Direct Synthesis of Medium-Bridged Twisted Amides via a Transannular Cyclization Strategy
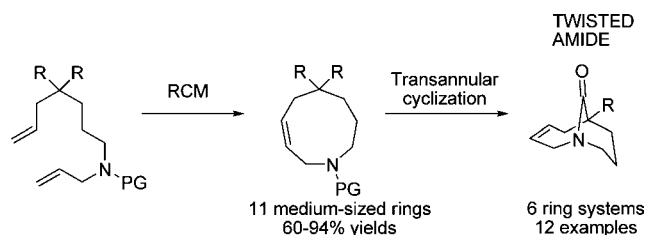
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ABSTRACT

The sequential RCM to construct a challenging medium-sized ring followed by a transannular cyclization across a medium-sized ring delivers previously unattainable twisted amides from simple acyclic precursors.

Many lactams incorporating nitrogen at a bridgehead position contain nonplanar or "twisted" amides.[1] Due to limited overlap of the nitrogen lone pair of electrons with the π-system of the carbonyl group, such compounds are extremely sensitive to hydrolysis and display other kinds of reactivity that are sharply divergent from that of standard lactams.[2] Moreover, since a fully twisted amide represents the transition state of the cis–trans amide bond isomerization essential in protein folding,[3] it has been suggested that compounds that contain nonplanar amides could be useful

as inhibitors of proline isomerases.[4] However, due to inherent strain and the enhanced lability to water, twisted amides have not fulfilled their promise as biological tools.

The vast majority of bridged amides place the carbonyl group on a bridge containing two or more carbons (Figure 1a). Although less common, we have recently shown that
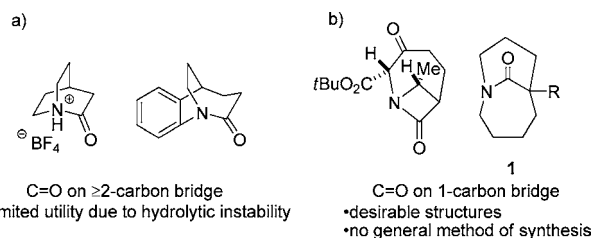
Figure 1. Some twisted amides (a) with the C=O bond placed on a 2- or 3-carbon[7] or (b) on a 1-carbon bridge.[8]

one-carbon bridged twisted amides **1** (Figure 1b) are substantially more persistent in aqueous solutions.[5] This
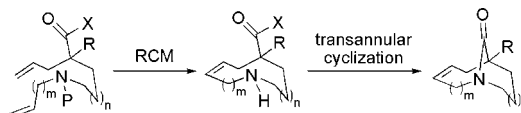
(1) For reviews, see: (a) Hall, H. K.; Elshekeil, A. *Chem. Rev.* **1983**, *83*, 549. (b) Greenberg, A., In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Ed.; Wiley-Interscience: New York, 2000; p 47. (c) Clayden, J.; Moran, W. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7118.

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arises from the relatively relaxed ring sizes present in **1** and the fact that the ring-opened amino acid corresponding to this structure is destabilized by transannular interactions. However, the amide bond in **1** is substantially distorted from planarity and the lactam displays reactivity that belies this nature.[6]

In general, existing synthetic approaches to one-carbon bridged twisted amides are limited to particular structural types[9] and do not allow for synthesis of larger number of diverse analogues.[10] There is no general method of synthesis of one-carbon bridged twisted amides. The observation that lactams **1** can reform in water once hydrolyzed, plus the rich history of transannular cyclizations in synthesis[11] (including limited precedent from the twisted amide chemistry),[12] suggested that such ring systems might be accessible using a direct cyclization approach. Although only limited precedent supported the synthesis of medium-ring nitrogen-containing heterocycles with appropriately placed amine and carboxylic acid derivative functionalities,[13] we believed that, if successful, RCM would allow for rapid construction of diverse precursors to the key cyclization.[14] Herein, we report the realization of these ideas to provide a highly general

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(9) For previous examples of one-carbon medium-bridged amides, see: (a) Refs 5 and 8. (b) Arata, Y.; Kobayashi, T. *Chem. Pharm. Bull.* **1972**, *20*, 325. (c) Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3747.

(10) Failed approaches to one-carbon bridged twisted amides include a variety of strategies. Amide coupling reactions: (a) Ref 9c. Intramolecular S$_N$2 displacement: (b) Smissman, E. E.; Wirth, P. J.; Abernethy, D.; Ayres, J. W. *J. Org. Chem.* **1972**, *37*, 3486. (c) Smissman, E. E.; Ayres, J. W. *J. Org. Chem.* **1971**, *36*, 2407. (d) Smissman, E. E.; Robinson, R. A.; Matuszak, A. J. *J. Org. Chem.* **1970**, *35*, 3823. (e) Brouillette, W. J.; Friedrich, J. D.; Muccio, D. D. *J. Org. Chem.* **1984**, *49*, 3227. Selenium-mediated electrophilic cyclization: (f) Toshimitsu, A.; Terao, K.; Uemura, S. *Tetrahedron Lett.* **1984**, *25*, 5917. (g) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018. Claisen condensation: (h) Smissman, E. E.; Wirth, P. J.; Glynn, D. R. *J. Org. Chem.* **1975**, *40*, 281. Direct RCM: (i) Doodeman, R. University of Amsterdam, 2002. (j) Preston, A. J.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2006**, *71*, 6573. (k) Lei, Y. University of Kansas, 2006 (bond isomerization was observed rather than formation of strained twisted amides). [2 + 2] cycloaddition: (l) Booker-Milburn, K. I.; Anson, C. E.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, *8*, 1473. Oxidative coupling: (m) Szostak, M.; Aubé, J. Unpublished results.

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solution to the problem of one-carbon bridged twisted amide synthesis (Scheme 1).

Scheme 1. RCM/Cyclization Strategy

Our initial investigations focused on the preparation of the [4.3.1] bicyclic ring system previously studied in this laboratory.[5,6,8b] Thus, malonate **2a** was prepared and subjected to range of RCM conditions. After extensive experimentation, it was found that Hoveyda–Grubbs 2 catalyst[15]

Table 1. Optimization of RCM

entry	diene (P)	catalyst	mol (%)	T (°C)	time (h)	yield[a] (%)
1	Ts (**2a**)	G1	100	40	26	87
2	Ts (**2a**)	Fürstner	50	24	25	54
3	Ts (**2a**)	Fürstner	20	40	22	41
4	Ts (**2a**)	G2	50	40	21	43
5	Ts (**2a**)	G2	20	80	21	76
6	Ts (**2a**)	G2	5	80	21	72
7	Ts (**2a**)	G2[c]	5	80	21	69
8	Ts (**2a**)	HG2	5	80	21	81
9	Ts (**2a**)	HG2[d]	5	80	8	87[b]
10	Ts (**2a**)	HG2[e]	5	80	8	95[b]
11	Ns (**2b**)	HG2[d]	5	80	16	93[b]
12	Boc (**2c**)	HG2[d]	5	80	17	85[b]
13	Cbz (**2d**)	HG2[e]	5	80	8	89[b]

[a] Determined by ^{1}H NMR. [b] Isolated yields. [c] With Ti(O-i-Pr)$_4$. [d] Argon bubbled through the reaction. [e] Open to air. G1 = Grubbs catalyst 1, G2 = Grubbs catalyst 2, Fürstner = Fürstner catalyst, HG2 = Hoveyda–Grubbs catalyst 2. RCM = ring-closing metathesis. Ns = 2-nitrobenzenesulfonyl. Cbz = carbobenzyloxy.

most effectively led to the 9-membered heterocycle **3a** (Table 1). Use of these conditions allowed synthesis of a series of analogues containing various amine substitutions, including

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(15) For a review, see: (a) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8. For recent examples of the use of Hoveyda–Grubbs catalysts in demanding RCM reactions, see: (b) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904. (c) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250.

readily removable carbamate groups (Table 1, entries 12 and 13).[16]

We now wished to determine whether the desired lactams could be obtained via direct cyclization of the substrates. Previously, we had determined that some bicyclic amino acids analogous to **3** were in equilibrium with their closed forms (even in water) but that the hydrolysis reactions were irreversible if the medium-sized ring adopted a conformation with the carboxylic acid in an exo position. In the present cases, we controlled this through the use of *gem*-diester substitution. In the event, deprotection and cyclization of the Ns precursor could be carried out in a single operation to deliver **4b** under very mild conditions (Scheme 2). Although

Scheme 2. Synthesis of [4.3.1] Lactam
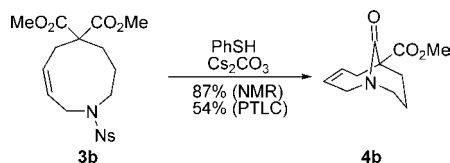
this material showed modest sensitivity to flash chromatography, it could be isolated in ca. 50% yield after PTLC.

We have also determined that the Boc precursor **3c** could be utilized for preparation of twisted amides (Scheme 3, top).

Scheme 3. Synthesis from Orthogonally Protected Systems
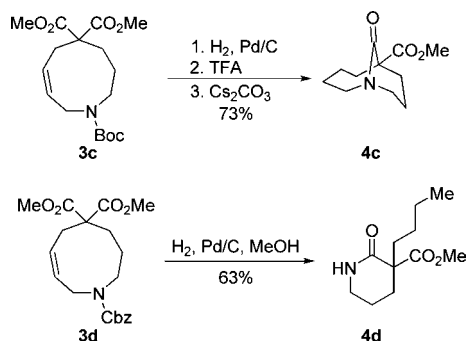
In contrast, the use of Cbz derivatives could be problematic. Deprotection and cyclization of **3d** (Scheme 3, bottom) proceeded smoothly, but the twisted amide proved to be unstable to the hydrogenation conditions, giving piperidone **4d** by C—N ring cleavage.[6]

The sequential RCM/transannular cyclization strategy was extended to a series of dienes, thus providing a systematic series of twisted lactam ring systems (Table 2). In general, the RCM reactions proceeded in very good yields. All of

Table 2. Synthesis of Bridged Lactams

entry	series (n, m)	R	ring system	yields, steps 1/2 (%)	notes
1	**e** (1, 1)	CO_2Me	[4.2.1]	90/75	
2	**f** (1, 2)	CO_2Me	[5.2.1]	94/85	a
3	**g** (2, 2)	CO_2Me	[5.3.1]	90/64	b, c
4	**h** (1, 3)	CO_2Me	[6.2.1]	92/41	d
5	**i** (3, 1)	CO_2Me	[4.4.1]	79/0	
6	**j** (3, 1)	Ph	[4.4.1]	76/33	e
7	**j** (3, 1)	Ph[f]	[4.4.1]	60/86	g

a Step 2 run for 13 h. *b* Compound **3g** obtained as 5:1 mixture of *Z/E* isomers. *c* Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 200 °C, 3 h. *d* Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 180 °C, 12 h. *e* Step 2: (i) PhSH, Cs_2CO_3; (ii) DBU, PhMe, 220 °C, 10 h. *f* PhO_2C instead of MeO_2C. *g* Step 2 run at 110 °C for 16 h.
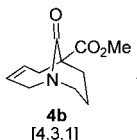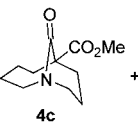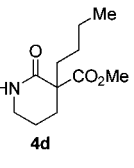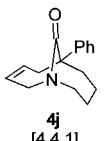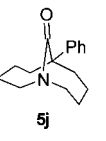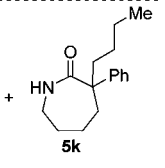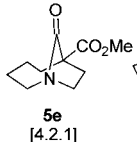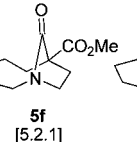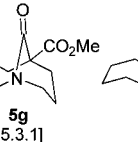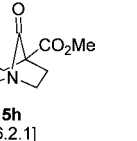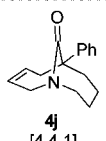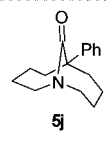
the medium-sized rings save one (entry 3) were obtained as exclusive cis double bond isomers. This study provides very rare examples of the successful use of catalytic RCM in the formation of 9- and 10-membered nitrogen-containing ring systems with minimal conformational constraints.[17] Furthermore, the cyclization of the medium ring amino diesters to bridged lactams proved gratifyingly general. Although the cyclization of compound **3g** proved sluggish under our initially identified conditions, the [5.3.1] twisted amide could be generated by treatment with DBU after deprotection (entry 3). While malonate could not be applied for preparation of the [4.4.1] system (entry 5) due to competing decarboxylation, use of the phenyl acetate (entry 6) allowed for preparation of the desired compound, albeit in a conservative yield. The experiment in entry 7 was performed to explore the effect of leaving group on cyclization reaction. Replacing methoxide with phenoxide dramatically improved the yield of the transannular cyclization, delivering lactam **4j** in 86% yield.

Several methods to prepare saturated lactams were also investigated (Table 3). This normally straightforward process was complicated by the tendency of some twisted amides to undergo unusual C—N cleavage reaction under mild hydrogenolysis conditions.[6] Thus, when twisted amides prepared in the current study were treated with standard hydrogenolysis conditions, [4.3.1] and [4.4.1] scaffolds showed the highest reactivity, participating in C—N cleavage to the corresponding monocyclic amides (Table 3; entries 1 and 2), while [4.2.1], [5.2.1], [5.3.1], and [6.2.1] twisted amides were less reactive, undergoing only traditional reduction to

(16) For selected examples of RCM reactions influenced by the presence of carbamate or ester functionalities, see: (a) Campagne, J. M.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 6175. (b) Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662. (c) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(17) For selected examples of RCM reactions in the formation of 9- and 10-membered nitrogen-containing ring systems, see: (a) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, *3*, 345. (b) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.—Eur. J.* **2001**, *7*, 4811. (c) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M. I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538.

Table 3. Hydrogenation/Hydrogenolysis of Bicyclic Lactams

 a Only products of hydrogenation of corresponding unsaturated lactams **4e−h** shown.

Table 4. Spectroscopic Properties of Saturated Lactams

entry	lactam	ring system	lactam C=O ^{13}C (ppm)	lactam IR νC=O (cm^{-1})
1	**5e**	[4.2.1]	183.4	1716
2	**5f**	[5.2.1]	180.1	1693
3	**5h**	[6.2.1]	173.4	1685
4	**4c**	[4.3.1]	181.0	1679
5	**5g**	[5.3.1]	176.6	1647
6	**5j**	[4.4.1]	186.3	1643

the saturated analogues (entry 3; only products shown). As expected, allylic olefins are more susceptible to hydrogenolysis than isolated bonds. Interestingly, when hydrogenation of [4.4.1] scaffold was carried out in the presence of Willkinson's catalyst, the amide bond remained intact and the saturated amide was obtained in high yield (entry 4).

One goal of the present project is to obtain a series of varied ring systems to allow systematic exploration of the effect of amide twist on chemical and spectroscopic properties. For example, nonplanar amides often display spectral features consistent with less "amide-like" and greater "ketone-like" nature of the carbonyl group.[18] Although the medium-bridged lactams prepared herein do not contain perfectly orthogonal $N_{lone\ pair}$−carbonyl groupings, most of the ring systems prepared here show substantially higher ^{13}C chemical shifts for the carbonyl carbon and higher carbonyl stretches in the infrared spectra, consistent with a substantial degree

of twist (Table 4). As expected, several of the ring systems containing larger rings are able to relax into values closer to those of analogous fused lactams (entries 3 and 5). We note that the infrared stretching frequencies cover a range that begins at that for a "normal" amide (entry 6) and go all the way to a value that would be expected for a saturated, "normal" ketone (entry 1). This bodes well for the use of this suite of compounds for the systematic evaluation of the effect of amide bond geometry on reactivity. Interestingly, there is not a perfect correlation between IR stretching frequencies and ^{13}C NMR carbonyl chemical shifts (also noted by Yamada[18]), suggesting that subtle electronic effects beyond bond angle likely effect these parameters.

In summary, a sequential RCM/transannular cyclization strategy has been developed that provides access to an expanded family of one-carbon bridged lactams. This route highlights the rapid assembly of previously inaccessible, functionalized ring systems from readily available starting materials. The mild conditions for the transannular cyclization allow for isolation of strained amides by a route similar to classical amide bond formation but facilitated by close proximity of the reactive functionalities. Work is currently underway on further development of this methodology and its application to the synthesis of a whole gamut of twisted amides. As already exemplified by hydrogenolysis reactions, this in turn will allow for the systematic study of strain influence on chemical and biological properties of amide bonds.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901449Y

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