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Novel Extension of Meyers' Methodology: Stereoselective Construction of Axially Chiral 7,5-Fused Bicyclic Lactams†

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Abstract: A novel extension of Meyer's lactamization is reported for the preparation of seven-membered ring lactams **1a**−**d** incorporating a biaryl unit. The required keto-esters **2a**−**c** were readily accessible via the Suzuki coupling reaction. A borylation−Suzuki coupling (BSC) sequence was successfully developed for the high-yielding preparation of keto-ester **2d**. Cyclization of the resulting keto-esters **2a**−**d** or keto-acids **5a,c,d** in the presence of (*R*)-phenylglycinol afforded the desired lactams **1a**−**d** in high yields (72−93%) and excellent diastereoselectivities (>95%). This methodology provides a facile stereoselective access to new axially chiral bridged biaryls.

Meyers' bicyclic lactam methodology has been widely used in the stereoselective construction of five- and six-membered ring nitrogen heterocycles. These lactams provide a number of highly functionalized chiral building blocks which may be used further, in a wide range of stereoselective transformations, making these intermediates powerful tools in asymmetric synthesis.[1] Although this methodology demonstrated to be highly versatile for the preparation of five- and six-membered rings, the stereoselective preparation of higher-membered ring systems still remains almost unexplored. Only one paper has recently attempted to extend this methodology to the preparation of seven-membered lactams such as 2-alkylperhydroazepines. However, lactams were obtained in low yields and poor diastereoselectivities (Figure 1).[2] These rather disappointing results may be ascribed to the increased flexibility of the larger seven-membered ring size.

As part of a research program dealing with the development of new axially chiral ligands, we became interested in the stereoselective preparation of biaryl lactams **1** (Figure 2). The key structural element of such chiral ligands is the presence of the chiral bridge, linking

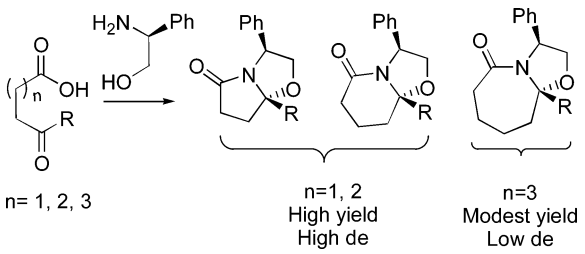

FIGURE 1. Scope and limitations of Meyers' methodology.

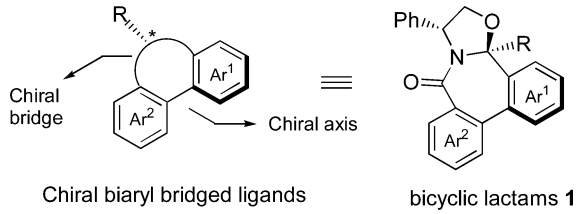

FIGURE 2. Design of new axially chiral bridged ligands by means of Meyers' methodology.

the diaryl groups. The first purpose of this chiral bridge is to dispose of rigid chiral biaryl ligands with tunable dihedral angles between the two aryl units.[3] The second role is to ensure the configurational control of the resulting chiral axis of the biaryl motif.[4,5] In this context, we felt that Meyers' lactamization could provide a straightforward stereoselective access to seven-membered bridged biaryls **1**.[6] We reasoned that the presence of this biaryl unit in keto-esters **2** might exhibit important conformational restrictions which may possibly restore a high level of stereoselectivity and a reactivity comparable to that obtained in the case of five- and six-membered lactams (Figure 2).[1]

To investigate this approach, the required keto-esters **2a**−**c** were prepared from commercially available boronic acid **4a** and aryl halides **3a**−**c**, **3′a** via a Suzuki cross-coupling reaction. As can be appreciated from Table 1, yields are excellent ranging from 71 to 91%. Given that

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(1) For leading references on chiral bicyclic lactams see: (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1−8. (b) Amat, M.; Canto, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335−337. (c) Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343−5351. (d) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919−1928. (e) Ennis, M. D.; Hoffman R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813−5817. (f) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464−9467.

(2) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413−1419.

(3) For examples of chiral biaryl bridged ligands with tunable dihedral angles see: (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223−6226. (b) Wu, S.; Wang, W.; Tang, W.; Lin. M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495−4497.

(4) For examples on the configurational control of chiral axis in biaryl moieties by means of a chiral bridge see: (a) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656−5657. (b) Brecht, R.; Büttner, F.; Böhm, M.; Seitz, G.; Frenzen, G.; Pilz, A.; Massa, W. *J. Org. Chem.* **2001**, *6*, 2911−2917.

(5) Conformational analysis of bicyclic lactams **1** by molecular modelling shows a dihedral angle between the two aryl units of 40−50° (MM2, PCMODEL).

(6) During the preparation of the manuscript, Wallace et al. reported the condensation of 2′-formylbiphenyl-2-carboxylic acid with (*S*)-valinol providing the corresponding bicyclic lactam as a mixture of two epimers (*aS*,*R*,*S*) and (*aR*,*S*,*S*) with medium diastereoselectivity (de = 75%). Edwards, D. J.; Pritchard, R. G.; Wallace, T. W. *Tetrahedron Lett.* **2003**, *44*, 4665−4668.

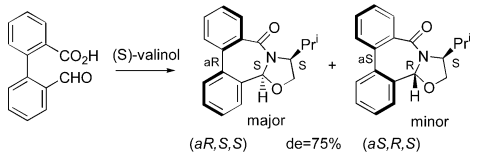

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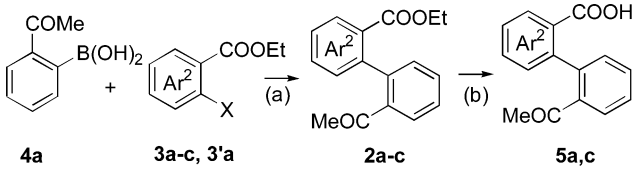
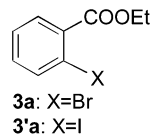
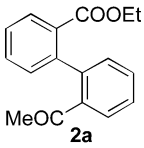
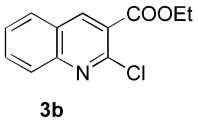
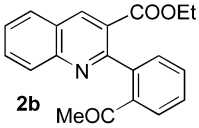
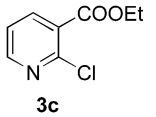
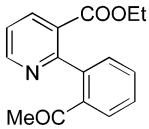
TABLE 1. Preparation of Biaryls 2a−c via the Suzuki Cross-Coupling Reaction



4a **3a-c, 3'a** **2a-c** **5a,c**

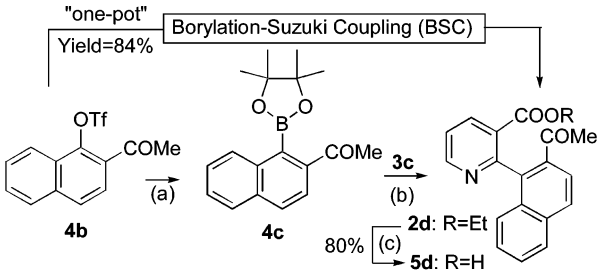
Reagents and conditions: (a) $Pd(PPh_3)_4$ (8%)/K_2CO_3/toluene:water/reflux/48 h; (b) aqueous NaOH/EtOH/rt/48h.

entry	esters **3a-c**, **3'a**	biaryls **2a-c**		**5a,c**
1	 **3a**: X=Br **3'a**: X=I	 **2a**	X= Br (90%) X= I (91%)	96%
2	 **3b**	 **2b**	82%	
3	 **3c**	 **2c**	71%	76%

the Meyers' lactamization is usually reported from keto acid derivatives, esters **2a,c** were converted into the corresponding carboxylic acids **5a,c** in 96 and 76% yields, respectively.

The desired 2-naphthylpyridine **2d** was readily prepared from aryl triflate **4b** by a one-pot procedure using a borylation−Suzuki coupling (BSC) sequence, recently developed by Baudoin et al.[7] We first optimized the borylation step. Under Masuda et al.'s conditions,[8] the use of $PdCl_2$(dppf) or $PdCl_2(PPh_3)_2$ as catalysts led, in our case, to naphthylboronate **4c** in modest yields (Table 2, entries 1, 2).[9] After screening various conditions, we found that using $Pd(PPh_3)_4$ provided notably higher yields (Table 2, entries 3−6). The presence of two equivalents of pinacolborane was found to be critical to reach nearly quantitative yields of naphthylboronate **4c** (Table 2, entry 6). The Suzuki cross-coupling step was carried out in the presence of $Pd(PPh_3)_4$ and $Ba(OH)_2$ in dioxane to afford **2d** in 84% yield after flash chromatography. As both the borylation and Suzuki cross-coupling steps may be conducted under the same conditions with excellent yields, we next investigated a one-pot procedure (BSC). Thus, at the end of the borylation step, ethyl 2-chloronicotinate **3c** and $Ba(OH)_2$ were added, and the reaction mixture was heated at 100 °C for a further 24 h to provide the desired biaryl **2d** in 84% overall yield. This borylation−Suzuki coupling sequence was found to be highly sensitive to the reagent concentrations and gives reproducible yields only when the whole process is conducted at a concentration lower than 0.3−0.4 mol L^{-1}.

TABLE 2. Borylation−Suzuki Coupling (BSC)



4b **4c**

Reagents and conditions: (a) catalyst/NEt_3/pinacolborane/dioxane/80°C/2 h; (b) $Pd(PPh_3)_4$/$Ba(OH)_2$/100°C/dioxane/24h/84%; (c) NaOH/rt/24h

entry	catalyst	pinacolborane (equiv)	yield of 4c[a] (%)
1	$PdCl_2$(dppf)	1.5	66
2	$PdCl_2(PPh_3)_2$	1.5	30
3	$Pd(PPh_3)_4$	1.1	58
4	$Pd(PPh_3)_4$	1.3	76
5	$Pd(PPh_3)_4$	1.5	85
6	$Pd(PPh_3)_4$	2	95

[a] Determined by ^{1}H NMR analysis of the crude reaction product.

With keto-esters **2a**−**d** and keto-acids **5a,c,d** in hand, we turned to the proposed 5,7-fused bicyclic lactams construction. In the presence of (*R*)-phenylglycinol and under the classical dehydrating conditions used by Meyers,[1] the keto-acid **5a** afforded the desired lactam **1a** in 88% yield and 86% de. Both diastereoisomers (*aR,3R,13bS*)-**1a** and (*aS,3R,13bR*)-**1a** were isolated by column chromatography. The relative stereochemistry of the minor diastereoisomer (*aS,3R,13bR*)-**1a** was determined by a nuclear Overhauser enhancement spectroscopy (NOESY) experiment. On treating the keto-ester **2a** under the same conditions, we were pleased to isolate the desired lactam **1a** in greater than 90% yield as a single isomer (de > 95%). This constitutes the first highly stereoselective formation of a 5,7-fused bicyclic lactam employing Meyers' methodology (Scheme 1).

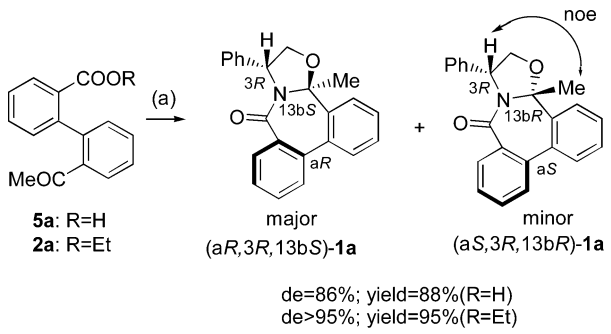
At this stage, some comments related to the presence of conformational constraints, occurring during the lactamization of the oxazolidine intermediate, are appropriate to account for the stereochemical course of the process. The stereochemical outcome in lactam **1a** is coherent with Meyer's observations,[1] that is, the major stereoisomer (*aR,3R,13bS*)-**1a** displays both phenyl groups of the oxazoline moiety in a trans relationship. The *trans*-oxazolidine intermediate **A** lactamizes via a "*pro-(aR)* rotation" about the biaryl axis, giving rise to the exclusive formation of bicyclic lactam (*aR,3R,13bS*)-**1a** (Figure 3). Conformational restrictions in the 5,7-fused bicyclic lactam **1a** prevents the lactamization of the *trans*-oxazolidine intermediate **A** from taking place through a "*pro-(aS)* rotation" about the biaryl axis (Figure 3). In contrast, the only way for the *cis*-oxazolidine intermedi-

(7) (a) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271. (b) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2002**, *67*, 1199−1207.

(8) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168.

(9) Substantial amounts of undesirable 2-acetylnaphthalene was identified by ^{1}H NMR analysis of the crude reaction product and account for the modest yield of **4c**. Reductive dehalogenation has already been reported during palladium-catalyzed borylation (see ref 7b).

SCHEME 1 . Seven-Membered Lactam 1a Formation[a]



[a] Key: (a) (*R*)-phenylglycinol, toluene; reflux 18 h for **5a** and 138 h for **2a**.

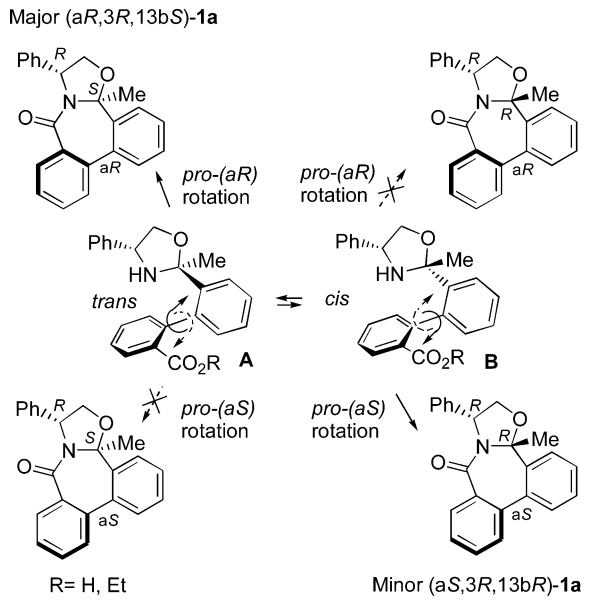


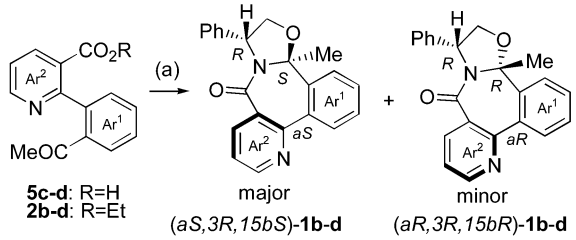
FIGURE 3. Stereochemical course of the lactamization step.

ate **B** to further react with the carboxylic acid or ester is to initiate a "*pro-(aS)* rotation" about the biaryl axis to produce (*aS*,*3R*,*13bR*)-**1a**. The absolute configuration of the chiral axis present in the biaryl unit is therefore subordinated to that of the N,O-acetal center in the oxazolidine intermediate (Figure 3).[10]

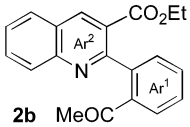
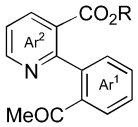
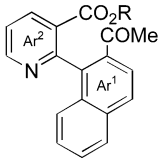
The above methodology could be extended to the preparation of 5,7-fused bicyclic lactams **1b**−**d** incorporating a heterocyclic ring in the biaryl motif. Thus, treating 2-phenylquinoline **2b** with (*R*)-phenylglycinol in toluene under Dean−Stark conditions for 138 h gave 81% of lactam **1b** as a single diastereoisomer (de > 95%). The keto-ester **2c** and keto-acid **5d** were subjected to the same conditions to furnish lactams **1c** and **1d** in 72 and 78% yield, respectively, as a single diastereoisomer in both cases. Surprisingly, despite the high level of stereoselectivity, the lactamization reaction of keto-acid **5c** and keto-ester **2d** resulted in the formation **1c** and **1d** in rather low yields. In summary, a highly stereoselective preparation of 5,7-fused bicyclic lactams using Meyer's methodology has been developed with success. The excellent stereoselectivity observed appears to be tightly connected with the presence of the biaryl motif. Further investigations of this stereoselective lactamization with other biaryl systems are underway for the preparation of new axially chiral bridged ligands with a view to explore their potential in asymmetric catalysis.

(10) For conformational and configurational analysis of related axially chiral lactams see: (a) Vasse, J.-L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4613−4616. (b) Vasse, J.-L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 3713−3716. (c) Vasse, J.-L.; Levacher, V.; Bourguignon, J.; Dupas. G. *Chem. Commun.* **2002**, 2256−2257.

TABLE 3. Seven-Membered Lactams 1b−d Formation



Reagents and conditions: (a) (*R*)-phenylglycinol/toluene/reflux

entry	Ar^2-Ar^1	Time	**1b-d** Yield	de
1	 **2b**	138 h	**1b:** 81%	>95%
2	 **2c**: R=Et **5c**: R=H	**2c**: 138 h **5c**: 72 h	**1c**: 72% **1c**: 7%	>95% >95%
3	 **2d**: R=Et **5d**: R=H	**2d**: 48 h **5d**: 72 h	**1d**: 8% **1d**: 78%	>95% >95%

Experimental Section

(a*R*,3*R*,13b*S*)-13b-Methyl-3-phenyl-2,3-dihydro-13b*H*-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-5-one (1a) (General Procedure). Keto-ester **2a** (1.21 g, 4.5 mmol) and (*R*)-phenylglycinol (618 mg, 4.5 mmol) were dissolved in toluene (50 mL) in a Dean−Stark apparatus. The mixture was stirred at reflux for 138 h, and toluene was evaporated under reduced pressure. ^{1}H NMR analysis of the crude product indicated the formation of only one diastereoisomer (de > 95%). Flash chromatography of the residue on silica gel (EtOAc/CH_2Cl_2/cylohexane: 1/8/1) provided lactam (a*R*,3*R*,13b*S*)-**1a** (1.46 g, 95%) as a colorless solid (mp 90 °C). $[\alpha]^{20}_D = +56.4°$ (*c* 0.62, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.78 (dd, J = 1.0 and 7.0 Hz, 1H), 7.57 (m, 1H), 7.50−7.14 (m, 11H), 7.35 (d, J = 6.0 Hz, 1H), 4.31 (dd, J = 7.0 and 9.0 Hz, 1H), 4.16 (dd, J = 1.0 and 9.0 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.0, 142.3, 141.3, 137.5, 136.3, 133.8, 131.7, 131.2, 130.8, 129.3, 129.2, 129.0 (2 C), 128.7, 128.5, 128.0, 127.3 (2 C), 122.7, 94.3, 71.4, 62.1, 26.1. IR (KBr) ν_{max}: 3061, 2986, 2936, 2877, 1632, 1450, 1395, 1238, 1037, 742, 697 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.84; H, 5.68, N, 4.11.

(a*S*,3*R*,13b*R*)-13b-Methyl-3-phenyl-2,3-dihydro-13b*H*-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-5-one (1a). Prepared according to the general procedure from keto-acid **5a** (500 mg, 2.08 mmol) and (*R*)-phenylglycinol (286 mg, 2.08 mmol) for 18 h. ^{1}H NMR analysis of the crude product indicated the formation of two diastereoisomers (de = 86%). Flash chromatography of the residue on silica gel (EtOAc/CH_2Cl_2/cyclohexane, 1/8/1) afforded lactam (a*R*,3*R*,13b*S*)-**1a** (624 mg, 88%) and its diastereoisomer (a*S*,3*R*,13b*R*)-**1a** as a colorless oil (14 mg, 2%). Data for the minor diastereoisomer (a*S*,3*R*,13b*R*)-**1a**: $[\alpha]^{20}_D = -18.0°$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.97 (d, J = 7.0 Hz, 1H), 7.72 (dd, J = 2.0 and 7.0 Hz, 1H), 7.57 (dd, J = 2.0 and 7.0 Hz, 1H), 7.52 (dd, J = 1.0 and 3.0 Hz, 2H), 7.44−7.36 (m, 3H), 7.05 (m, 3H), 6.84 (m, 2H), 5.34 (dd, J = 5.0 and 6.0 Hz, 1H), 4.50 (dd, J = 6.0 and 9.0 Hz, 1H), 4.05 (dd, J = 5.0 and 9.0 Hz, 1H), 1.41 (s, 3H). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.84; H, 5.68, N, 4.11.

(3*R*,15b*S*,a*S*)-15b-Methyl-3-phenyl-2,3-dihydro-15b*H*-benz[*c*]oxazolo[3,2-*a*]quinolino[2,3-*e*]azepin-5-one (1b). Prepared according to the general procedure from keto-ester **2b** (1.83 g, 5.72 mmol) and (*R*)-phenylglycinol (785 mg, 5.72 mmol). ^{1}H NMR analysis of the crude product indicated the formation of only one diastereoisomer (de > 95%). Flash chromatography of the residue on silica gel (EtOAc/CH_2Cl_2/cyclohexane: 1/8/1) afforded lactam (a*S*,3*R*,15b*S*)-**1b** as a white solid (1.825 g, 81%, mp 79 °C). $[\alpha]^{20}_D = -54.6°$ (*c* 0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 8.15 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.64 (m, 1H), 7.55−7.44 (m, 5H), 7.34 (t, J = 7.0 Hz, 2H), 7.27 (d, J = 7.0 Hz, 1H), 5.42 (d, J = 6.0 Hz, 1H), 4.43 (dd, J = 6.0 and 9.0 Hz, 1H), 4.27 (d, J = 9.0 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 163.9, 153.5, 149.3, 142.7, 141.0, 140.5, 136.3, 132.7, 132.1, 130.2, 130.0, 129.5, 129.1 (2 C), 128.8, 128.2, 128.1, 127.8, 127.4, 127.0, 122.4, 94.2, 71.5, 62.5, 27.9. IR (KBr) ν_{max}: 2924, 1636, 1618, 1455, 1402, 1307, 760, 701 cm^{-1}. Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.52; H, 5.16, N, 7.11.

(a*S*,3*R*,13b*S*)-13b-Methyl-3-phenyl-2,3-dihydro-13b*H*-benz[*c*]oxazolo[3,2-*a*]pyrido[2,3-*e*]azepin-5-one (1c). Prepared according to the general procedure from keto-ester **2c** (129 mg, 0.48 mmol) and (*R*)-phenylglycinol (66 mg, 0.48 mmol). ^{1}H NMR analysis of the crude product indicated the formation of only one diastereoisomer (de > 95%). Flash chromatography of the residue on silica gel (EtOAc) afforded lactam (a*S*,3*R*,13b*S*)-**1c** as a white solid (118 mg, 72%, mp 149 °C). $[\alpha]^{20}_D = +24.9°$ (*c* 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.82 (dd, J = 1.0 and 8.0 Hz, 1H), 8.18 (dd, J = 1.0 and 9.0 Hz, 1H), 8.06 (m, 1H), 7.65 (m, 1H), 7.50 (m, 4H), 7.39−7.23 (m, 4H), 5.40 (d, J = 6.0 Hz, 1H), 4.41 (dd, J = 2.0 and 8.0 Hz, 1H), 4.28 (dd, J = 1.0 and 8.0 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 163.7, 153.7, 152.3, 142.3, 140.9, 139.2, 135.8, 132.0, 130.2, 129.9, 129.3, 129.1 (2 C), 128.2, 127.4 (2 C), 123.1, 122.5, 94.2, 71.4, 62.4, 27.2. IR (KBr) ν_{max}: 1633, 1402, 763, 748, 701 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.12; H, 5.46, N, 8.08.

(a*S*,3*R*,15b*S*)-15b-Methyl-3-phenyl-2,3-dihydro-15b*H*-naphth[2,1-*c*]oxazolo[3,2-*a*]pyrido[2,3-*e*]azepin-5-one (1d). Prepared according to the general procedure from keto-acid **5d** (220 mg, 0.75 mmol) and (*R*)-phenylglycinol (102 mg, 0.75 mmol) for 72 h. ^{1}H NMR analysis of the crude product indicated the formation of only one diastereoisomer (de > 95%). Flash chromatography of the residue on silica gel (EtOAc/CH_2Cl_2/cyclohexane, 1/8/1) afforded (a*S*,3*R*,15b*S*)-**1d** as a colorless oil (229 mg, 78%). $[\alpha]^{20}_D = -67.5°$ (*c* 0.4, CH_2Cl_2) ^{1}H NMR ($CDCl_3$): δ 8.82 (dd, J = 1.0 and 1.5 Hz, 1H), 8.14 (dd, J = 2.0 and 5.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.80−7.73 (m, 2H), 7.43−7.20 (m, 8H), 5.30 (d, J = 6.0 Hz, 1H), 4.28 (dd, J = 6.0 and 10.0 Hz, 1H), 4.19 (d, J = 10.0 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 163.8, 153.8, 151.1, 142.2, 140.9, 138.4, 134.6, 132.8, 132.0, 131.8, 130.6, 129.1 (2 C), 128.4, 128.2, 127.4, 127.4, 127.3 (2 C), 126.8, 122.9, 120.1, 95.0, 71.6, 61.7, 26.6. HRMS (EI): calcd for $C_{26}H_{20}N_2O_2$ 392.1516, found 392.1517.

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Supporting Information Available: Experimental procedures for compounds **3′a**, **3b,c**, **4b,c**, **2a−d**, and **5a,c,d**; spectroscopic data for all compounds (including ^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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