Synthesis of Chiral Bicyclic Lactams Using Ring Closure Metathesis: Synthesis of (-)-Coniceine and (*S*)-Pyrrolam A

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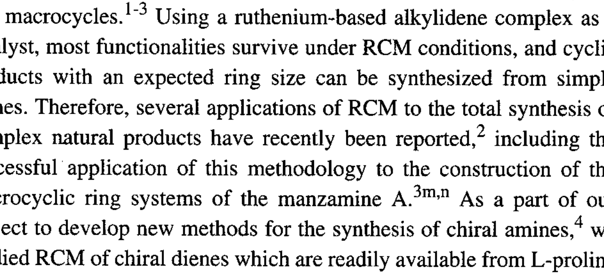
Abstract: Chiral (-)-coniceine and (*S*)-pyrrolam A were synthesized from dienes prepared from L-proline by ring closure metathesis.

Ring closure metathesis (RCM) has recently become a powerful method for the synthesis of cyclic molecules, such as carbocycles, heterocycles and macrocycles.[1-3] Using a ruthenium-based alkylidene complex as a catalyst, most functionalities survive under RCM conditions, and cyclic products with an expected ring size can be synthesized from simple dienes. Therefore, several applications of RCM to the total synthesis of complex natural products have recently been reported,[2] including the successful application of this methodology to the construction of the macrocyclic ring systems of the manzamine A.[3m,n] As a part of our project to develop new methods for the synthesis of chiral amines,[4] we studied RCM of chiral dienes which are readily available from L-proline (Scheme 1). We report here a simple method for the preparation of chiral 1,2-cyclopenteno-, 1,2-cyclohexeno- and 1,2-cyclohepteno-pyrrolidines (**2**-**4**, R_3=H).[5]



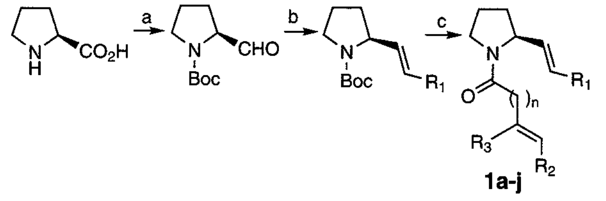
Scheme 1

Methyl *N*-Boc-*L*-prolinate was converted to the aldehyde by reduction with DIBAH (Scheme 2). Wittig olefination followed by deprotection gave 2-ethenyl-, 2-(2-methoxycarbonyl)ethenyl-, 2-(1-propenyl)-, and 2-(2-phenyl)ethenylpyrrolidine. Acylation of these pyrrolidine derivatives with unsaturated acids in the presence of diethyl phosphorocyanidate gave chiral dienes (**1a**-**j**, Table 1).

Table 1. Acylation of Pyrrolidines

diene	R_1	R_2	R_3	n	yield, %
1a	H	H	H	0	80
1b	H	CH_3	H	0	82
1c	H	H	CH_3	0	82
1d	H	H	H	1	73
1e	H	H	H	2	87
1f	CO_2CH_3	H	H	2	66
1g	CH_3	H	H	2	90
1h	Ph	H	H	2	83
1i	H	H	H	3	85
1j	H	H	H	4	100

When a solution of **1d** (0.3 mmol), which was expected to give a six-membered ring, in degassed benzene (10 mL) was stirred for 2.6 days at room temperature in the presence of 5 mol% of ruthenium carbene complex **7**,[6] a cyclized product, cyclohexenopyrrolidine **3**, was isolated in 68% yield along with 31% of recovered **1d**. (Table 2, run 1). A longer reaction period in the presence of 10 mol% of the catalyst gave a better result, and **3** was obtained in 77% yield (run 2). Cyclization using 2.9 mmol of **1d** proceeded efficiently in the presence of 5 mol% of **7**, and **3** was obtained in a yield of 93% (run 3).



Scheme 2

a) i. NaOH, $(Boc)_2O$, dioxane (79%), ii. K_2CO_3, CH_3I, DMF (93%), iii. DIBAH, toluene, -78 °C (91%); b) $KN(TMS)_2$, Ph_3PCH_2RBr, THF (R_1=H: 73%, R_1=CO_2CH_3: 80%, R_1=CH_3: 70%, R_1=Ph: 67%); c) i. 10% HCl-MeOH, ii. $HOOC(CH_2)_nC(R_3)$=CHR_2, diethyl phosphorocyanidate, Et_3N, see Table 1.

Table 2. Ring Closure Metathesis of 1d-j

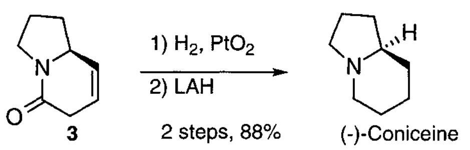
run	diene (mmol)	catalyst (mol %)	temp. (°C)	time (h)	product	yield %	recovery of **1**, %
1	**1d** (0.3)	**7** (5)	rt	62	**3**	68	31
2	**1d** (0.3)	**7** (10)	rt	444	**3**	77	17
3	**1d** (2.9)	**7** (5)	rt	72	**3**	93	
4	**1d** (1.8)	**8** (5)	rt	18	**3**	66	5
5	**1e** (0.3)	**7** (5)	rt	15	**4**	29	58
6	**1e** (0.3)	**7** (5)	rt	276	**4**	58	31
7	**1e** (0.3)	**7** (10)	rt	552	**4**	91	
8	**1e** (0.3)	**7** (2)	rt - 50	15	**4**	11	46
9	**1e** (0.3)	**7** (2)	80	7	**4**	0	
10	**1e** (0.3)	**8** (5)	rt	92	**4**	73	
11	**1f** (0.3)	**7** (5)	rt	15	**4**	0	83
12	**1g** (0.3)	**7** (5)	rt	15	**4**	0	51
13	**1h** (0.3)	**7** (5)	rt	15	**4**	0	76
14	**1i** (0.3)	**7** (5)	rt	15	**5**	0	86
15	**1j** (0.3)	**7** (5)	rt	15	**6**	0	58

Commercially available catalyst **8**[6] was also effective for this cyclization, and a comparable yield of **3** was obtained in a shorter reaction period (run 4).

A seven-membered ring was also formed using **1e**. When **1e** was treated with 5 mol% of **7** for 15 h, **4** was isolated in a yield of 29% and 58% of **1e** was recovered (run 5). A longer reaction period improved the yield (58% yield, run 6). The best result (91% yield) was obtained when stirring was continued for 23 days in the presence of 10 mol% of **7** (run 7). The yield of the product decreased (rt - 50 °C) or the reaction stopped (80 °C) at an elevated temperature, provably due to decomposition of the catalyst (runs 8 and 9). Using catalyst **8**, cyclization proceeded faster and **4** was obtained in 73% yield (run 10).

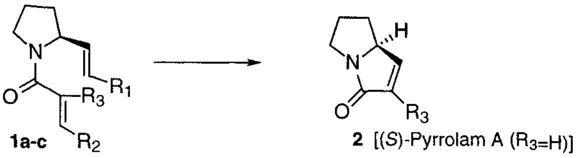
The reactions of **1f**-**h** were carried out to test the substitution effect at R_1. However, none of these substrates gave the corresponding cyclized product (runs 11-13). Attempts for the synthesis of eight- and nine-membered rings were also unsuccessful (runs 14 and 15).

Product **3** was converted to (-)-coniceine[7] $[[\alpha]_D^{25}$ -20.5° (*c* 0.98, EtOH); lit. $[\alpha]_D^{23}$ -10.2±0.6° (*c* 1.76, EtOH)[7c]], the simplest indolizidine alkaloid, by an easy two-step conversion, as shown in eq 1.



(1)

Table 3. Ring Closure Metathesis of 1a-c



run	diene (mmol)	catalyst (mol %)	temp. (°C)	time (h)	product	yield %	recovery of **1**, %
1	**1a** (0.3)	**7** (5)	rt	15	**2**	0	73
2	**1a** (0.3)	**7** (10)	rt	326	**2**	0	45
3	**1b** (2.9)	**7** (10)	rt	425	**2**	0	71
4	**1c** (0.3)	**7** (5)	rt	15	**2** (R_3=CH_3)	0	37
5	**1b** (0.3)	**7** (5)	50	20	**2**	29	64
6	**1b** (0.3)	**8** (5)	rt	190	**2**	0	79
7	**1b** (1.7)	**8** (5)	50	3	**2**	30	48

We next focused our attention on the cyclization of **1a**, since this reaction should directly give (*S*)-pyrrolam A (**2**).[8] We first examined the reaction using the conditions described above. However, the reaction did not proceed even with 10 mol% of **7** (Table 3, runs 1 and 2). Since the formation of a stable chelate by the catalyst and the amide moiety may explain the failure of this cyclization,[1a] the reactions of the methyl-substituted **1b** and **1c** were attempted (runs 3 and 4). However, we could not isolate any of the cyclized product. On the other hand, when **1b** was treated with **7** for 20 h at 50°C, we could isolate (*S*)-pyrrolam A [$[\alpha]_D^{21}$ +26.2° (*c* 0.97, $CHCl_3$); lit. (*R*)-pyrrolam: $[\alpha]_D^{20}$ -29.3° (*c* 1.00, $CHCl_3$)[8a]] in 29% yield (run 5). Cyclization in the presence of **8** also proceeded at 50°C, similar to that using **7** (run 7). The structure of (*S*)-pyrrolam A was confirmed by a comparison of NMR spectral data, which were kindly provided by Professor Ohta.[8b]

In conclusion, we have demonstrated here an efficient synthesis of chiral bicyclic lactams, including (*S*)-pyrrolam A, from L-proline using ring closure metathesis. Cyclization was influenced by the size of the ring and the substituents of the alkene. The low yield observed in the formation of a five-membered ring appeared to be due to the instability of the product under these reaction conditions. The extension of these results to the synthesis of other heterocycles and manzamine A is in progress.

Acknowledgment

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