

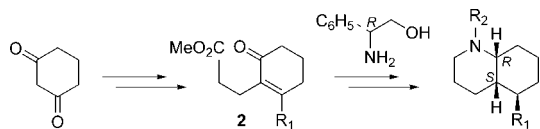
## A General Synthetic Route to Enantiopure 5-Substituted *cis*-Decahydroquinolines

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A practical synthetic route to enantiopure 5-substituted *cis*-decahydroquinolines has been developed, the key steps being a stereoselective cyclocondensation of 2-substituted 6-oxocyclohexenepropionates **2** with (*R*)-phenylglycinol, the stereoselective hydrogenation of the resulting unsaturated tricyclic lactams, and the stereoselective reductive cleavage of the oxazolidine ring.

The decahydroquinoline ring system is the central structure of many naturally occurring biologically active alkaloids, isolated not only from plants but mainly from other terrestrial (amphibians, arthropods)<sup>1</sup> and marine (tunicates, flatworms)<sup>2</sup> organisms. A common structural feature of these alkaloids is the presence of a carbon side chain, of variable length, at the C-5 position. Although decahydroquinoline alkaloids have received considerable synthetic attention,<sup>3</sup> the enantioselective synthesis of 5-substituted *cis*-decahydroquinolines has not been explored so far.

We present herein a general synthetic route to enantiopure 5-substituted *cis*-decahydroquinolines, the key steps being a stereoselective cyclocondensation of (*R*)-phenylglycinol with a 2-substituted 6-oxocyclohexenepropionate (**2**) and the stereoselective reduction of the resulting tricyclic lactam **3** (Scheme 1).

(1) (a) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21. (b) Jones, T. H.; Gorman, J. S. T.; Snelling, R. R.; Delabie, J. H. C.; Blum, M. S.; Garraffo, H. M.; Jain, P.; Daly, J. W.; Spande, T. F. *J. Chem. Ecol.* **1999**, *25*, 1179–1193. (c) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73–85. For a recent review, see: (d) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.

(2) (a) Steffan, B. *Tetrahedron* **1991**, *47*, 8729–8732. (b) Kubanek, J.; Williams, D. E.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189–6192. (c) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454–457.

(3) For a review, see: Kibayashi, C.; Aoyagi, S. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, pp 3–88.

### SCHEME 1. Synthetic Strategy

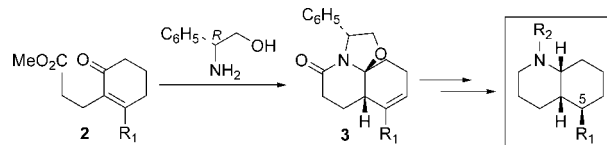


TABLE 1. Synthesis of 2-Substituted 6-Oxocyclohexenepropionates

entry	series	R <sub>1</sub>	method <sup>a</sup>	product	yield (%)
1	a	CH <sub>3</sub>	A	<b>2a</b>	70
2	b	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	A	<b>2b</b>	54
3	c	C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OCH <sub>3</sub>	B	<b>2c</b>	58
4	d	(CH <sub>2</sub> ) <sub>2</sub> CH(O <sub>2</sub> C <sub>2</sub> H <sub>4</sub> )	C	<b>2d</b>	88
5	e	(CH <sub>2</sub> ) <sub>5</sub> OTBDMS	C	<b>2e</b>	88
6	f	(CH <sub>2</sub> ) <sub>5</sub> OTBDPS	C	<b>2f</b>	89

<sup>a</sup> Method A: R<sub>1</sub>Li, (C<sub>6</sub>H<sub>5</sub>)SCu. Method B: R<sub>1</sub>MgBr, CuI. Method C: 9-R<sub>1</sub>-(9-BBN), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, DMF.

Crucial for the implementation of this route is to have available a practical method for the preparation of the starting unsaturated  $\delta$ -oxo esters **2** that allows a variety of R<sub>1</sub> substituents present in natural products to be introduced at the  $\beta$  position of the cyclohexenone ring. For this purpose, 1,3-cyclohexanedione was converted to bromo enone **1** in two steps, by alkylation with methyl acrylate<sup>4</sup> and subsequent bromination of the resulting diketo ester with (Ph<sub>3</sub>P)Br<sub>2</sub>.<sup>5</sup>

The introduction of an alkyl substituent into bromo enone **1** to give  $\beta$ -alkyl  $\alpha,\beta$ -unsaturated cyclohexenones **2a** and **2b** was effected by reaction of **1** with the corresponding lithium phenylthio(alkyl)cuprates<sup>6</sup> (Table 1, entries 1 and 2). In the butyl series, minor amounts of the ketone resulting from the attack of the butyl residue on the ester carbonyl group were also formed. To evaluate the versatility of the procedure we also studied the introduction of an aryl substituent. In this case, the organocuprate was generated by treatment of the corresponding Grignard reagent with CuI<sup>7</sup> (entry 3). Finally, functionalized carbon chains incorporating a protected aldehyde or hydroxy group were introduced in excellent yield via a Suzuki coupling.<sup>8</sup> Thus, regioselective hydroboration of 4-vinyl-1,3-dioxolane (entry 4) or silyl-protected (TBDMS or TBDPS) 4-penten-1-ols (entries 5 and 6) with 9-BBN, followed by a cross-coupling reaction of the resulting 9-R<sub>1</sub>-9-BBN derivatives with bromo enone **1** in the presence of a catalytic amount of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> gave the respective substitution products **2d–f**.

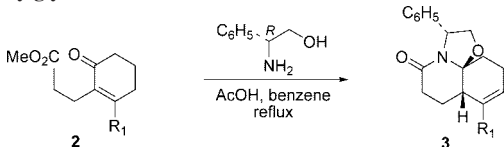
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(5) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210–223.

(6) (a) Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694–2696. (b) Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256–1263.

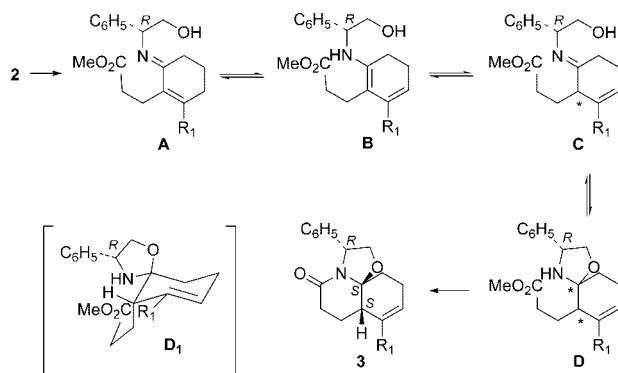
(7) *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994.

(8) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

**TABLE 2.** Cyclocondensation Reactions of  $\delta$ -Oxo Esters **2** with (*R*)-Phenylglycinol


entry	$\delta$ -oxo ester	R <sub>1</sub>	product <sup>a</sup>	yield (%) <sup>a</sup>
1	<b>2a</b>	CH <sub>3</sub>	<b>3a</b>	89
2	<b>2b</b>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	<b>3b</b>	76
3	<b>2c</b>	C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OCH <sub>3</sub>	<b>3c</b>	77
4	<b>2d</b>	(CH <sub>2</sub> ) <sub>2</sub> CH(O <sub>2</sub> C <sub>2</sub> H <sub>4</sub> )	<b>3d</b>	77
5	<b>2e</b>	(CH <sub>2</sub> ) <sub>5</sub> OTBDMS	<b>3e</b>	43
6	<b>2f</b>	(CH <sub>2</sub> ) <sub>5</sub> OTBDPS	<b>3f</b>	51
7	<b>2g</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	<b>3g</b>	77
8	<b>2h</b>	H	<b>3h</b>	42
9	<b>1</b>	Br	<b>3i</b>	15

<sup>a</sup> Compound **3** and the diastereoisomer at the hydroquinoline ring fusion carbons in a ratio of ~4:1.

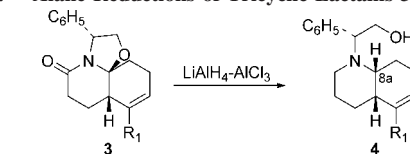
**SCHEME 2.** Proposed Mechanistic Pathway

With a versatile method in hand for the preparation of the required  $\delta$ -oxo esters **2**,<sup>9</sup> we next studied their cyclocondensation with (*R*)-phenylglycinol.<sup>10</sup> The reactions were performed in a Dean–Stark apparatus, in refluxing benzene containing a catalytic amount of AcOH. Under these conditions,  $\delta$ -oxo esters **2a–f** led to the corresponding tricyclic *cis*-hydroquinolones **3a–f**, in which the migration of the carbon–carbon double bond has occurred, in the yields indicated in Table 2 (entries 1–6). Similarly, the known oxo esters **2g**<sup>9</sup> and **2h**<sup>11</sup> were converted to the respective cyclocondensation products **3g** and **3h** (entries 7 and 8). These transformations result in the generation of two stereogenic centers with a well-defined absolute configuration in a single synthetic step from an achiral precursor. In all cases, minor amounts (approximate ratio 4:1) of the diastereoisomers

(9) For the preparation of **2a** and **2g** (ethyl ester) by a less general procedure, namely an aldol cyclocondensation of 1,5-polycarbonyl derivatives, see: Amat, M.; Grier, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348–3351.

(10) For reviews on the use of phenylglycinol-derived lactams as chiral building blocks for the enantioselective synthesis of piperidine-containing derivatives, 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.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848. (f) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439. (g) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923. (h) Soteras, I.; Lozano, O.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, F. J. *J. Org. Chem.* **2008**, *73*, 7756–7763.

(11) Hwu, J. R.; Hakmelahi, G. H.; Chou, C.-T. *Tetrahedron Lett.* **1992**, *33*, 6469–6472.

**TABLE 3.** Alane Reductions of Tricyclic Lactams **3**


entry	series	R <sub>1</sub> <sup>a</sup>	product	yield (%)
1	<b>a</b>	CH <sub>3</sub>	<b>4a</b>	54
2	<b>b</b>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	<b>4b</b>	59
3	<b>c</b>	C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OCH <sub>3</sub>	<b>4c</b>	55
4	<b>d</b>	(CH <sub>2</sub> ) <sub>2</sub> CH(O <sub>2</sub> C <sub>2</sub> H <sub>4</sub> )	<b>4d</b>	64
5	<b>f</b>	(CH <sub>2</sub> ) <sub>5</sub> OTBDPS	<b>4f</b>	52
6	<b>g</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	<b>4g'</b>	55

<sup>a</sup> The **g'** series: R<sub>1</sub> = (CH<sub>2</sub>)<sub>4</sub>OH.

at the hydroquinoline ring fusion carbons were also formed. The absolute configuration of the hydroquinoline ring fusion carbons in tricyclic lactams **3** was confirmed when lactam **3h** was reduced to the known lactam **6h** (see below).

The stereoselective formation of lactams **3** involves the initial generation of an imine **A**, which is in equilibrium via dienamine **B** with two diastereoisomeric imines **C** and four diastereoisomeric oxazolidines **D** (Scheme 2). A final irreversible lactamization occurs most rapidly from oxazolidine **D**<sub>1</sub> through a chairlike six-membered transition state in which the propionate chain avoids repulsive interactions with R<sub>1</sub> (A<sup>1,2</sup> strain) and C<sub>6</sub>H<sub>5</sub> groups.<sup>12</sup>

An alternative route to lactams **3** involving an initial cyclocondensation of bromo enone **1** with (*R*)-phenylglycinol and a subsequent cross-coupling reaction from the resulting tricyclic alkenyl bromide **3i** was not further explored due to the low yield of the cyclocondensation step (Table 2, entry 9).

The conversion of tricyclic lactams **3** to the target *cis*-decahydroquinolines required the stereoselective reductive cleavage of the C–O oxazolidine bond, reduction of the lactam carbonyl group, debenzoylation of the phenylethanol moiety, and the stereoselective hydrogenation of the hydroquinoline carbon–carbon double bond. The first two transformations were satisfactorily accomplished by alane reduction, which took place with retention of the configuration<sup>13</sup> at the 8a stereocenter, leading to *cis*-octahydroquinolines **4a–g'** in the yields indicated in Table 3. Minor amounts (5–10%) of the corresponding 8a epimers were also formed. Under the reaction conditions, the butyrate chain of **3g** underwent reduction to hydroxybutyl (compound **4g'**).

However, catalytic hydrogenation of **4a**, **4f**, and **4g'** under a variety of conditions [Pd–C or Pd(OH)<sub>2</sub>, MeOH, Boc<sub>2</sub>O; PtO<sub>2</sub>, MeOH, then Pd–C or Pd(OH)<sub>2</sub>, Boc<sub>2</sub>O] was not stereoselective as C-5 epimeric mixtures of the respective decahydroquinolines **5a**, **5f**, and **5g'** (Figure 1) were obtained. In the 5-aryl series, all attempts to hydrogenate the conjugated carbon–carbon double bond of **4c** were unsuccessful.

As could be expected, taking into account the conformational rigidity of tricyclic lactams **3**, this inconvenience was overcome by reversing the order of the above transformations. Thus, hydrogenation of **3a** using PtO<sub>2</sub> as the catalyst took place in

(12) For the stereochemical outcome of related cyclocondensation reactions from  $\gamma$ -substituted  $\delta$ -keto esters, see: (a) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343–5351. (b) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem.–Eur. J.* **2006**, *12*, 7872–7881.

(13) Fréville, S.; Célrier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron Asymmetry* **1995**, *6*, 2651–2654. See also ref 12a.

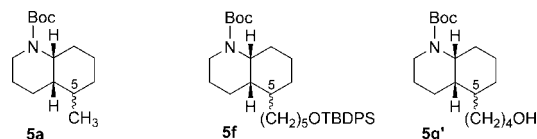
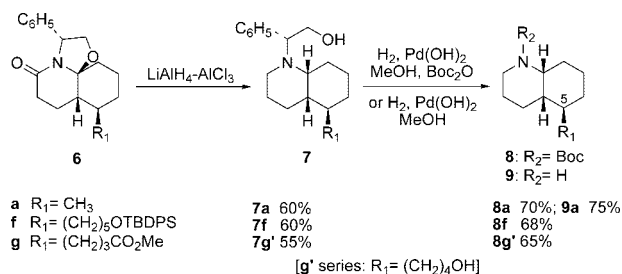


FIGURE 1. Decahydroquinolines resulting from the hydrogenation of hexahydroquinolines 4.

TABLE 4. Catalytic Hydrogenation of Tricyclic Lactams 3

entry	series	R <sub>1</sub>	catalyst	product	yield (%)
1	a	CH <sub>3</sub>	A	6a	98
2	b	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	B	6b	96
3	c	C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OCH <sub>3</sub>	A	6c	
4	e	(CH <sub>2</sub> ) <sub>5</sub> OTBDMS	B	6e	84
5	f	(CH <sub>2</sub> ) <sub>5</sub> OTBDPS	A	6f	85
6	g	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	A	6g	97
7	h	H	B	6h	95

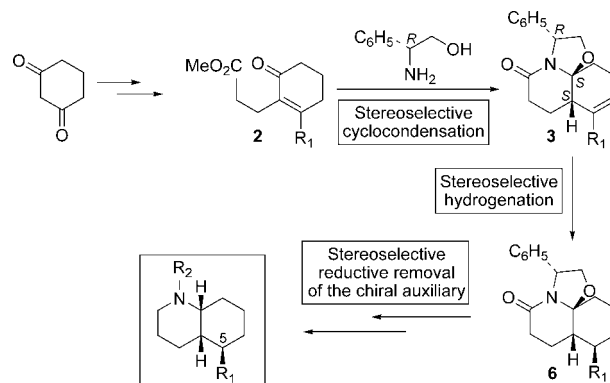
SCHEME 3. Synthesis of Enantiopure 5-Substituted *cis*-Decahydroquinolines



nearly quantitative yield and complete stereoselectivity to give saturated lactam **6a** (Table 4, entry 1). The absolute configuration of **6a** was unambiguously established by X-ray crystallographic analysis.<sup>14</sup> Similarly, hydrogenation of **3b,e–g** using either Pd–C or PtO<sub>2</sub> as the catalyst took place in excellent yield and stereoselectivity to give the respective decahydroquinoline derivatives **6b,e–g**. However, as in the above reduction of **4c**, the conjugated carbon–carbon double bond of the aryl-substituted derivative **3c** was reluctant to undergo reduction (entry 3). On the other hand, hydrogenation of the unsubstituted derivative **3h** led to lactam **6h** (entry 7), which was identical (NMR, specific rotation) to that previously prepared by direct cyclocondensation of 2-oxocyclohexanepropionic acid with (*R*)-phenylglycinol, whose absolute configuration had been unambiguously determined by X-ray crystallography.<sup>12b</sup>

To complete the synthesis, removal of the chiral auxiliary was performed in two steps. Thus, reduction of **6a, 6f**, and **6g** with alane brought about both the reductive opening of the oxazolidine ring, with retention of the configuration,<sup>13</sup> and the reduction of the lactam and ester carbonyl groups to give the respective *cis*-decahydroquinolines **7a, 7f**, and **7g'** (Scheme 3). A final hydrogenation in the presence of Pd(OH)<sub>2</sub> and (Boc)<sub>2</sub>O led to the enantiopure *N*-protected derivatives **8a, 8f**, and **8g'**. Alternatively, hydrogenation of **7a** in the absence of (Boc)<sub>2</sub>O gave the *N*-unsubstituted *cis*-decahydroquinoline **9a**.<sup>15</sup>

SCHEME 4. A General Synthetic Route to Enantiopure 5-Substituted *cis*-Decahydroquinolines



In summary, we have developed an expeditious practical route to enantiopure 5-substituted *cis*-decahydroquinolines from achiral  $\delta$ -oxo esters **2**, which are easily accessible from 1,3-cyclohexanedione. A stereoselective cyclocondensation reaction with (*R*)-phenylglycinol results in the straightforward construction of the hydroquinoline system. Two subsequent stereoselective reductive processes complete the synthesis (Scheme 4).

## Experimental Section

**General Procedure for the Synthesis of 2-Substituted 6-Oxocyclohexenepropionates. Method A (with 2a as an Example).** MeLi (32 mL, 1.6 M in Et<sub>2</sub>O) was added to a suspension of C<sub>6</sub>H<sub>5</sub>SCu (8.6 g, 50 mmol) in anhydrous THF (260 mL) at –20 °C, and the mixture was stirred at this temperature for 15 min. After cooling at –78 °C, bromo enone **1** (6.5 g, 25 mmol) in anhydrous THF (50 mL) was added, and the mixture was allowed to reach 0 °C, stirred for 2.5 h, and poured into saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with EtOAc, and the organic extracts were dried and concentrated. The residue was chromatographed (9:1 hexane–EtOAc) to give **2a** (3.4 g, 70%): <sup>1</sup>H NMR (300 MHz)  $\delta$  1.88–1.96 (m, 2H), 1.97 (s, 3H), 2.33–2.40 (m, 6H), 2.59–2.64 (m, 2H), 3.65 (s, 3H); <sup>13</sup>C NMR (75.4 MHz)  $\delta$  21.0 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 51.4 (CH<sub>3</sub>), 133.6 (C), 156.5 (C), 173.5 (C), 198.2 (C); HMRS calcd for [C<sub>11</sub>H<sub>16</sub>O<sub>3</sub> + Na]: 219.100, found: 219.099.

**Method B (with 2c as an Example).** CuI (340 mg, 1.78 mmol) was added to a solution of bromo enone **1** (300 mg, 1.15 mmol) in anhydrous THF (6 mL), and the resulting suspension was vigorously stirred at –10 °C. *p*-Methoxyphenylmagnesium bromide (6.8 mL, 0.5 M in THF) was slowly added, and the mixture was stirred at –10 °C for 16 h, poured into saturated aqueous NH<sub>4</sub>Cl (5 mL) and Et<sub>2</sub>O (5 mL), and stirred for 1 h. The aqueous layer was extracted with Et<sub>2</sub>O, and the organic extracts were dried and concentrated. The residue was chromatographed (3:2 hexane–Et<sub>2</sub>O) to give **2c** (192 mg, 58%) as a yellow oil: <sup>1</sup>H NMR (300 MHz)  $\delta$  2.04–2.11 (m, 2H), 2.31–2.37 (m, 2H), 2.47–2.56 (m, 4H), 2.58–2.62 (m, 2H), 3.58 (s, 3H), 3.83 (s, 3H), 6.90–6.94 (m, 2H), 7.08–7.12 (m, 2H); <sup>13</sup>C NMR (75.4 MHz)  $\delta$  22.3 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 33.5 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 37.9 (CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 113.9 (CH), 128.0 (CH), 133.1 (C), 134.3 (C), 158.3 (C), 159.3 (C), 163.2 (C), 173.3 (C), 199.2 (C); HMRS calcd for [C<sub>17</sub>H<sub>20</sub>O<sub>4</sub> + H]: 289.1434, found: 289.1428. Anal. Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>4</sub>·1/2H<sub>2</sub>O: C, 68.67; H, 7.12. Found: C, 68.85; H, 7.00.

**Method C (with 2d as an Example).** 2-Vinyl-1,3-dioxolane (0.29 mL, 2.9 mmol) was added to a solution of 9-BBN (5.8 mL, 0.5 M in THF) at 0 °C, and the mixture was stirred at rt for 3 h. Then,

(14) For a preliminary report on the preparation of **3a** and its reduction to **6a**, see ref 9.

(15) The <sup>1</sup>H and <sup>13</sup>C NMR data of **9a** were coincident with those reported in the racemic series: Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652–6660.

DMF (12 mL),  $K_3PO_4$  (407 mg, 1.92 mmol),  $PdCl_2(PPh_3)_2$  (42 mg, 0.06 mmol), and bromo enone **1** (500 mg, 1.92 mmol) were added, and the mixture was heated at 60 °C for 16 h.  $H_2O$  (12 mL) was added, and stirring was continued for 30 min. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with  $H_2O$ , dried, and concentrated. The residue was chromatographed (1:1 hexane–EtOAc) to give **2d** (475 mg, 88%) as a yellow oil:  $^1H$  NMR (300 MHz)  $\delta$  1.76–1.84 (m, 2H), 1.89–1.97 (m, 2H), 2.28–2.32 (m, 8H), 2.56–2.64 (m, 2H), 3.62 (s, 3H), 3.82–3.91 (m, 2H), 3.92–3.99 (m, 2H), 4.83–4.90 (m, 1H);  $^{13}C$  NMR (75.4 MHz)  $\delta$  21.5 ( $CH_2$ ), 22.4 ( $CH_2$ ), 29.3 ( $CH_2$ ), 31.0 ( $CH_2$ ), 32.3 ( $CH_2$ ), 33.9 ( $CH_2$ ), 38.5 ( $CH_2$ ), 51.8 ( $CH_3$ ), 65.7 ( $2CH_2$ ), 104.0 (CH), 134.2 (C), 159.8 (C), 173.8 (C), 198.3 (C); HMRS calcd for  $[C_{15}H_{22}O_5 + H]$ : 283.1540, found: 283.1533. Anal. Calcd for  $C_{15}H_{22}O_5 \cdot 1/2H_2O$ : C, 61.84; H, 7.96. Found: C, 61.98; H, 7.98.

**General Procedure for Cyclocondensation Reactions (with **3g** as an Example).** (*R*)-Phenylglycinol (5.8 g, 42.6 mol) was added to a solution of keto ester **2g** (4 g, 14.2 mol) and AcOH (1.2 mL, 21.3 mol) in benzene (200 mL). The mixture was heated at reflux for 48 h with azeotropic elimination of  $H_2O$  produced by a Dean–Stark apparatus. The resulting mixture was cooled and concentrated to give an oil. Flash chromatography (from 3:2 to 1:1 hexane–EtOAc) afforded lactam **3g** (3.2 g, 61%) and its C-7a, C-11a diastereoisomer (0.8 g, 16%). **3g** (higher  $R_f$ ):  $^1H$  NMR (300 MHz)  $\delta$  1.58–1.91 (m, 6H), 1.99–2.12 (m, 4H), 2.17–2.25 (m, 1H), 2.28–2.40 (m, 2H), 2.42–2.55 (m, 1H), 2.68 (dd,  $J$  = 18.6, 6 Hz, 1H), 3.67 (s, 3H), 3.81 (t,  $J$  = 8.4 Hz, 1H), 4.55 (t,  $J$  = 8.4 Hz, 1H), 5.28–5.47 (m, 2H), 7.17–7.35 (m, 5H);  $^{13}C$  NMR (75.4 MHz)  $\delta$  22.9 ( $CH_2$ ), 23.0 ( $CH_2$ ), 25.0 ( $CH_2$ ), 25.9 ( $CH_2$ ), 31.3 ( $CH_2$ ), 33.3 ( $CH_2$ ), 33.5 ( $CH_2$ ), 43.2 (CH), 51.4 ( $CH_3$ ), 58.4 (CH), 69.4 ( $CH_2$ ), 94.2 (C), 120.9 (CH), 125.2 (2CH), 127.0 (CH), 128.4 (2CH), 136.2 (C), 140.2 (C), 169.4 (C), 173.7 (C); mp 90–94 °C;  $[\alpha]^{22}_D$  –101.3 ( $c$  1.1, MeOH). Anal. Calcd for  $C_{22}H_{27}NO_4$ : C, 71.52; H, 7.37; N, 3.79. Found: C, 71.50; H, 7.42; N, 3.84.

**General Procedure for Alane Reductions of Tricyclic Lactams **3** and **6** (with **4g'** as an Example).** To a suspension of  $AlCl_3$  (362 mg, 2.71 mmol) in anhydrous THF (50 mL) at 0 °C was slowly added  $LiAlH_4$  (340 mg, 8.94 mmol). After the mixture was stirred at 25 °C for 30 min and cooled to –78 °C, a solution of lactam **3g** (500 mg, 1.35 mmol) in anhydrous THF (5 mL) was slowly added. The stirring was continued for 90 min at –78 °C and for 90 min at 25 °C. Then, the mixture was cooled to 0 °C, and the reaction was quenched with  $H_2O$ . The aqueous layer was extracted with

$CH_2Cl_2$ , and the combined organic extracts were dried and concentrated. Column chromatography (from 8:2 to 1:1 hexane–EtOAc) afforded a mixture of **4g'** (245 mg, 55%) and its C-8a epimer (22 mg, 5%). **4g'** (lower  $R_f$ ):  $^1H$  NMR (400 MHz)  $\delta$  1.26–1.73 (m, 10H), 1.86–2.15 (m, 5H), 2.5 (m, 1H), 2.69–2.79 (m, 2H), 3.61 (t,  $J$  = 6.4 Hz, 2H), 3.79 (dd,  $J$  = 10.6, 5.4 Hz, 1H), 3.85 (dd,  $J$  = 10.6, 6.2 Hz, 1H), 3.92 (t,  $J$  = 6.0 Hz, 1H), 5.24 (s, 1H), 7.26–7.33 (m, 5H);  $^{13}C$  NMR (100.6 MHz)  $\delta$  18.9 ( $CH_2$ ), 24.1 ( $2CH_2$ ), 24.9 ( $CH_2$ ), 26.4 ( $CH_2$ ), 32.5 ( $CH_2$ ), 34.4 ( $CH_2$ ), 38.8 (CH), 44.0 ( $CH_2$ ), 55.0 (CH), 61.9 ( $CH_2$ ), 62.8 ( $CH_2$ ), 65.0 ( $CH_2$ ), 120.5 (CH), 127.5 (2CH), 128.3 (CH), 128.4 (2CH), 139.0 (C), 140.3 (C);  $[\alpha]^{22}_D$  –27.4 ( $c$  1.2, MeOH); HMRS calcd for  $[C_{21}H_{31}NO_2 + H]$  330.2428, found 330.2426.

**General Procedure for Catalytic Hydrogenation of Tricyclic Lactams **3** (with **6g** as an Example).** A solution of lactam **3g** (500 mg, 1.35 mmol) in MeOH (40 mL) containing 40%  $PtO_2$  (200 mg) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration and washed with MeOH. The combined organic solutions were concentrated affording pure compound **6g** (486 mg, 97%) as an oil:  $^1H$  NMR (300 MHz)  $\delta$  1.39–1.86 (m, 13H), 2.05–2.21 (m, 1H), 2.30–2.35 (m, 2H), 2.40–2.53 (dd,  $J$  = 11.1, 6.9 Hz, 1H), 2.60–2.68 (dd,  $J$  = 18.2, 6.9 Hz, 1H), 3.67 (s, 3H), 3.82 (dd,  $J$  = 8.8, 8.1 Hz, 1H), 4.49 (t,  $J$  = 8.8 Hz, 1H), 5.29 (t,  $J$  = 8.8 Hz, 1H), 7.15–7.34 (m, 5H);  $^{13}C$  NMR (75.4 MHz)  $\delta$  17.9 ( $CH_2$ ), 23.6 ( $CH_2$ ), 24.1 ( $CH_2$ ), 24.6 ( $CH_2$ ), 30.4 ( $CH_2$ ), 31.2 ( $CH_2$ ), 32.6 ( $CH_2$ ), 34.1 ( $CH_2$ ), 39.6 (CH), 43.4 (CH), 51.4 ( $CH_3$ ), 58.0 (CH), 69.6 ( $CH_2$ ), 95.3 (C), 125.3 (2CH), 127.0 (CH), 128.4 (2CH), 140.2 (C), 169.3 (C), 174.1 (C);  $[\alpha]^{22}_D$  –67.7 ( $c$  1.0, MeOH); HMRS calcd for  $[C_{22}H_{29}NO_4 + H]$  372.2169, found 372.2163. Anal. Calcd for  $C_{22}H_{29}NO_4$ : C, 71.13; H, 7.87; N, 3.77. Found: C, 70.84; H, 7.81; N, 3.69.

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**Supporting Information Available:** Complete experimental procedures and copies of the  $^1H$  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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