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Synthesis of *cis*-2,5-disubstituted pyrrolidines via diastereoselective reduction of *N*-acyl iminium ions

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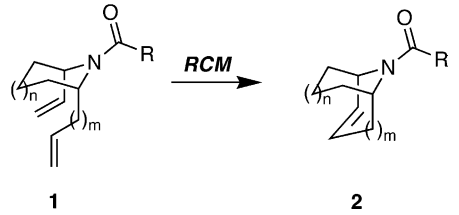
Abstract—A new procedure for forming *cis*-2,5-disubstituted pyrrolidines having unsaturated side chains has been developed that features the diastereoselective reduction of *N*-acyl iminium ions, which were formed in situ by acid-catalyzed cyclizations of unsaturated γ-keto carbamates, with triphenylsilane. The sequence was applied to a very concise synthesis of **16**, a subunit in the nonpeptide cholecystokinin antagonist (+)-RP-66803.

1. Introduction

In the context of our general interest in applying ring closing metathesis to the synthesis of bridged azabicyclic systems according to Scheme 1,[1,2] it became necessary to prepare a number of *cis*-2,5-disubstituted pyrrolidines bearing unsaturated side chains such as **1** ($n = 0$). In contrast to the methodology that is available for the stereoselective synthesis of *cis*-2,6-disubstituted piperidines **1** ($n = 1$),[2] methodology for preparing the corresponding pyrrolidines **1** ($n = 0$) is rather limited.[3–5] For example, additions of carbon nucleophiles to cyclic five-membered iminium ions typically proceed with only modest diastereoselection,[4] presumably because of the greater conformational flexibility of five-membered rings. The reductions of 2,5-disubstituted 1-pyrrolines by catalytic hydrogenation are highly stereoselective,[5] but such methods are not applicable to preparing compounds having other carbon–carbon double bonds. We therefore sought to develop a stereoselective procedure for the construction of *cis*-2,5-disubstituted pyrrolidines of the form **1** ($n = 0$), and we now wish to report these findings.



1 **2**

Scheme 1.

2. Results and discussion

Inasmuch as our eventual goal was the preparation of *cis*-2,5-disubstituted pyrrolidines that could be elaborated into alkaloid natural products, we wanted to use a substituted pyrrolidine derivative that was readily available and possessed functionality that might be used in subsequent transformations. Toward that end, we sought to develop an efficient protocol for converting the known imide **4**,[6] which is easily prepared from commercially available L-pyroglutamate (**3**), into products of the general form **5**. The essence of the plan was that this would be achieved via sequential nucleophilic addition of a carbon nucleophile to **4** followed by stereoselective hydride reduction of an intermediate *N*-acyl iminium ion (Scheme 2).

Our first experiments, which were inspired by the work of Yoda et al.,[7] involved the addition of 3-butenyl magnesium bromide to **4** to give the γ-keto carbamate **6**

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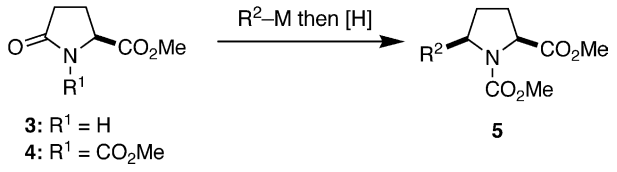
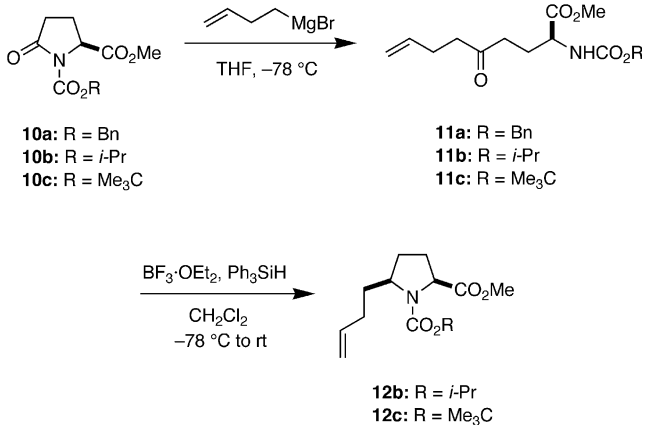


Scheme 2.

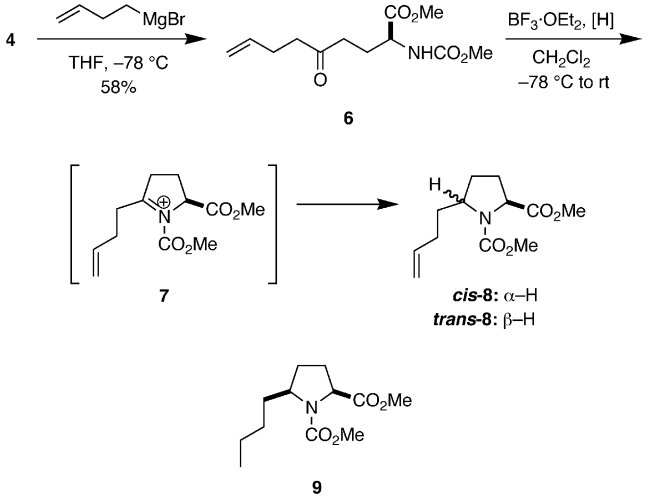


Scheme 4.

together with lesser amounts of **3** arising from attack on the carbamate carbonyl group.[8,9] Subsequent treatment of **6** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ provided a mixture (1.1:1) of *cis*-**8** and *trans*-**8** in 83% unoptimized yield. Although the yield in the cyclization/reduction of **6** was very good, the stereoselectivity of the reduction step was disappointing, especially in view of Yoda's successes in similar systems. We then examined a number of other reducing agents including $NaBH_4$, $NaCNBH_3$, and *n*-Bu_3SiH, but in every case the diastereoselectivity of the reduction was modest, ranging from 1.3 to 4.7:1. We examined other silane reagents in this step and ultimately discovered that when **6** was treated with Ph_3SiH in the presence of $BF_3{\cdot}OEt_2$, *cis*-**8** was obtained with excellent (16:1) diastereoselectivity and yield (94% combined yield). Based upon this observation, Ph_3SiH was selected as the reducing agent for further studies (Scheme 3).

In order to support our assignment of the *cis*-relationship of the substituents at C2 and C5, **6** was converted to **9** by reaction with $BF_3{\cdot}OEt_2$ under an atmosphere of hydrogen in the presence of Pd/C, a procedure reported to give *cis*-2,5-disubstituted prolines.[5c] Catalytic hydrogenation of *cis*-**8** also gave **9**.

Satisfied with the efficiency of the cyclization/reduction step, we turned to improving the yield in the first step of the sequence. The isolation of significant amounts of **3** from the reaction of **4** with 3-butenyl magnesium bromide, suggested that competing attack of the Grignard reagent at the exocyclic carbonyl group of the imide was the major source of our difficulty. Hence, we examined



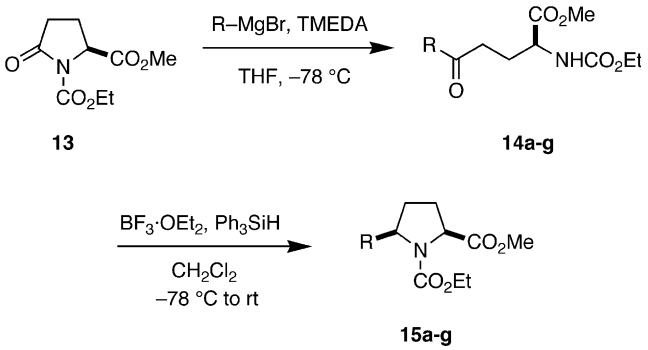
Scheme 3.

the imides **10a**–**c** as substrates in order to probe the consequences of increasing the steric bulk of the carbamate alkyl group. Whereas the efficiency and the regioselectivity in the addition of 3-butenyl magnesium bromide to **10a** was slightly worse than for **4**, additions to **10b** and **10c** proceeded cleanly to give **11b** and **11c** in 89–92% yield with only small amounts of **3** being formed (Scheme 4). The reduction/cyclization of **11b** then proceeded in 97% yield to give **12b**, but the Boc group was cleaved upon exposure of **11c** to these conditions.

While these experiments would seem to suggest that the isopropyloxy carbonyl group would be nicely suited for the preparation of *cis*-2,5-disubstituted prolines related to **12b**, we recognized that such a carbamate function could only be removed with difficulty under strongly acidic or basic conditions.[10] It was thus necessary to devise another tactic to increase the regioselectivity in the additions of organometallic reagents to pyroglutamic acid derivatives bearing more readily removable carbamate protecting groups.

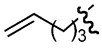
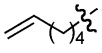
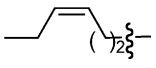
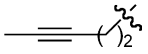
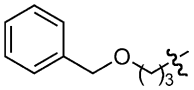
Reactions of organometallic reagents with electrophiles may often be altered by using different solvents or coordinating additives such as HMPA or amines.[11] Inasmuch as the three carbonyl groups have inherently different reactivities and Lewis basicities, we examined the effects of additives on the selectivity of the reactions of **4**, **10a**, and the corresponding ethyl carbamate **13** with 3-butenyl magnesium bromide. We thus discovered that the presence of TMEDA had a significant influence upon the efficiency and the regioselectivity of the reaction. Based upon these results, we selected **13** as the starting material for preparing a series of *cis*-2,5-disubstituted pyrrolidines as summarized in Scheme 5 and Table 1.[12,13] Use of Et_3SiH as the terminal reductant in the second step of the sequence invariably gave poorer (ca. 1.1–3.5:1) *cis*/*trans* ratios.[14]

As is evident from examination of the results in Table 1, the conversion of **13** to the pyrrolidines **15a**–**g** proceeded in very good overall yields and with high diastereoselectivity. The transformation appears reasonably general, although when the double bond in the side chain is so positioned relative to the carbon atom in the intermediate



Scheme 5.

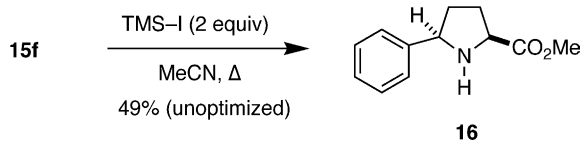
Table 1. Synthesis of *cis*-2,5-disubstituted pyrrolidines

Entry	R	Yield (%) **14**	Yield (%) **15**[a]	*cis*/*trans*[13]
a		83	99	17:1
b		75	83[b]	16:1[c]
c		80	99	23:1
d		79	95	23:1
e		62	94	8:1
f		71	99	>30:1[d]
g		72	96	11:1

[a] Yield is combined yield of *cis*- and *trans*-isomers.
[b] Two equivalents of Ph_3SiH were used.
[c] Mixture containing *cis*- and *trans*-pyrrolidines (ca. 80%) and spirocyclic isomers of undetermined structure.
[d] The *trans*-isomer was not observed by GLC.

N-acyl iminium ion, spirocyclization may be a competing side reaction (entry **b**).[15] Use of 2 equiv of Ph_3SiH was found to minimize this undesired process, but it could not be completely suppressed, even by using 6 equiv of Ph_3SiH. The geometry of *Z*-olefins is maintained (entry **d**). Triple bonds (entry **e**) and benzyl ethers (entry **g**) are also compatible with the reaction conditions.

While this methodology was specifically designed for preparing *cis*-2,5-disubstituted pyrrolidines having unsaturated side chains, other *cis*-2,5-disubstituted pyrrolidines are important intermediates for the synthesis of biologically active compounds. For example, compound **15f** was converted into **16**, a critical subunit of the potent, nonpeptide CCK antagonist (+)-RP-66803,[16,17] by selective *N*-deprotection using trimethylsilyliodide (Scheme 6). This is the most concise synthesis of **16** to date.



Scheme 6.

In summary, we have developed a useful protocol for the stereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines bearing unsaturated side chains. The utility of this methodology has recently been demonstrated by its application to a concise enantioselective synthesis of (+)-anatoxin-a.[18] Other applications of this useful transformation are being investigated and will be reported in due course.

Acknowledgements

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8. All new compounds were purified (>95%) by flash chromatography and were characterized by ^1H and ^{13}C NMR, IR, and HRMS.

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12. General Procedure. A solution of the appropriate Grignard reagent R–MgBr (10.0 mmol) was first prepared in THF. An equivalent of TMEDA (10.0 mmol) was added, the concentration of R–MgBr/TMEDA was adjusted to 0.5 M by adding anhydrous THF, and the resultant mixture was stirred for 30 min at room temperature. A portion of the solution of R–MgBr/TMEDA (6 mL, 3 mmol) was added dropwise to a solution of **13** (430 mg, 2.0 mmol) in anhydrous THF (5 mL) at −78 °C. The solution was stirred for 30 min at −78 °C, whereupon *i*PrOH (1 mL) and saturated aqueous NH_4Cl (1 mL) were added. The dry ice/acetone bath was removed, and the mixture was stirred 1 h. The reaction mixture was then partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to afford **14a**–**g**. $BF_3{\cdot}OEt_2$ (1.1 mmol) was added to a solution of **14a**–**g** (1.0 mmol) and triphenylsilane (1.1 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C. The solution was stirred for 15 min at −78 °C, whereupon the dry ice/acetone bath was removed and stirring continued for 1 h (6 h for **15f**). Aqueous 1 N NaOH (1 mL) was added, and then the mixture was partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to afford **15a**–**g**.
13. Ratios were determined by gas chromatographic analyses using a Hewlett Packard 5890 Series II gas chromatograph fitted with an Alltech EC-5 (30 m×0.25 mm ID×0.25 μm) column; **15a**,**g** (isothermal, 150 °C), **15b**–**f** (temperature gradient, 130–250 °C at 2 °C/min).
14. Et_3SiH has been reported to give higher *cis*/*trans*-ratios than Ph_3SiH in a related reduction, see: van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Rutjes, F. P. J. T. *Synlett* **2003**, 2354–2358.
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17. ^1H and ^{13}C NMR data for **16** were consistent with those reported; $[\alpha]_D^{26}$ +24.9 (*c* 0.9, CH_2Cl_2). Values for $[\alpha]_D^{20}$ ranging from +11 to +18.4 have been reported in the literature. See Ref. 16b,c,d.
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