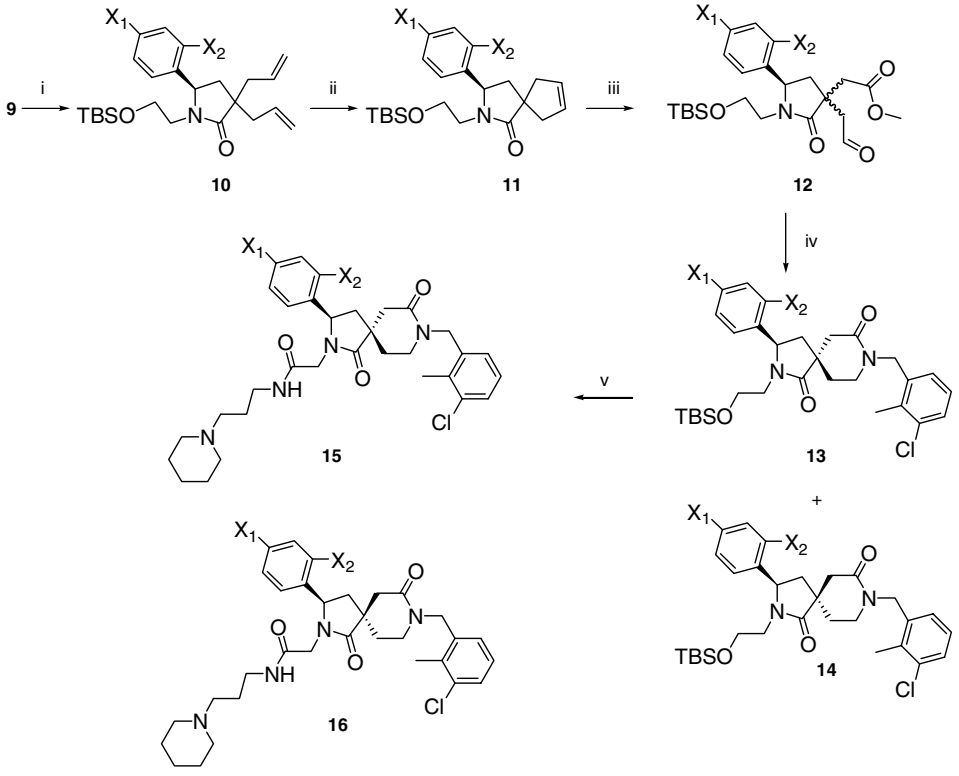


Scheme 1. Reagents and conditions: (i) toluene, reflux, Dean–Stark, 16 h, 100%; (ii) $TiCl_4$, DCM, Et_3SiH, −78 °C to rt, 16 h, 80%; (iii) TBDMSCl, imidazole, DMF, 95%; (iv) a—$SOCl_2$, THF, 0 °C to rt, 95%; b—NaOEt, EtOH, 45 °C, 80%; (v) 1 N HCl (aq), THF, reflux, 85%; (vi) KH, DMF, (2-bromoethoxy)-*tert*-butyldimethylsilane, rt, 1 h, 75%.

overall conversion of 65%. Treatment of lactam **8** with potassium hydride in DMF, followed by alkylation with (2-bromoethoxy)-*tert*-butyldimethylsilane afforded enantiopure lactam **9** in 75% yield. Chiral HPLC of enantiopure lactam **9** ($X_1 = Cl$, $X_2 = H$ or $X_1 = X_2 = Cl$) indicated it to be >95% ee.[9] It is at this point the racemic and enantiomeric syntheses converge.

As detailed in Scheme 2, the spirocycle was assembled by sequential di-alkylation of lactam **9** with LDA and allylbromide at −78 °C to afford di-allyllactam **10** in 50% overall yield. Ring closing metathesis utilizing Grubbs' second generation catalyst[10] at 0.05 or 0.10 molar concentration in refluxing 1,2-dichloroethane yielded spirolactam **11** in 80% yield after filtration through a silica gel plug. At this point, we envisioned opening the cyclic olefin of the spirolactam via ozonolysis followed by a reductive workup method described by Claus and Schreiber,[11] to achieve differentiated oxidation states. Therefore, ozonolysis of lactam **11** in DCM/MeOH at −78 °C followed by workup with acetic anhydride and triethylamine in DCM at 0 °C provided ester-aldehyde **12** as a 1:1 mixture of diastereomers in 75% yield. Reductive cyclization occurred by subjecting ester-aldehyde **12** to 3-chloro-2-methyl benzylamine in the presence of sodium triacetoxyborohydride. Silica gel chromatography provided each spirolactam **13** and **14** in 50% combined overall yield. Alternatively, separation of the diastereomers could be performed at a later stage. NMR studies on lactam **13** confirmed the stereochemistry at the spirocyclic carbon.[12] During the course of our work, several benzyl amines were incorporated to expand the structure–activity relationships.



Scheme 2. Reagents and conditions: (i) a—LDA, THF, −78 °C then allylbromide, 70%, b—LDA, THF, −78 °C then allylbromide, 70%; (ii) Grubbs' second generation catalyst, 1,2-DCE, reflux, 80%; (iii) a—ozone, DCM/MeOH, $NaHCO_3$, −78 °C; b—Ac_2O, TEA, DCM, 0 °C, 75%; (iv) (3-chloro-2-methylphenyl)methanamine, $NaBH(OAc)_3$, 1,2-DCE, 50%; (v) a—Jones reagent, acetone, 80%; b—CDI, CH_2Cl_2, 3-(piperidin-1-yl)propan-1-amine, 40%.

With the spirocycle in place, we now focused on functionalizing the left arm of the molecule. Immersing spirolactam **13** and **14** (as a mixture of diastereomers or separate) in Jones reagent in acetone facilitated the deprotection of the TBS ether and oxidation of the resultant alcohol to the acid in one pot. Amide bond formation on the crude acid with carbonyl diimidazole in DCM with 3-(piperidin-1yl)propane-1-amine and preparative thin layer chromatography to separate diastereomers provided diastereomerically and enantiomerically pure spirolactams **15** and **16** in 40% combined yield. It should be noted that the carbonyl in the six-membered ring of lactam **15** is in a trans disposition to the aromatic ring on the five-membered ring lactam. This diastereomer proved to be more potent[1] than its counterpart **16**, an observation we made in our non-spiroseries.[4,5] Again, several amines were used at this stage in order to expand the scope of our SAR studies.

To ascertain the role of the carbonyl of the six-membered ring on spirolactam **2**, we undertook a program to prepare a series of 2,8-diaza-spiro[4.5]decan-1-ones (spiropiperidines), where the carbonyl is removed as exemplified in Figure 2. Recent studies have utilized this scaffold as HIV-1 protease inhibitors.[13]

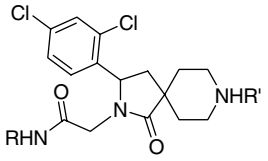
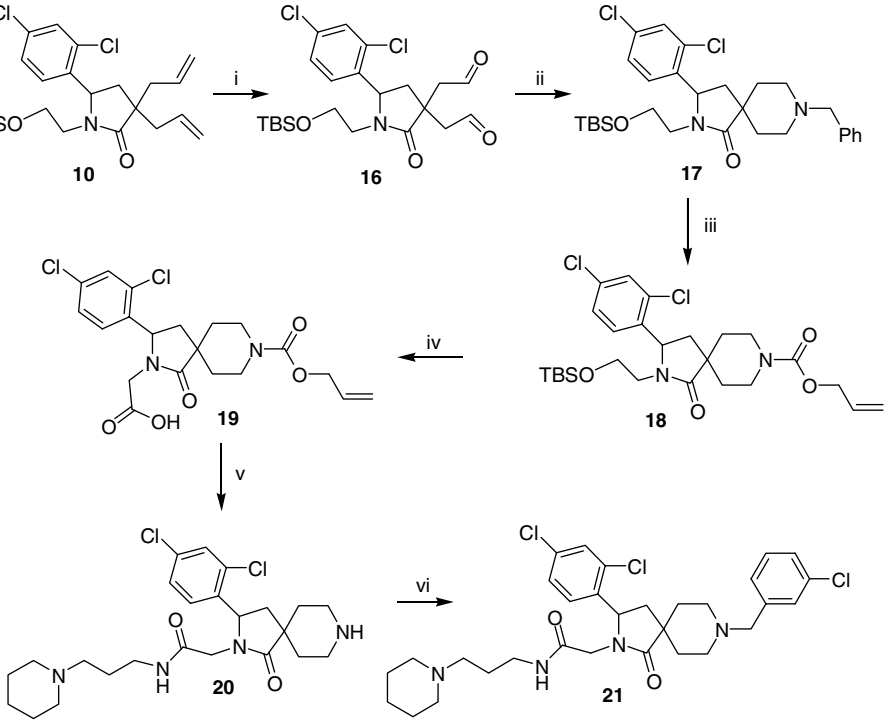


Figure 2. Spirocyclic core with carbonyl excised or placed outside of ring.

As outlined in Scheme 3, we employed racemic lactam **10** (from Scheme 2, $X_1 = X_2 = Cl$) as a starting point. Ozonolysis of di-allyllactam **10** at −78 °C in DCM followed by reductive workup using polymer bound triphenylphosphine conveniently afforded di-aldehyde **16**. Reductive amination of **16** with benzyl amine provided the spiropiperidine in 55% yield. With the requisite spiropiperdine ring structure complete, it was desirable to switch protecting groups to avoid oxidation of piperidine. To this end, a von Braun like N-debenzylation[14] was performed by refluxing **17** in acetonitrile with allylchloroformate affording the spiropiperidine **18** in 98% yield. Functionalization of the TBS ether was then smoothly accomplished using the sequence described in Scheme 2.

To further functionalize the piperidine nitrogen, palladium mediated deprotection of the allylcarbamate provided spiropiperidine **20**, a useful intermediate for acylations, sulfonylations, or reductive aminations. Piperidine was treated with 3-chlorobenzaldehyde and sodium triacetoxyborohydride in 1,2-dichloroethane to give spiropiperidine **21**. Again, several acid chlorides, sulfonyl chlorides, and aldehydes were employed to expand the SAR of this series.

In conclusion, we have demonstrated efficient racemic and chiral syntheses of spirolactams and spiropiperidines. Both series of compounds can take advantage of



Scheme 3. Reagents and conditions: (i) ozone, DCM, −78 °C then PS-TPP, warm to rt, 100%; (ii) benzyl amine, $NaBH(OAc)_3$, 1,2-DCE, 55%; (iii) allylchloroformate, AcCN, reflux, 98%; (iv) Jones reagent, acetone, 79%; (v) a—PyBop, DIEA, 3-(piperidin-1-yl)propan-1-amine, 40%; b—$Pd(PPh_3)_4$, THF–DEA; (vi) 3-chlorobenzaldehyde, $NaHB(Oac)_3$, 1,2-DCE.

di-allyllactam **10**, an intermediate that can be readily synthesized on large scale racemically or in enantiomerically pure form. Three crucial steps are required to generate the spirolactams: ring closing metathesis, ozonolytic cleavage, and reductive cyclization. From lactam **10**, spiropiperidines require ozonolysis to dialdehyde and reductive cyclization to create the six-membered ring which conveniently circumvents diastereomeric mixtures.

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