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An Enantioselective Synthetic Route to *cis*-2,4-Disubstituted and 2,4-Bridged Piperidines

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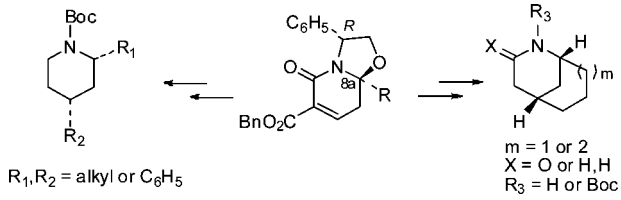
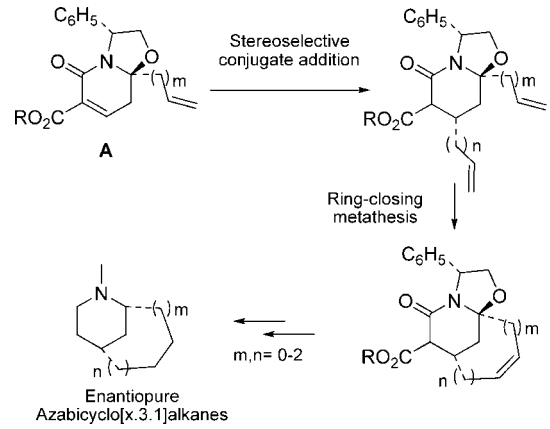


A synthetic route to enantiopure *cis*-2,4-disubstituted and 2,4-bridged piperidines is reported, the key step being a stereoselective conjugate addition of an organocuprate to a phenylglycinol-derived unsaturated lactam bearing a substituent at the 8a-position.

Aminoalcohol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds.[1] These lactams allow the substituents to be introduced at the different ring positions in a regio- and stereocontrolled manner, providing easy access to enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern.[2] In particular, the conjugate addition to α,β-unsaturated oxazolopiperidone lactams allows the stereocontrolled formation of a C−C bond at the piperidine 4-position and has successfully been used to generate either *cis* or *trans* 3,4-disubstituted enantiopure piperidine-containing

SCHEME 1. Synthetic Strategy



derivatives, including the antidepressant drug (−)-paroxetine,[3] *cis*-fused perhydrocycloalka[*c*]pyridines,[4] and the indole alkaloid (+)-uleine.[5]

To further expand the potential of these lactams, we decided to explore a synthetic route to enantiopure 2,4-bridged piperidine derivatives, as outlined in Scheme 1. The key step would be the stereocontrolled introduction of an appropriate unsaturated chain at the 4-position of the piperidine ring by conjugated addition of an organocuprate to an unsaturated lactam **A** bearing an unsaturated substituent at the 2-position. A subsequent ring-closing metathesis from the resulting *cis*-2,4-disubstituted piperidine derivative would lead to the target bridged azabicyclo.

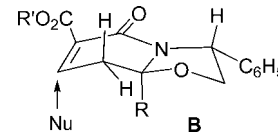


FIGURE 1. Stereoelectronic control in the conjugate addition.

It has previously been established[6] that the conjugate addition of organocuprates to unsaturated oxazolopiperidone lactams **B** (when R = H) is highly stereoselective as a consequence of the conformational rigidity of the bicyclic system. The nucleophilic attack occurs under stereoelectronic control[7] on the *exo* face, axial to the electrophilic carbon of the conjugate double bond (Figure 1).[8] However, it could be expected[9] a priori that the presence of a substituent at the angular position (R ≠ H) could alter the stereochemical

(1) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1–8. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207. For more recent work, see: (e) Amat, M.; Santo, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907−2910. (f) Allin, S. M.; Duffy, L. J.; Page, P. C. B.; Mckee, V.; McKenzie, M. J. *Tetrahedron Lett.* **2007**, *48*, 4711–4714. (g) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348–3351.

(2) For recent reviews on the synthesis of piperidines, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781–1813. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. For a recent review on the synthesis of pharmaceutically active compounds containing a disubstituted piperidine framework, see: (d) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601–635.

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(4) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848.

(5) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693.

(6) (a) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614. (b) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787–2790. See also refs 3 and 5.

(7) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983, p 221. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992, p 25.

(8) For recent related examples, see: (a) Brewster, A. G.; Broady, S.; Hughes, M.; Moloney, M. G.; Woods, G. A. *Org. Biomol. Chem.* **2004**, *2*, 1800–1810. (b) Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, *47*, 1961–1964.

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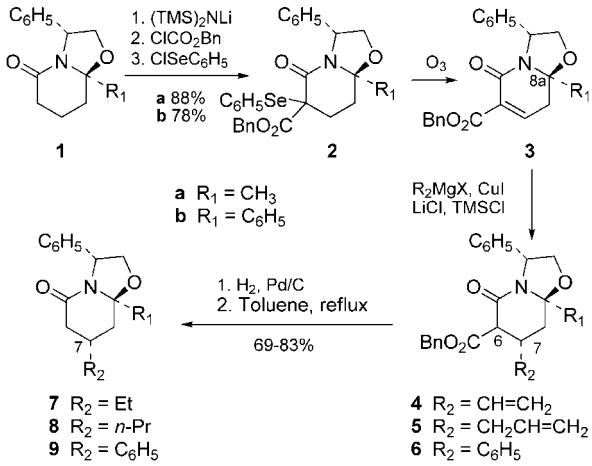
SCHEME 2. Conjugate Addition to 8a-Substituted Unsaturated Oxazolopiperidone Lactams



outcome of the conjugate addition as a consequence of the 1,3-*syn* diaxial interactions between this substituent and the incoming nucleophile. For this reason, to evaluate the viability of our synthetic plan, we decided to carry out a preliminary study on the stereoselectivity of similar conjugate addition reactions from the model, more easily accessible, unsaturated lactams **3a** and **3b**. These lactams were prepared,[10] via the corresponding selenides **2** (diastereomeric mixtures), from the known lactams **1a** and **1b**[11] (Scheme 2). The easily removable benzyloxy-carbonyl electron-withdrawing group was used to enhance the reactivity of the conjugated system.[12]

The conjugate addition of a vinyl group to lactam **3a** was satisfactorily accomplished (62% overall yield from **2a**) with vinylmagnesium bromide in the presence of LiCl, CuI, and trimethylsilyl chloride[13] in THF. The high *exo* facial stereoselectivity of the conjugate addition was confirmed after removal of the benzyloxycarbonyl substituent present in **4a** by hydrogenolysis, which took place with simultaneous hydrogenation of the vinyl group, followed by thermal decarboxylation. Under these conditions, a 93:7 mixture (calculated by NMR) of lactam **7a** and its C-7 epimer was obtained (see Table 1).

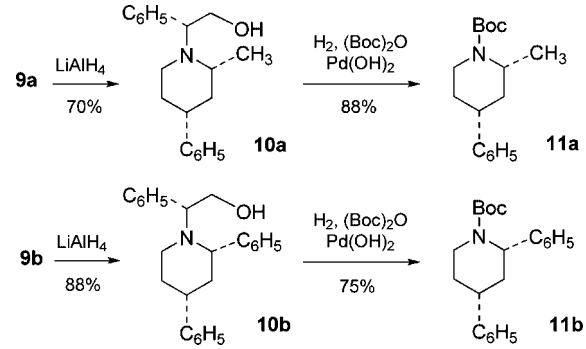
Under the same conditions the sterically more demanding 8a-phenyl-substituted lactam **3b** gave a similar result: the conjugate addition of a vinyl residue took place in 61% yield (from **2b**) and the subsequent debenzyloxycarbonylation afforded (73%) a 94:6 diastereomeric mixture of **7b** and its C-7 epimer.

TABLE 1. Conjugate Addition Reactions from Unsaturated Lactams 3

unsaturated lactam	product	yield (%)[a]	R_1/R_2 *cis*:*trans* ratio[b]
3a	**4a**	62	93:7
3a	**5a**	70	78:22
3a	**6a**	74	85:16
3b	**4b**	61	94:6
3b	**5b**	91	85:15
3b	**6b**	72	92:8

[a] Overall yield from selenides **2**. [b] Calculated by NMR after debenzyloxycarbonylation

SCHEME 3. Synthesis of Enantiopure *cis*-2,4-Disubstituted Piperidines



Similar conjugate additions of allylmagnesium chloride to unsaturated lactams **3a** and **3b** took place with lower stereoselectivity, and after removal of the benzyloxycarbonyl group as in the above series, lactams **8a** and **8b** were obtained along with the corresponding C-7 epimers (78:22 and 85:15 ratio, respectively) in acceptable overall yield (50% from **2a**; 65% from **2b**).

A moderate stereoselectivity was also observed in the conjugate addition of the organocuprate derived from phenylmagnesium chloride to **3a**: a 84:16 mixture of lactam **9a** and its C-7 epimer was isolated in 51% overall yield from **2a**.

In contrast, somewhat surprisingly, the conjugate addition of this organocuprate to the 8a-phenyl-substituted lactam **3b** took place in excellent yield and very high *exo* stereoselectivity (Table 1), ultimately leading to lactam **9b** in 60% overall yield (from **2b**). A π-stacking interaction between the incoming- and 8a-phenyl groups could account for the high stereoselectivity.

To illustrate the synthetic usefulness of the above methodology, the phenyl-substituted lactams **9a** and **9b** were converted to enantiopure *cis*-2,4-disubstituted piperidines as shown in Scheme 3. Thus, treatment of lactams **9** with $LiAlH_4$ brought about both the reduction of the amide carbonyl group and the reductive opening of the oxazolidine ring, which took place with complete retention of configuration,[14] to give piperidines **10a** and **10b**. The *cis*-relationship of the piperidine substituents at C-2 and C-4 in **10** was evident from the multiplicity of the axial 2 and 4 protons in the NMR spectra (see Supporting Information), thus confirming the stereochemical outcome of the above conjugate additions. A subsequent debenzylation in the presence of $(Boc)_2O$ gave enantiopure piperidines **11a** and **11b**.

The above results made evident that the presence of a substituent at the angular 8a-position has little effect on the

(9) (a) Muller, M.; Schoenfelder, A.; Didier, B.; Mann, A.; Wermuth, C.-G. *Chem. Commun.* **1999**, 683–684. (b) Hanessian, S.; van Otterlo, W. A. L.; Nilsson, I.; Bauer, U. *Tetrahedron Lett.* **2002**, *43*, 1995–1998. (c) García, E.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2006**, *71*, 6776–6784.

(10) Unsaturated lactams **3** and **14** are acid- and base-sensitive and must be prepared immediately before the next reaction and used without further purification.

(11) The starting lactams **1a** and **1b** were prepared by cyclocondensation of (*R*)-phenylglycinol with 5-oxohexanoic acid[11a] and 5-oxo-6-phenylpentanoic acid,[11b] respectively. (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085. (b) Amat, M.; Bassas, O; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872–7881.

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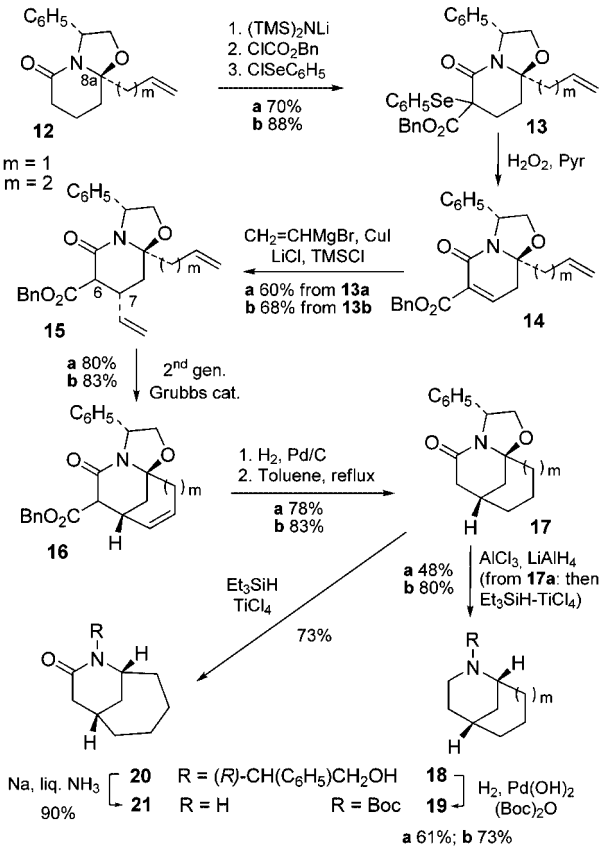
(13) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047–1050. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

(14) For a discussion on the stereochemical outcome in the reduction of 8a-substituted oxazolopiperidone lactams, see ref 11b and references therein.

SCHEME 4. Synthesis of Enantiopure 2-Azabicyclo[3.3.1]nonanes and 7-Azabicyclo[4.3.1]decanes



stereoselectivity of the conjugate addition. However, to access bridged piperidine derivatives following the strategy outlined in Scheme 1, we decided to take advantage of the higher stereoselectivity of the vinyl conjugate additions and chose starting lactams **A** bearing an allyl or 3-butenyl substituent at the 8a-position, which should ultimately lead to 6,6- and 6,7-bridged azabicyclic systems, respectively.

The synthetic sequence is outlined in Scheme 4. The required unsaturated lactams **14**[10] were prepared from lactams **12a**[15] and **12b**[16] via the corresponding selenides **13**. As could be expected from the above model experiments, the conjugate addition of the organocuprate derived from vinylmagnesium bromide to crude lactams **14** took place in good yield (~60% from **13**) and excellent facial diastereoselectivity to give the *exo* compounds **15** as C-6 epimeric mixtures (only trace amounts of C-7 *endo* epimers were detected by NMR), which were directly cyclized (~80% yield) in the presence of the second generation Grubbs catalyst.[17] A subsequent catalytic hydrogenation of the resulting bridged derivatives **16** brought about both the reduction of the C−C double bond and debenzylation to lead, after thermal decarboxylation, to tricyclic lactams 1**7a** (78%) and **17b** (83%). In the 6,7-bridged series, lactam **17b** was converted to the enantiopure 7-azabicyclo[4.3.1]decane (B-homomorphan) **19b** (58% overall yield) by alane reduction followed by hydrogenolysis in the presence of $(Boc)_2O$.[18] However, in **17a** the reductive cleavage of the C−O bond of the oxazolidine ring was more difficult, probably because the process involves the bridgehead carbon of a 6,6-bridged system. In this series, alane reduction of **17a** caused only the reduction of the lactam carbonyl. A subsequent prolonged (48 h) treatment of the resulting tricyclic amine with Et_3SiH-$TiCl_4$ led to bicyclic amine **18a** (48% overall yield from **17a**), which was then converted to the enantiopure 2-azabicyclo[3.3.1]nonane (morphan) **19a** as in the above 6,7-bridged series.[19] Alternatively, in the B-homomorphan series, tricyclic lactam **17b** was converted to lactam **21** in two steps (65% overall yield) as depicted in Scheme 4.

In summary, the *exo* facial stereoselectivity observed in the conjugate addition of organocuprates to 8a-unsubstituted unsaturated oxazolopiperidone lactams **B** (R = H) is maintained in the 8a-substituted derivatives, in particular when the incoming group is vinyl. By choosing the appropriate substituent at the 8a position in the starting oxazolopiperidone and the appropriate organocuprate in the conjugate addition step, the reported methodology provides a versatile route to enantiopure *cis*-2,4-disubstituted and 2,4-bridged piperidines.[20]

Experimental Section

General Procedure for the Conjugate Addition to Unsaturated Lactams (with 4a as an Example). LiCl (189 mg, 4.5 mmol) was heated at 80 °C for 1 h under vacuum (10−15 mmHg) in a three-necked, 500-mL round-bottomed flask. Then, CuI (357 mg, 4.5 mmol) and THF (5 mL) were added at room temperature, and the mixture was stirred at room temperature for 5 min. The suspension was cooled at −78 °C, and vinylmagnesium bromide (1 M in THF, 4.5 mL), TMSCl (0.57 mL, 4.5 mmol), and the crude of unsaturated lactam **3a** (1.8 mmol) in THF (8 mL) were successively added. The resulting mixture was stirred at −78 °C for 20 h. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layer was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (1:4 EtOAc/hexane) gave lactams **4a** (major) and 7-*epi*-**4a** as mixtures of C-6 epimers (508 mg, 62% overall yield from **2a**). **4a** (major C-6 epimer): IR (NaCl) 1665, 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.54 (s, 3H, CH_3), 1.94 (dd, J = 14.4, 8.4 Hz, 1H, H-8), 2.38 (dd, J = 14.4, 7.2 Hz, 1H, H-8), 3.15 (m, 1H, H-7), 3.40 (d, J = 10.8 Hz, 1H, H-6), 4.03 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 4.41 (t, J = 8.4 Hz, 1H, H-2), 5.09 (m, 2H, CH_2=), 5.17 (d, J = 12.4 Hz, 1H, CH_2 benzyl), 5.24 (d, J = 12.4 Hz, 1H, CH_2 benzyl), 5.42 (t, J = 7.2 Hz, 1H, H-3), 5.74 (ddd, J = 17.2, 10.4, 7.2 Hz, 1H, CH=), 7.25−7.36 (m, 10H ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.7 (CH_3), 36.0 (C-7), 39.5 (C-8), 53.7 (C-6), 59.1 (C-3), 67.0 (CH_2 benzyl), 69.2 (C-2), 93.2 (C-8a), 116.5 (CH_2=), 124.5−128.5 (C-*o*, *m*, *p*), 135.6, 139.7 (C-*i*), 138.1 (CH=), 166.7 (NCO), 168.7 (COO). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.30; H, 6.58; N, 3.51.

(15) Lactam **12a** was prepared in three steps [(1) H_2, Pd/C; (2) *n*-Bu_3P, *o*-$NO_2(C_6H_4)SeCN$; (3) H_2O_2, Pyr.; 40% overall yield] from the known[11a] 8a-benzyloxypropyl-substituted lactam.

(16) Lactam **12b** was prepared in 57% yield by cyclocondensation of (*R*)-phenylglycinol with the known 5-oxo-8-nonenoic acid: Mazur, P.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047–1051.

(17) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. 1−3. (b) Felpin, F.-X.; Lebreton, J *Eur. J. Org. Chem.* **2003**, 3693–3712. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(18) To our knowlewdge this is the first synthetic route to enantiopure 7-azabicyclo[4.3.1]decanes.

(19) The synthesis of enantiopure 2-azabicyclo[3.3.1]nonanes has been little explored: (a) Quirante, J.; Torra, M.; Diaba, F.; Escolano, C.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2399–2410. (b) Karig, G.; Fuchs, A.; Büsing, A.; Brandstetter, T.; Scherer, S.; Bats, J. W.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1049–1078.

(20) For previous syntheses of *cis*-2,4-disubstituted piperidines, see: (a) Beak, P.; Lee, W.-K. *J. Org. Chem.* **1990**, *55*, 2578–2590. (b) Dwyer, M. P.; Lamar, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 8965–8968. (c) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.

General Procedure for the Ring-Closing Metathesis Reaction (with 16a as an Example). Second-generation Grubbs catalyst (3 mg) was added to a solution of lactams **15a** (20 mg, 0.05 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred at room temperature for 2 h, concentrated, and purified by flash column chromatography (1:9 to 1:4 EtOAc/hexane) to yield tricyclic lactam **16a** as a mixture of C-6 epimers (ratio 2:1, 16 mg, 80% yield). **16a** (major): IR (NaCl) 1659, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, HETCOR) δ 2.30−2.45 (m, 3H, 2H-10, CH_2), 2.35 (dd, J = 12.0, 4.0 Hz, 1H, CH_2), 3.24 (d, J = 4.0 Hz, 1H, H-7), 3.67 (d, J = 6.4 Hz, 1H, H-6), 4.00 (t, J = 8.8 Hz, 1H, H-2), 4.61 (t, J = 8.4 Hz, 1H, H-2), 5.18 (d, J = 12.4 Hz, 1H, CH_2 benzyl), 5.22 (d, J = 12.4 Hz, 1H, CH_2 benzyl), 5.48 (t, J = 8.0 Hz, 1H, H-3), 5.64 (m, 1H, CH═), 5.76 (m, 1H, CH═), 7.05−7.20 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.8 (C-10), 34.4 (C-7), 36.1 (CH_2), 52.0 (C-6), 58.7 (C-3), 67.2 (CH_2 benzyl), 70.1 (C-2), 92.3 (C-11), 125.0−129.9 (C-*o, m, p,* CH═), 135.4, 139.2 (C-*i*), 164.2 (NCO), 169.7 (COO). **16a** (minor): ^1H NMR (400 MHz, $CDCl_3$, selected resonances) δ 2.19 (ddd, J = 12.4, 4.4, 1.6 Hz, 1H, H-10), 3.05 (br, 1H, H-7), 3.53 (s, 1H, H-6), 4.02 (dd, J = 9.2, 7.6 Hz, 1H, H-2), 4.57 (t, J = 8.8 Hz, 1H, H-2), 5.45 (t, J = 7.6 Hz, 1H, H-3), 5.76 (m, 1H, CH═), 5.90 (m, 1H, CH═); ^{13}C NMR (100.6 MHz, $CDCl_3$, selected resonances) δ 30.9 (C-10), 33.3 (C-7), 36.2 (CH_2), 53.5 (C-6), 57.9 (C-3), 67.0 (CH_2 benzyl), 70.1 (C-2), 92.4 (C-11), 164.5 (NCO), 168.9 (COO); HMRS calcd for [$C_{24}H_{23}NO_4$ + H] 390.1699, found 390.1704.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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