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Concise Construction of Novel Bridged Bicyclic Lactams by Sequenced Ugi/RCM/Heck Reactions

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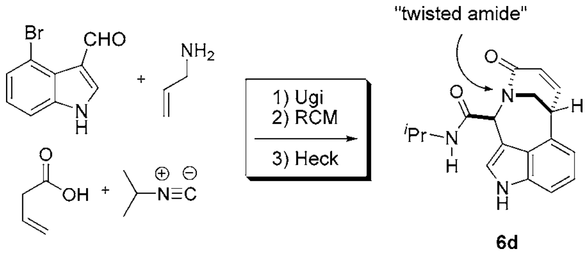
ABSTRACT



6d

Herein we report a concise protocol for the diastereoselective synthesis of novel bridged bicyclic lactams from commercially available components by the sequence of Ugi, ring-closing metathesis (RCM), and Heck reactions. X-ray diffraction studies revealed that the bicyclic products contain varying degrees of pyramidalization of the bridgehead nitrogen atom.

The tactic of combining a multicomponent reaction (MCR)[1] with a postcondensation reaction to prepare diverse arrays of structures with calculated lead- and drug-like properties has received considerable attention.[2] Indeed, we have recently reported several protocols that provide unique molecular scaffolds after a single post-Ugi transformation.[3] However, the strategy of scaffold synthesis by an MCR followed by two sequential postcondensation modifications remains relatively unexploited.[4] As a continuation of our ongoing studies, we became interested in the potential of an Ugi/ring-closing metathesis (RCM)/Heck reaction sequence as a method to rapidly construct complex molecular architectures. A recent disclosure by Martin and co-workers, which details a related post-MCR sequence, has prompted us to report our initial findings in this area.[5]

As shown for an archetypal example in Scheme 1, Ugi four-component coupling followed by ring-closing metathesis was envisaged to provide the unsaturated lactam **2**. Subsequent intramolecular Heck reaction of **2** would form bicyclic **3** with concomitant relay of the alkene to an activated position, which would conceivably enable facile incorporation of a fifth element of diversity by conjugate addition. Notably, the reaction sequence would provide a series of

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(1) For a recent review, see: Doemling, A. *Chem. Rev.* **2006**, *106*, 17−89.

(2) (a) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963−4968. (b) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227−7230. (c) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149−1152. (d) Short, K. M.; Ching, B. W.; Mjalle, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 7489−7492. (e) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987−5990.

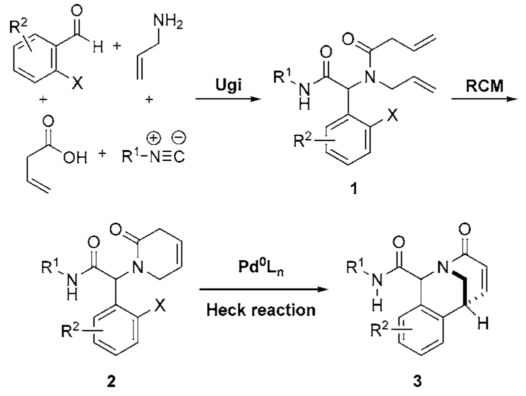
(3) (a) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299−1302. (b) Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417−420. (c) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421−3423. (d) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439−8441.

(4) (a) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Doemling, A. *Org. Lett.* **2003**, *5*, 1047−1050. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830−8837. (c) El Kaim, L.; Gizolme, M.; Grimaud, L. *Synlett* **2007**, 227−23.

(5) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223−4226.

10.1021/ol7023373 CCC: $37.00

Scheme 1. A Proposed Ugi/RCM/Heck Sequence to Give Bridged Bicyclic Lactams

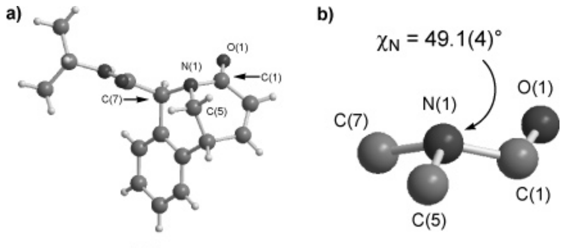


bridged bicyclic lactams, a class of compounds of extensive theoretical interest for their propensity to display nonplanar deformations of the amide bond. For example, the structure and reactivity of such “twisted amides”[6] may provide insight into the processes of “ground-state destabilization” suggested to occur during enzymatic hydrolysis of peptides.[7] Herein we wish to report the development of a library-amenable Ugi/RCM/Heck sequence that yields several novel bridged bicyclic lactams in high diastereoselectivity and good yield in three steps from commercially available starting materials.

As summarized in Table 1, our studies commenced with an Ugi reaction of commercially available components to give the β,γ-unsaturated amide **4a** in 84% yield. RCM of the diene proceeded without event in CH_2Cl_2 at rt after the addition of a single aliquot of the Grubbs second generation metathesis initiator (**G-2**). In our initial attempt of the key intramolecular Heck reaction, we were pleased to find that cyclization to give the [3.3.1] bicyclic system **6a** occurred with very high diastereoselectivity and good yield under microwave conditions with a soluble catalyst (see Table 1, entry 1).

Encouraged by this preliminary result, we sought to develop a protocol more suitable for automated synthesis. To this end, we assayed the utility of FibreCat 1032 and polystyrene-bound $Pd(Ph_3P)_4$ in the microwave-heated Heck reaction (see Table 1). These immobilized palladium catalysts mediated reactions with diastereoselectivities equal to that of the homogeneous system. However, compared to PS−$Pd(Ph_3P)_4$, the FibreCat 1032 resin consistently rendered cleaner reactions (as determined by ^1H NMR spectra of the crude reaction mixtures) that provided products in higher yield. In all respects, the FibreCat 1032-catalyzed protocol was equal to that of the $Pd(Ph_3P)_2Cl_2$ system, yet it provided the added benefit of an automation-compatible workup that consisted of a simple filtration and concentration.

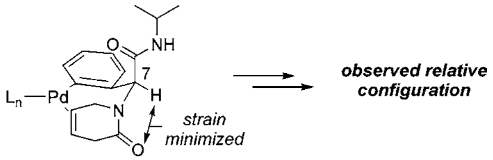
X-ray diffraction studies confirmed the relative configuration of the adduct **6a** (see Figure 1a). Hence, we speculate that diminution of the pseudo-$A^{1,3}$ strain in the palladium complex **7** (see Scheme 2), which forces the C(7) amide side chain into a pseudoaxial position on the *exo* face of the bicyclic system, may contribute to the diastereoselection process.[8]



6a

Figure 1. (a) A ball-and-stick depiction of the X-ray structure determined for **6a**. (b) Pyramidalization of the bridgehead nitrogen in **6a**.

Scheme 2. Diastereoselective Ring Closure



7

Close inspection of the X-ray structure of **6a** revealed notable deformation of the bridgehead amide moiety. In fact, the measured distortion parameter[9] $\chi_N = 49.1(2)°$ of the bridgehead nitrogen atom indicated extensive pyramidalization, approaching that of an sp^3 atom[10] (see Figure 1b). Twisted amides often display enhanced reactivity at the carbonyl group. For example, hydrolysis of the distorted amide bond in 1-aza-2-adamantanone occurs readily in water in the presence of 0.5 equiv of HCl,[5g] and 2-quinuclidonium tetrafluoroborate hydrolyzes in pure water with a half-life of less than 15 s.[5b] In this context, it is interesting to note that **6a** is unreactive in acidic aqueous media to a pH of ∼2 but is consumed at pH ∼1 (and at pH ∼9 and above).

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[6] For a review of twisted amides, see: (a) Greenberg, A. *Mol. Struct. Energ.* **1988**, *7*, 139−178. For recent reports of twisted amides, see: (a) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731−734. (b) Ly, T.; Krout, M.; Pham, D. K.; Kousuke, T.; Stoltz, B. M.; Julian, R. R. *J. Am. Chem. Soc.* **2007**, *129*, 1864−1865. (c) Yao, L.; Aube, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766−2767. (d) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268−3272. (e) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785−786. (f) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248−2260.

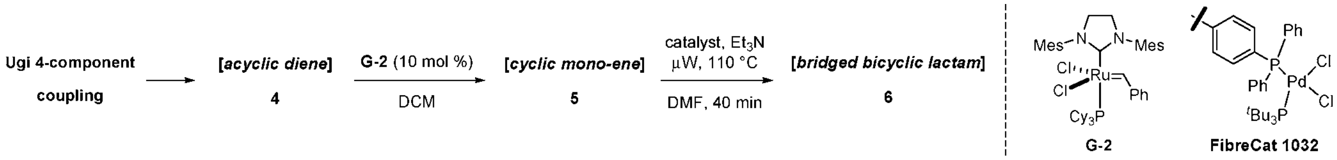
[7] (a) Bennet, A.; Somayaji, V.; Brown, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 7563−7571. (b) Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676−2686.

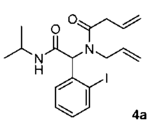
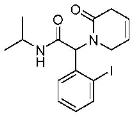
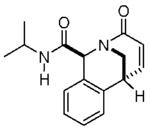
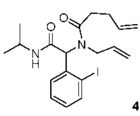
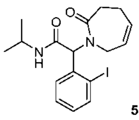
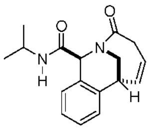
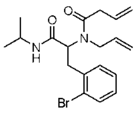
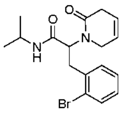
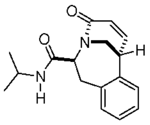
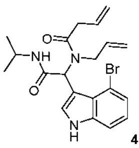
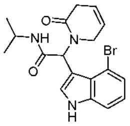
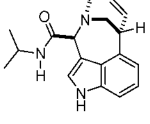
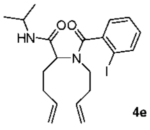
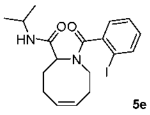
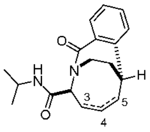
[8] (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499.

[9] Dunitz, J., D.; Winkler, F. K. *Acta Crystallogr.* **1975**, *B31*, 251−263.

[10] Note that for planar formamide $\chi_N = 0°$, while for a fully pyramidalized sp^3 atom $\chi = 60°$. See also: Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169−182.

Table 1. Sequential Ugi/RCM/Heck Reactions Yield Bridged Bicyclic Lactams Containing Twisted Amides



entry	Ugi Product (yield)[a]	RCM product (yield)[a]	Heck Product[b]	$Pd(Ph_3P)_2Cl_2$ Heck reaction[c] yield[a] (d.r.)[d]	FibreCat 1032 Heck reaction[c] yield[a] (d.r.)[d]	PS-$Pd(Ph_3P)_4$ Heck reaction[c] yield[a] (d.r.)[d]	χ_N for bridgehead *N* (**6a-6e**)
1	 **4a** (84%)	 **5a** (90%)	 **6a**	83% (>98:2)	85% (>98:2)	50% (>98:2)	49.1(4)°
2	 **4b** (36%)	 **5b** (96%)	 **6b**	91% (>98:2)	84% (>98:2)	--	35.3(1)°
3	 **4c** (60%)	 **5c** (95%)	 **6c**	72% (92:8)	62% (91:9)	--	26.2(3)°
4	 **4d** (73%)	 **5d** (94%)	 **6d**	86% (>98:2)	89% (94:6)	--	29.1(2)°[f] 31.1(2)°[f]
5	 **4e** (57%)	 **5e** (57%)	 **6e**: 4,5-alkenyl **6f**: 3,4-alkenyl	78% (95:5)[e]	84% (74:26)[e]	--	**6e**: 15.9(2)°

[a] Isolated yields after normal phase chromatography. [b] The relative configurations of the products **6a**–**e** were determined by X-ray crystallography (see Supporting Information). [c] 20 mol % of Pd was used in each case. The catalyst loadings for the resin-bound reagents FibreCat 1032 and PS–$Pd(PPh_3)_4$ were 0.45 and 0.07 mmol/g, respectively. [d] The dr was determined from the ^1H NMR (300 MHz) spectrum of the crude reaction mixture. An entry of >98:2 implies that a minor diastereomer could not be detected by this method. [e] The ratio refers to the proportion of the 4,5-alkene regioisomer **6e** to that of the 3,4-alkene isomer **6f**. [f] The pyramidalization angle[9,10] for each of **6a**–**e** was calculated from the single-crystal X-ray structure. Two crystallographically independent molecules were observed in the unit cell.

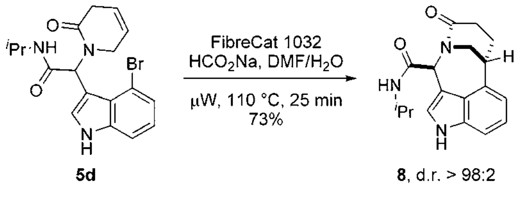
Satisfied with the three-step synthesis of the lactam **6a**, we briefly surveyed the generality of the synthetic protocol (see Table 1, entries 2–5). Further, we hoped to demonstrate the effect of bicyclic ring structure on the pyramidalization of the bridgehead nitrogen atom. In general, the Ugi and RCM reactions provided the dienes **4** and unsaturated lactams **5**, respectively, with good to excellent yields. Heck reaction of **5b** provided the homologous [4.3.1] bicyclic system **6b** as a single detectable diastereomer without isomerization to the α,β-unsaturated system. As shown in entry 3, the diastereoselectivity of a 7-exo-*trig*-type Heck cyclization was slightly eroded compared to the analogous 6-type (consider **5a** → **6a** vs **5c** → **6c**). However, 7-exo-*trig* closure of the more constrained indole **5d** proceeded with excellent selectivity to give the unique indole scaffold **6d**. Finally, in a more significant departure, a [4.3.2] bicycloundecane scaffold was synthesized according to Table 1, entry 5. The Heck cyclization was again highly diastereoselective, with cyclization occurring from the opposite face of the C(2) amido side chain. However, the reaction yielded a mixture of the alkene regioisomers **6e** and **6f**, presumably by palladium-hydride-mediated isomerization of the initial product **6e**. Interestingly, the FibreCat 1032 system showed a higher preponderance for the alkene regioisomer **6f** than the soluble $PdCl_2(Ph_3P)_2$ system. Albeit, in general, the FibreCat 1032-catalyzed Heck reactions were equally efficient and diastereoselective as their $Pd(Ph_3P)_2Cl_2$ counterparts across the systems surveyed in this work.

The crystalline bridged bicyclic lactams **6a**–**e** each afforded single crystals suitable for X-ray crystallographic structure determination. As shown in Table 1, entry 2, expansion of the six-membered α,β-unsaturated lactam in **6a** to the homologous seven-membered β,γ-unsaturated lactam **6b** resulted in attenuated deformation of the bridgehead amide bond as evidenced by the $\chi_N = 35.3(1)°$. Yet a more profound effect was observed on expanding the *N*-acylpiperidine moiety within **6a** to the *N*-acylazepane contained in **6c**. This structural modification resulted in the alleviation of half the amide distortion observed in the parent system **6a** (see Table 1, entry 3 vs entry 1). Crystals of the indole **6d** contained two crystallographically independent molecules in the unit cell. The measured χ_N's for each of the twins are in good agreement (29.1(2) and 31.1(2)°) and lend some insight into the effects of local environment on the bridgehead nitrogen pyramidalization. Finally, the [4.3.2] bicycloundecane scaffold **6e** embodied the least distorted amide of the series, having a measured $\chi_N = 15.9(2)°$.

With a series of related twisted amides of known N-pyramidalization in hand, we thought it instructive to test their relative reactivity to aqueous acid. Contrary to **6a**, **6b**−**d** were stable to incubation in 10% HCl in CH_3CN at ambient temperature. These data suggest that, in this system, the threshold amide deformation required for enhanced reactivity to aqueous acid is demarcated by a χ_N between 30 and 49°.

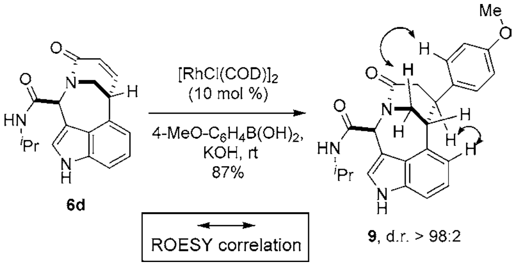
α,β-Unsaturated lactams are generally considered slowly reactive to biological nucleophiles (by hetero-Michael addition, for example). However, the potential for enhanced reactivity due to the twisted nature of the bridgehead amide in compounds such as **6a**,**c**,**d** gave reason to pursue reductive conditions for the final ring closure. After a brief optimization, we found that a reductive Heck transformation[11] could be imparted in good yield and with excellent diastereoselectivity under conditions suitable for automated synthesis. Thus, microwave heating of the lactam **5d** in the presence of FibreCat 1032 and 10 equiv of sodium formate gave the saturated bridged bicyclic lactam **8** as a single detectable diastereomer (see Scheme 3).

Scheme 3. Reductive Intramolecular Heck Reaction



Alternatively, the α,β-unsaturated lactam functionality in compounds such as **6a**,**c**,**d** provided a productive handle for diversification via Michael reaction. We focused our efforts on conditions that might be amenable to library synthesis and were pleased to find that rhodium-catalyzed cross couples of aryl boronic acids[12] could be induced under very mild conditions. For example, as shown in Scheme 4, the cross couple of 4-MeO-phenyl boronic acid occurred with complete diastereoselectivity from the *exo* face of the [4.3.1] bicyclic system of the indole **6d** at room temperature. The reaction is highly efficient, delivering 87% yield of **9** after automated reverse-phase purification of the sample.

Scheme 4. Diastereoselective Rh-Catalyzed Michael Addition



In conclusion, we have developed a concise and highly diastereoselective Ugi/RCM/Heck reaction sequence for the synthesis of novel bridged bicyclic lactams. The rigid and biased topology of the bicyclic systems enabled further diversification with complete diastereoselectivity. Finally, the bridged bicyclic lactam structures characterized in this study may be of theoretical interest as X-ray diffraction studies have shown they contain "twisted amides" of varying degree. With respect to this, the reactivity of the series **6a**−**d** to hydrolysis conditions is of particular interest, and detailed studies thereof will be reported in due course.

Acknowledgment. The authors would like to thank Dr. Paul R. West and Jan Waters of Abbott Laboratories for obtaining HR-MS and VT ^1H NMR spectra, respectively. T.P.R. is grateful to Abbott Laboratories for a summer internship.

Supporting Information Available: Experimental procedures, spectral data for new compounds, X-ray data for compounds **6a**−**e**, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] (a) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017−3020. (b) Larock, R., C.; Johnson, P., L. *J. Chem. Soc., Chem. Commun.* **1989**, 1368−1370.

[12] For a review, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196.