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Novel Asymmetric Approach to Proline-Derived Spiro-*β*-lactams

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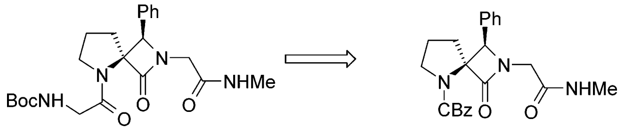
Abstract: We describe a novel asymmetric approach using Staudinger chemistry to proline-derived spiro-*β*-lactams. A chiral group at C-4 of the acid chloride of proline directs the stereoselectivity of Staudinger chemistry and later is sacrificed to obtain optically active 5.4-spiro-*β*-lactams. The scope, limitations, and mechanistic rationale for the observed results of Staudinger Chemistry of the acid chloride of 4-alkyl(aryl)sulfonyloxy-L-proline with imines are also discussed.

The conceptual approach of peptidomimetics uses peptides and proteins as leads to discover novel classes of compounds of biological importance. One approach to the advancement of a peptide lead to a therapeutically desirable small molecule drug uses cyclic peptide derivatives and conformational constraints as logical steps in the process.[1] Conformational constraints induced on introduction of cyclic amino acids (such as proline) into peptides or proteins is enhanced by quarternization of the stereocenter. Efficient methods were developed to synthesize such unusual amino acids, and one such method was recently published by Kawabata et al.[2] Alonso et al. combined the features of a spiro system[3] and α,α-disubstituted *β*-lactams[4] to propose the introduction of a 5.4-spirolactam, which was validated using high-level ab initio calculations and thereby introduced (±)-**1** as a novel *β*-turn mimetic.[5,6] The tripeptidic *β*-turn (±)-**1** was obtained from the spirolactam (±)-**2** derived from a Staudinger reaction between the acid chloride of *N*-carbonyloxybenzyl-L-proline and *N*-methyl-2-[[(1*E*)-phenylmethylene]amino]acetamide. Our combined interest in the area of *β*-turn mimetics[7] and the synthetic use of D- and L-proline led us to explore an optically active approach to proline-derived 5.4-spiro *β*-lactams.[8,9]



(±)-1 **(±)-2**

While asymmetric Staudinger chemistry of optically active acid chloride of D- or L-proline with achiral imines is impossible due to the loss of stereochemistry at C-2,[10] the use of chiral ketenes[11] or chiral imines[12] are viable options. We have developed a strategy that exploits the asymmetric center resident in C-4 of *trans*-4-hydroxy-L-proline to influence the diastereoselectivity in the Staudinger reaction and which may be sacrificed after the fact. Whereas, utilization of the asymmetry resident in C-4 of proline to influence the stereoselectivity in Staudinger was reported by Croce and Rosa,[13] the concept of sacrificing the asymmetry to eventually deliver optically active "proline-derived" Staudinger products from achiral imines is novel. We herein present the details of the first direction to such a strategy highlighting the fact that our results are similar in regards to the configuration at the spiranic carbon of the predominant product (vide infra), but are in contrast with the overall outcome from those of Croce and Rosa's possibly due to differences in mechanistic pathways predetermined by the reaction conditions employed.[14−16]

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[1] Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039−3049.

[2] Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012−13013.

[3] (a) Ward, P.; Ewan, G. B.; Jordan, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *33*, 1848−1851. (b) Hinds, M. G.; Welsh, J. H.; Brennand, D. M.; Fisher, J.; Glennie, M. J.; Richards, N. G. J.; Turner, D. L.; Robinson, J. A. *J. Med. Chem.* **1991**, *34*, 1777−1789. (c) Müller, G.; Hessler, G.; Decornez, H. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 894−896.

[4] Palomo, C.; Aizpurua, J. M.; Benito, A.; Galarza, R.; Khamrai, U. K.; Vazquez, J.; Pascual-Teresa, B.; Nieto, P. M.; Linden, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3056−3058.

[5] Alonso, E.; Lopez-Ortiz, F.; Del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333−6338.

[6] For references on 5.*n*-spirolactams (where $n \neq 4$), see: Fernández, M. M.; Diez, A.; Rubiralta, M.; Montenegro, E.; Casamitjana. N.; Kogan, M. J.; Giralt, E. *J. Org. Chem.* **2002**, *67*, 7587−7599 and references therein.

[7] Chianelli, D.; Kim, Y.-C.; Lvovskiy, D.; Webb, T. R. *Bioorg. Med. Chem.* **2003**, *11*, 5059−5068.

[8] This work was presented at 225th National Meeting of the American Chemical Society, New Orleans, LA, 2003; Abstract ORGN 452.

[9] The "*R*" and "*S*" configurations at the spiranic carbon of spirolactam induce different conformations when incorporated in a peptide: (a) Brown, J. R.; Clegg, S. P.; Ewan, G. B.; Hagan, R. M.; Ireland, S. J.; Jordan, C. C.; Porter, B.; Ross, B. C.; Ward, P. In *Molecular Recognition: Chemical and Biochemical Problems;* Roberts, S. M., Ed.; Royal Society of Chemistry Special Publication No. 78; Royal Society of Chemistry: Lechtworth, 1989; pp 94−111. (b) Ward, P.; Ewan, G. B. Eur. Patent 0 360 390 A1, 1989. (c) Reference 3a.

[10] Staudinger reaction proceeds via ketene mechanism when base is used in conjunction with an acid chloride. In the absence of a base, a direct attack of the imine on acid chloride is the first step in the mechanism.

[11] For the first efficient approach, see: (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787−3790. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783−3786.

[12] For first report on this approach, see: Hubschwelen, C.; Scgmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206−2209.

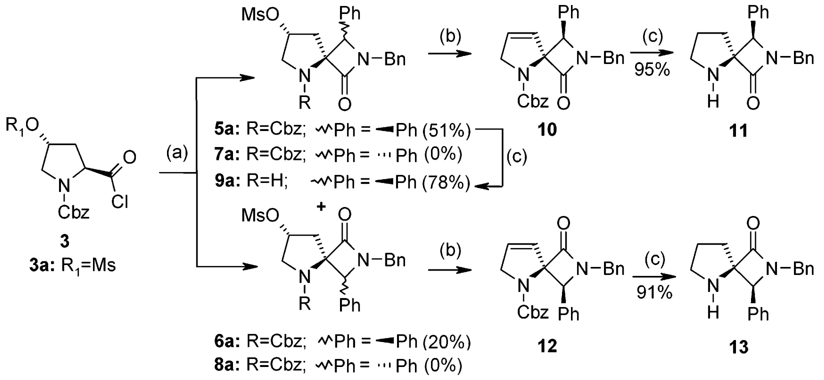
[13] Croce, P. D.; Rosa, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1193−1199.

[14] For variety of mechanistic possibilities for Staudinger reaction, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-lactams;* Georg, G. I., Ed.; VCH: New York 1992; pp 295−368.

[15] For theoretical study on ketene mechanistic pathway, see: (a) Cossío, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085−2093. (b) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995−1004. (c) Venturini, A.; González, J. *J. Org. Chem.* **2002**, *67*, 9089−9092.

10.1021/jo049430o CCC: $27.50

SCHEME 1[a]

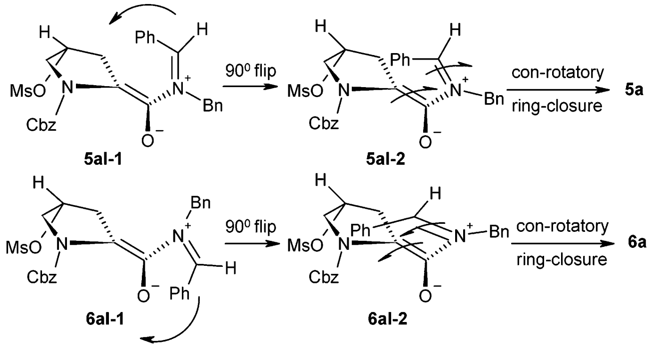


[a] Reaction conditions: (a) *E*-PhCH=NBn (**4a**), Et_3N/DCM, rt, 14 h; (b) K_2CO_3/MeOH, rt (16 h), 70 °C (3 h); (c) H_2, 10% Pd/C, EtOH.

The Staudinger reaction between an in-situ generated ketene[10] derived from optically active acid chloride **3a** and *N*-benzyl-*N*-[(1*E*)-phenylmethylene]amine (**4a**) was conducted in dichloromethane using Et_3N as the base at ambient temperature (Scheme 1). While four diastereomers (**5a**–**8a**) are theoretically possible, analysis of the crude reaction mixture by TLC indicated two major products while HPLC showed a 99:1 ratio of two peaks. Flash chromatography purification of the crude afforded two diastereomerically pure β-lactams **5a** and **6a** (single enantiomers in each case) in 51% and 20% isolated yields, respectively, exhibiting identical retention times in HPLC. The structures of **5a** and **6a** could not be deciphered at this stage since the ^{1}H NMR was complicated by the existence of rotamers arising from the *N*-Cbz group. To demonstrate that this was in fact the case, the Cbz group of **5a** was removed to give pyrrolidine **9a** as a single diastereomer as evidenced by its simplified ^{1}H NMR. Furthermore, the structure of **5a** was shown beyond doubt by obtaining its X-ray crystal structure. We moved toward our goal by eliminating methanesulfonic acid in **5a** using K_2CO_3/MeOH to obtain a single dihydropyrrole isomer **10**.[17] Olefin **10** was deprotected and hydrogenated in one-pot to afford the "proline-derived" Staudinger product **11**.

The structure of **6a** was shown to be as indicated by converting it to proline-derived Staudinger product **13** via the elimination of methanesulfonic acid, hydrogenation of the resultant double bond of **12**, and concomitant removal of the Cbz protecting group. The ^{1}H NMR of **13** was identical to **11**; and, being derived from two different compounds (or diastereomers) **5a** and **6a**, compounds **11** and **13** are enantiomeric to each other as evidenced by their optical rotations (see the Experimental Section). Since **11** and **13** are enantiomers, and since **13** was derived from **6a**, β-lactam **6a** should have the structure as displayed.

SCHEME 2. Proposed Mechanism of Staudinger Chemistry on Proline-Derived Ketenes



Scheme 2 shows the mechanism of Staudinger reaction involving the well-accepted attack of the imine lone pair from the least hindered side of the ketene (opposite of the side housing the Cbz group). Additionally, the asymmetric carbon of the ketene differentiates the two faces of the pyrrolidine ring. As a result, the imine either attacks from the top (β) or from the bottom (α) face of the proline to give the corresponding zwitterionic intermediates **5aI-1** and **6aI-1**. It is conceivable that C–N$^+$ bond in **5aI-1** could rotate by 270° to form intermediate **6aI-2** and C–N$^+$ bond of intermediate **6aI-1** could also rotate the same angle to form **5aI-2**. As the rotation from **5aI-1** and **6aI-1** to **5aI-2** and **6aI-2**, respectively, is only 90 °C, the principle of least motion could be invoked to form the proposed intermediates.[14] In either intermediate, a 90° flip is necessitated by the impending con-rotatory ring closure of **5aI-2** and **6aI-2** leading to β-lactams **5a** and **6a**, respectively. In essence, an attack on the less hindered side of the ketene carbonyl by the imine either via β-face or an α-face approach followed by con-rotatory ring-closure leads to **5a**, and **6a**, respectively.

The effect of substituents R_1 of **3**, and R_2 and R_3 of the imine **4** on diastereoselectivity of the Staudinger chemistry was probed. Keeping R_1 and R_2 unchanged as methanesulfonyl and benzyl, repectively, and changing R_3 from aliphatic to aromatic, improves the yield and diastereoselectivity to afford the (3,4)-*syn* products [such as **5** and **6**; Table 1]. For example, when R_2 = *p*-methoxybenzyl, and R_3 is changed from being alkyl (entries 2–4) to aromatic (entries 5–6), the evaporative light-scattering detector (ELSD) yield of (3,4)-*syn* products improved drastically from 0%-28% to 97%-99%. None of the other respective diastereomeric (3,4)-*anti* products

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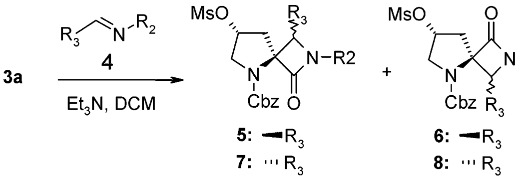
(16) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791.

(17) The alkene protons of **10** resonate at 6.07 and 5.83 ppm suggesting that the double bond is between C-7 and C-8; see: Donohoe, T. J.; House D. *J. Org. Chem.* **2002**, *67*, 5015–5018. Lack of signals at about 7.0 ppm precludes the possibility of a C-6, C-7 double bond in **10**; see: Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646–6652. In any event, the position of the double bond was immaterial to the outcome of the project.

TABLE 1. Dependence of Disatereoselectivity on Nature of Imine



entry	**5−8**	imine (**4**) R$_2$	R$_3$	(**5**,**6**)/(**7**,**8**)[a]	**5**/**6**[b]
1	**a**	benzyl	phenyl	99/0	51/20
2	**b**	*p*-OMe-benzyl	methyl	28/20	*c*
3	**c**	*p*-OMe-benzyl	cyclopropyl	0/0[d]	0/0[d]
4	**d**	*p*-OMe-benzyl	cyclohexyl	19/5	*c*
5	**e**	*p*-OMe-benzyl	*p*-OMe-phenyl	97/0	50/6
6	**f**	*p*-OMe-benzyl	*p*-F-phenyl	99/0	54/9
7	**g**	cyclopropyl	methyl	0/0[d]	0/0[d]
8	**h**	cyclopropyl	cyclopropyl	4/4	*c*
9	**i**	cyclopropyl	cyclohexyl	20/17	*c*
10	**j**	cyclopropyl	*p*-OMe-phenyl	87/0	41/12
11	**k**	cyclopropyl	*p*-F-phenyl	97/0	58/d

[a] Ratios are in percent from LCMS-ELSD of crude reaction mixtures. [b] The numbers in ratios are isolated yields of purified products. [c] Not isolated. [d] Could not be determined.

TABLE 2. Effect of Changing R$_1$ on Diastereoselectivity

entry	**5−8**	R$_1$	yields[a] (%) 5	6	7	8	(**5** + **6**)/(**7** + **8**)
1	**a**	Ms	51	20	0	0	100
2	**l**	Ts	34	24	4	0	14.5
3	**m**	Ns	18	13	13	5	1.7

[a] Yields are of pure products.

(such as **7/8**) are observed on such a change. Within the aromatic series, installing either an electron donating or withdrawing group such as *p*-methoxyphenyl (PMP, entry 5) or *p*-fluorophenyl (PFP, entry 6) provides β-lactam with a preference for the β-approach of the imine [PMP$_{\beta/\alpha}$(**5e**/**6e**) = 50/6 and PFP$_{\beta/\alpha}$(**5f**/**6f**) = 54/9 vs phenyl$_{\beta/\alpha}$(5**a**/6**a**) = 51/20].

While keeping R$_2$ and R$_3$ unchanged, we anticipated that bulking R$_1$ would bias the outcome of Staudinger chemistry toward products of the type **5a**. When R$_1$ was methanesulfonyl (**3a**), only the 3,4-*syn* products such as **5** and **6** were formed in a 2.6:1 ratio (entry 1, Table 2). When R$_1$ was changed from a methanesulfonyl (**3a**) to *p*-toluenesulfonyl group (**3l**) (entry 2, Table 2), we observed both the (3,4)-*syn* and the (3,4)-*anti* products in a 14.5/1 ratio; this ratio further deteriorated to 1.7/1 when R$_1$ was changed to 2-naphthylsulfonyl (Ns) (**3m**).

In conclusion, we have presented the utility of asymmetric center (C-4) on L-proline to conduct Staudinger chemistry *and* take it further through simple chemistry manipulations to optically active "proline-derived" Staudinger products such as **11** and **13**. We have also demonstrated that within the realms of our substituent-probing on imines and proline R$_1$ should be aliphatic, R$_2$ of the imine could be either aliphatic or aromatic, and R$_3$ should be aromatic for the achievement of good stereoselectivity in Staudinger reactions. Further expansion of this chemistry and utility of these Staudinger products and their analogues in synthesis of novel β-turns will be an area of future research.[18]

Experimental Section

General Procedure for Synthesis of Lactams 5 and 6. A 1.3 M solution of acid chloride **3** (1.0 equiv) in CH_2Cl_2 was added to a 0 °C solution of a 0.32 M solution of **4** (1.0 equiv) in CH_2Cl_2 containing triethylamine (1.5 equiv). After 14 h at room temperature, the reaction mixture was washed successively with 1 M HCl (2 × 5 mL), satd $NaHCO_3$ (2 × 5 mL), and brine (5 mL). The organic layer was separated, dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo to give crude products which were purified as indicated individually.

(−)-(3*R*,4*S*,7*R*)-2-Benzyl-5-benzyloxycarbonyl-7-methanesulfonyloxy-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (5a). The crude material was recrystallized from 5 mL of methanol to give (480 mg, 36%) of **5a** as a white solid. The mother liqour was evaporated and purified by flash chromatography to give additional **5a** (200 mg, 15%): mp 115−117 °C; $R_f = 0.34$ (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$; major rotamer) δ 7.45 (s, 1H), 7.04−7.30 (m, 13 H), 6.79 (d, J = 7.2 Hz, 1H), 4.71−5.26 (m, 4H), 4.31 (s, 1H), 4.06 (d, J = 14.8 Hz, 1H), 3.43−3.66 (m, 2H), 3.05 (s, 3H), 2.54−2.84 (m, 2H); ^{13}C NMR ($CDCl_3$; major rotamer) δ 166.7, 153.5, 136.3, 135.3, 133.7, 129.2, 128.7, 128.63, 128.59, 128.5, 128.2, 128.0, 127.6, 126.9, 74.1, 69.7, 69.2, 67.4, 51.8, 45.4, 39.5, 38.9. IR (neat) ν 1749, 1712, 1434, 1396, 1363 cm^{-1}. MS (m/z) 521.5 (MH$^+$); $[\alpha]^{20}{}_D = -100.34$ (c 0.87, CH_2Cl_2). FAB-HRMS calcd for ($C_{28}H_{28}N_2O_6S + H^+$) 521.1741, found 521.1739. Anal. Calcd for $C_{28}H_{28}N_2O_6S$: C, 64.60; H, 5.42; N, 5.38. Found: C, 64.48; H, 5.51; N, 5.35.

(+)-(3*S*,4*R*,7*R*)-2-Benzyl-5-benzyloxycarbonyl-7-methanesulfonyloxy-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (6a): oil (20%); $R_f = 0.12$ (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$; major rotamer) δ 6.99−7.12 (m, 15H), 4.75−5.30 (m, 4H), 4.55 (s, 1H), 3.44−4.09 (m, 3H), 3.01 (s, 3H), 2.50−2.78 (m, 2H); ^{13}C NMR ($CDCl_3$; major rotamer) δ 166.9, 153.3, 136.1, 135.2, 133.3, 128.9, 128.5, 128.42, 128.37, 128.1, 128.04, 127.99, 127.88, 127.7, 78.5, 76.8, 69.8, 67.2, 54.4, 44.9, 41.9, 38.9; IR (neat) ν 1760, 1713, 1456, 1403, 1348 cm^{-1}; MS (m/z) 521.5 (MH$^+$); $[\alpha]^{20}{}_D = +93.46$ (c 0.78, CH_2Cl_2); FAB-HRMS calcd for ($C_{28}H_{28}N_2O_6S + Na^+$) 543.1560, found 543.1560.

(−)-(3*R*,4*S*)-5-Benzyloxycarbonyl-2-benzyl-3-phenyl-2,5-diazaspiro[3.4]oct-7-en-1-one (10). Solid K_2CO_3 (109 mg, 0.79 mmol) was added to a solution of **5a** (157 mg, 0.30 mmol) in methanol (2 mL) and stirred for 16 h at room temperature and at 70 °C for another 3 h. The reaction mixture was concentrated in vacuo, and the resulting residue was partitioned between water (4 mL) and EtOAc (4 mL). The organic layer was separated and dried (Na_2SO_4), decanted, and concentrated in vacuo to afford **10** (125 mg, 98%) as colorless oil: ^{1}H NMR ($CDCl_3$; major rotamer) δ 6.7−7.5 (m, 15H), 6.07 (d, J = 6.3 Hz, 1H), 5.83 (d, J = 6.3 Hz, 1H), 5.18 (d, J = 14.8 Hz, 1H), 4.97 (d, J = 13.8 Hz, 1H), 4.79 (d, J = 13.8 Hz, 1H), 4.54 (d, J = 13.8 Hz, 1H), 4.41 (s, 1H), 4.2−4.4 (m, 2H); ^{13}C NMR ($CDCl_3$; major rotamer) δ 168.3, 168.0, 153.8, 153.8, 136.7, 135.9, 135.6, 135.3, 134.5, 134.3, 129.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.5, 126.6, 85.6, 84.7, 68.0, 67.5, 67.0, 55.6, 55.0, 45.5, 45.5; MS (m/z) 425.3 (MH$^+$); $[\alpha]^{20}{}_D = -126.33$ (c 0.47, CH_2Cl_2); FAB-HRMS calcd for ($C_{27}H_{24}N_2O_3$ + Na $^+$) 447.167, found 447.1678.

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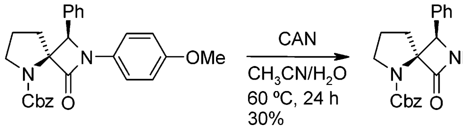
(18) Lactam nitrogen of racemic **14** was deprotected using CAN in 30% unoptimized yield to afford the azetidinone **15**. Further application of azetidinones such as **15** in optically active form toward synthesis of novel β-turns will be reported in due course: Siegel, D.; Khasanov, A.; Thiruvazhi, M. Unpublished results.



14 **15**

(+)-(3*S*,4*R*)-5-Benzyloxycarbonyl-2-benzyl-3-phenyl-2,5-diazaspiro[3.4]oct-7-en-1-one (12). Synthesized from **6a** in a similar manner as **10**: oil (69%); $R_f = 0.74$ (50% EtOAc/hexanes); ^{1}H NMR (CDCl$_3$; major rotamer) δ 6.70−7.50 (m, 15 H), 6.07 (d, $J = 6.3$ Hz, 1H), 5.83 (d, $J = 6.3$ Hz, 1H), 5.20 (d, $J = 15.09$ Hz, 1H), 4.98 (d, $J = 14.79$ Hz, 1H), 4.78 (d, $J = 12.57$ Hz, 1H), 4.54 (d, $J = 11.94$ Hz, 1H), 4.41 (s, 1H), 4.2−4.4 (m, 2H); ^{13}C NMR (CDCl$_3$; major rotamer) δ 168.1, 167.8, 153.6, 153.5, 136.4, 135.7, 135.4, 135.1, 134.3, 134.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.97, 127.95, 127.8, 127.6, 127.2, 126.4, 85.4, 84.4, 67.7, 67.2, 66.7, 55.3, 54.8, 45.3, 45.2; MS (*m*/*z*) 425.2 (MH$^+$); $[\alpha]^{20}_{D} = +125.0$ (*c* 0.27, CH$_2$Cl$_2$); FAB-HRMS calcd for (C$_{27}$H$_{24}$N$_2$O$_3$ + Na$^+$) 447.1679, found 447.1676.

(−)-(3*R*,4*S*)-2-Benzyl-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (11). A solution of **10** (30.0 mg, 0.071 mmol) in ethanol (2 mL) containing 5 mg of 10% Pd/C catalyst was hydrogenated at atmospheric pressure for 1 h. The mixture was filtered through Celite, and Celite was washed with methanol. The filtrate was concentrated in vacuo to give 19.7 mg (95%) of (3*R*,4*S*)-2-benzyl-3-phenyl-2,5-diazaspiro[3.4]octan-1-one as colorless oil: ^{1}H NMR (CDCl$_3$) δ 7.08−7.47 (m, 10 H), 4.93 (d, $J = 14.8$ Hz, 1H), 4.37 (s, 1H), 3.85 (d, $J = 14.8$ Hz, 1H), 2.84−2.96 (m, 1H), 2.52−2.66 (m, 1H), 2.28−2.38 (m, 1H), 2.04−2.12 (m, 1H), 1.62−1.95 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 173.2, 136.1, 135.8, 129.3, 129.0, 128.6, 128.6, 128.0, 127.2, 80.6, 69.9, 46.4, 44.3, 33.3, 24.7; MS (*m*/*z*) 293.4 (MH$^+$); $[\alpha]^{20}_{D} = -71.88$ (*c* 0.13, CH$_2$Cl$_2$); FAB-HRMS calcd for (C$_{19}$H$_{20}$N$_2$O + H$^+$) 293.1648, found 293.1650.

(+)-(3*S*,4*R*)-2-Benzyl-3-phenyl-2,5-diazaspiro[3.4]octan-1-one (13). Compound **13** was obtained from **12** in a similar fashion as described for **11**: colorless oil (91%); ^{1}H NMR (CDCl$_3$) δ 7.08−7.47 (m, 10 H), 4.94 (d, $J = 14.8$ Hz, 1H), 4.37 (s, 1H), 3.85 (d, $J = 14.8$ Hz, 1H), 2.84−2.96 (m, 1H), 2.52−2.66 (m 1H), 2.28−2.38 (m, 1H), 2.04−2.12 (m, 1H), 1.62−1.95 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 173.4, 136.1, 135.8, 129.3, 129.0, 128.6, 128.6, 128.0, 127.2, 80.6, 69.9, 46.4, 44.3, 33.3, 24.7; MS (*m*/*z*) 293.2 (MH$^+$); $[\alpha]^{20}_{D} = +71.70$ (*c* 0.11, CH$_2$Cl$_2$); FAB-HRMS calcd for (C$_{19}$H$_{20}$N$_2$O + H$^+$) 293.1648, found 293.1650.

Supporting Information Available: Experimental details for **3a**,**l**−**m**, **4a**, **5e**,**f**,**j**−**m**, **6e**,**f**,**j**,**m**, and **9a**, ^{1}H and ^{13}C NMR data for **5a**, **6a**, **9a** (only ^{1}H), and **10**−**13**, and X-ray crystallographic data for **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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