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Base-Controlled Diastereodivergent Synthesis of (*R*)- and (*S*)-2-Substituted-4-alkylidenepiperidines by the Wadsworth−Emmons Reaction

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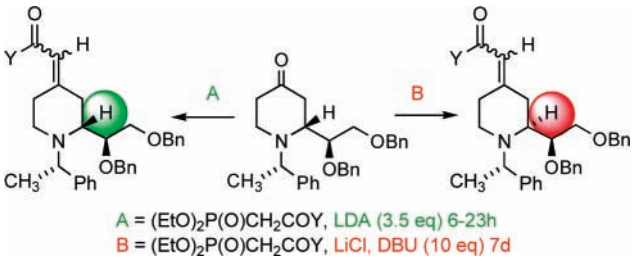


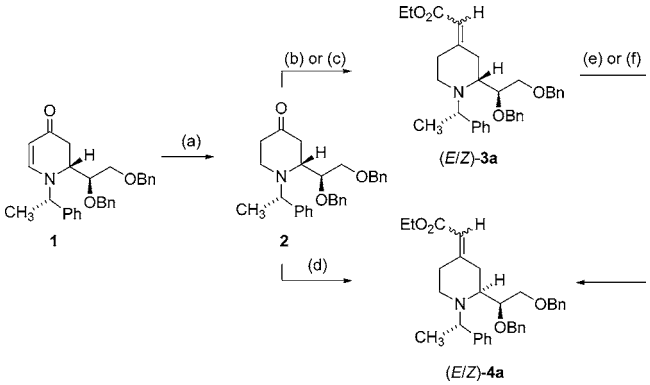
Significant base and reaction time effects have been observed in the Wadsworth−Emmons reaction between a chiral 2-substituted-4-oxopiperidine and phosphonates. In the reactions carried out using a large excess of DBU as the base and prolonged reaction times, the initially formed 2*R* products epimerized into thermodynamically more stable products through a retro-conjugate/conjugate addition sequence and 2-substituted-4-alkylidenepiperidines of 2*S* configuration were selectively synthesized. In contrast, when the reaction was carried out using LDA as the base, epimerization did not occur and 2-substituted-4-alkylidenepiperidines of 2*R* configuration were obtained with excellent yields.

The piperidine ring is a common structural feature in many natural products and synthetic compounds with biological activity.[1] The known activity and potential of such compounds as drugs has encouraged the development of numerous synthetic approaches,[2] usually directed to the stereoselective synthesis of target compounds but also to the development of some general synthetic methodologies in which preformed chiral nonracemic compounds are used as building blocks for the construction of a wide variety of simple or complex frameworks containing the piperidine ring. In this context, it is worth mentioning the use of chiral nonracemic *N*-cyanomethyloxazolidines,[3] *N*-alkoxycarbonyl 2,3-dihydro-4-pyridones,[4] 6-substituted-2,3-dihydropiperidine-2-carboxylates,[5] and bicyclic piperidones.[6]

As a contribution to this area, we synthesized[7] an enantiomerically pure chiral enaminone (**1**) and studied its utility as a building block for the synthesis of enantiomerically pure (*R*)-4-oxopipecolic acid[7] and (2*R*,4*S*)-*N*-Boc-4-hydroxypipecolic acid *tert*-butylamide.[8]

The Wittig reaction[9] and its later variants, the Horner[10] and Wadsworth−Emmons[11] reactions, are the most versatile syn-

SCHEME 1[a]



[a] Reagents and conditions: (a) L-Selectride, THF, 48 h, −78 °C, 85%; (b) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU (1.5 equiv), CH_3CN, 8 h, rt, 82%; (c) $(EtO)_2P(O)CH_2CO_2Et$, LDA (3.5 equiv), THF, 14 h, rt, 97%; (d) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU (10 equiv), CH_3CN, 7 days, rt, 78%; (e) LiCl, DBU (10 equiv), CH_3CN, 7 days, rt, 51%; (f) DBU (10 equiv), CH_3CN, 7 days, rt, 50%.

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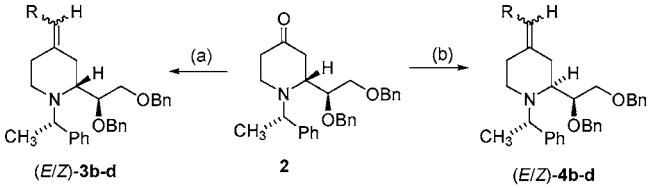
TABLE 1. Synthesis of (*R*)- and (*S*)-2-Substituted-4-ethoxycarbonylmethylpiperidines (*E*/*Z*)-3a

entry	base (equiv)	additive	reaction time	(*E*/*Z*)-**3a**/(*E*/*Z*)-**4a**	dr[a] *E*/*Z*	yield[b] (%)
1[c]	DBU (1.5)	LiCl	8 h	>98:<2	94:6	82
2[c]	DBU (10)	LiCl	7 days	8:92	88:12	78
3[c]	LDA (3.5)	none	14 h	>98:<2	97:3	97
4[d]	DBU (10)	LiCl	7 days	9:91	81:19	51
5[d]	DBU (10)	none	7 days	7:93	90:10	50

[a] *E*/*Z* ratio of major compound determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield after column chromatography on silica gel. [c]Wadsworth−Emmons reaction of compound **2** with triethylphosphonoacetate. [d]Conversion of 2*S* diastereoisomers into 2*R* diastereoisomers.

SCHEME 2[a]



b: R = CO_2CH_3; **c**: R = $CO_2{}^t$Bu; **d**: R = $CON(CH_3)OCH_3$

[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2R$, LDA (3.5 equiv), THF, 6−23 h, rt; (b) $(EtO)_2P(O)CH_2R$, LiCl, DBU (10 equiv), CH_3CN, 7 days, rt.

thetic routes for the preparation of alkenes from carbonyl compounds. To further explore the versatility of enaminone **1** as a synthetic intermediate, the behavior of 4-oxopiperidine **2**, obtained by chemoselective reduction of this enaminone with L-Selectride, in olefination reactions was tested as a tool for the introduction of various substituents at C_4.

In a recently reported[12] preliminary study, it was shown that conversion did not occur or was extremely low in the Wittig reaction of 4-oxopiperidine **2** with ethoxycarbonyltriphenylphosphonium methylide, but the Wadsworth−Emmons reaction of this substrate with triethyl phosphonoacetate led to variable mixtures of alkenes with 2*R* and/or 2*S* configurations depending on the reaction conditions. As a consequence, the reaction can be directed to the synthesis of olefins of 2*R* or 2*S* configuration by using the appropriate base and/or reaction time (Scheme 1).

In this paper, we report on the scope and limitations of this base-controlled process and its application to the diastereodivergent synthesis of (*R*)- and (*S*)-2-substituted-4-alkylidenepiperidines. The Wadsworth−Emmons reaction of 4-oxopiperidine **2** with triethyl phosphonoacetate using DBU as the base only occurred in the presence of lithium chloride[13] and led to mixtures of alkenes of 2*R* and 2*S* configuration. It is worth noting that compounds of 2*S* configuration could also be obtained from 2*R* compounds simply by adding a large excess of DBU (10 equiv) to an acetonitrile solution of (*E*/*Z*)-**3a** and stirring the mixture for 7 days. On the other hand, the Wadsworth−Emmons reaction of 4-oxopiperidine **2** with triethyl phosphonoacetate using LDA as the base led to the exclusive formation of *E*/*Z* olefins of 2*R* configuration in nearly quantitative yield after 14 h. These products did not evolve to the 2*S* diastereoisomers. Results are summarized in Table 1.

TABLE 2. Synthesis of (*R*)- and (*S*)-2-Substituted-4-alkylydenepiperidines (*E*/*Z*)-3b−d and (*E*/*Z*)-4b−d by Wadsworth−Emmons Reaction of Compound 2

entry	R	reaction conditions[a]	dr **3**/**4**	dr[b] *E*/*Z*	yield[c] (%)
1	CO_2CH_3	I	>98:<2	83:17	92
2	CO_2CH_3	II	3:97	88:12	83
3	$CO_2{}^t$Bu	I	>98:<2	98:2	99
4	$CO_2{}^t$Bu	II	7:93	75:25	76
5	$CON(CH_3)OCH_3$	I	>98:<2	79:21	99
6	$CON(CH_3)OCH_3$	II	3:97	73:27	78

[a] I: Wadsworth−Emmons reaction of **2** with the corresponding diethylphosphonate for 6 h (entry 5), 16 h (entry 3), or 23 h (entry 1) using LDA (3.5 equiv) as the base. II: Wadsworth−Emmons reaction of **2** with the corresponding phosphonate for 7 days in the presence of LiCl using DBU (10 equiv) as the base. [b]*E*/*Z* ratio of major isomer determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield after column chromatography on silica gel.

To extend the procedure to related substrates, the reaction was tested using other stabilized diethylphosphonates (Scheme 2, Table 2). Wadsworth−Emmons reactions using LDA as the base led to the exclusive formation of compounds with 2*R* configuration as variable *E*/*Z* mixtures in nearly quantitative yield. In all cases, the *E* olefin was the major diastereoisomer. On the other hand, the same phosphonates reacted with 4-oxopiperidine **2** using a large excess of DBU and long reaction times to afford *E*/*Z* mixtures of olefins in which epimerization at C_2 was almost complete. These reactions gave good yields, and the *E* alkene was the major isomer in all cases.

Having established that base-controlled diastereodivergent synthesis of (*R*)- and (*S*)-2-substituted-4-alkylydenepiperidines (*E*/*Z*)-**3a**−**d** and (*E*/*Z*)-**4a**−**d** can be achieved using LDA or a large excess of DBU as the base in the olefination reaction, we tried to extend this methodology using different diethyl β-ketophosphonates. Disappointingly, all attempts to perform the Wadsworth−Emmons reaction using these bases or Martinelli[14] or Mulzer[15] conditions were unsuccessful and compounds **3e**−**g** and **4e**−**g** could not be obtained using this synthetic approach.

An alternative route to the synthesis of (*E*/*Z*)-**3e**−**g** was attempted. This approach is based on the use of the *N*-methoxy-*N*-methylcarbamoyl group as a carbonylic equivalent in organometallic additions directed to the synthesis of ketones.[16] With these compounds in hand, the DBU-promoted epimerization at C_2 could be tested for the synthesis of compounds **4e**−**g**.

The reaction of a 79:21 *E*/*Z* mixture of compound **3d** with organolithium reagents at low temperature cleanly afforded the corresponding α,β-unsaturated ketones (*E*/*Z*)-**3e**−**g** in moderate to excellent yield depending on the organolithium reagent. Treatment of these compounds with excess DBU for 7 days at room temperature in the presence of LiCl led to almost total epimerization at C_2. Compounds **4e**−**g** were obtained as *E*/*Z* mixtures of olefins in which the *E* alkene was the major diastereoisomer (Scheme 3, Table 3).

The *E*/*Z* configuration for all compounds was clearly determined by 2D nuclear Overhauser enhancement experiments. The

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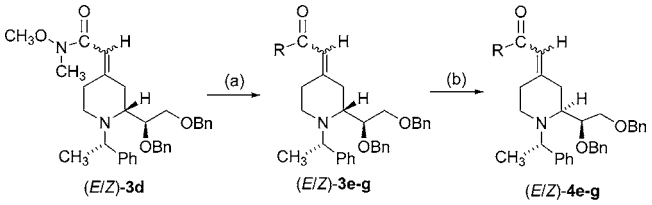
SCHEME 3[a]



[a] Reagents and conditions: (a) RLi, THF, −78 °C; (b) LiCl, DBU (10 equiv) CH_3CN, 7 days, rt.

2*R* configuration of (*E*)- and (*Z*)-**3a** was confirmed by X-ray diffraction analysis of the product with a cis relative configuration derived from hydrogenation of the exocyclic double bond at the C_4 position in the *E*/*Z* mixture obtained by Wadsworth−Emmons olefination of **2** with triethyl phosphonoacetate using LDA as the base.

In summary, an efficient diastereodivergent synthesis of *E*/*Z* mixtures of 2-[(*S*)-1,2-dibenzyloxyethyl]-4-alkylydenepiperidines of *R* and *S* configuration at C_2 starting from 4-oxopiperidone **2** has been developed. Compounds of 2*R* configuration were obtained by means of two different approaches: (a) base-controlled Wadsworth−Emmons reaction of chiral 2-substituted-4-oxopiperidine **2** with diethylphosphonates using LDA as the base and (b) reaction of alkene **3d**, obtained by Wadsworth−Emmons olefination of compound **2**, with organolithium reagents. On the other hand, olefins of 2*S* configuration were obtained using a large excess of DBU as the base also by means of two different approaches: (a) base-controlled Wadsworth−Emmons reaction of chiral 2-substituted-4-oxopiperidine **2** with diethylphosphonates or (b) base-promoted epimerization of compounds of 2*R* configuration.

Experimental Section

(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]-4-piperidone (2). This compound was prepared as previously described in the literature but with slight modifications and showed spectroscopic data consistent with those previously reported.[7b]

Representative Procedure for the Synthesis of (*E*/*Z*)-(*R*)-2-Substituted-4-alkylidenepiperidines 3a−d by Wadsworth−Emmons Reaction. To a solution of the corresponding diethylphosphonate (3.0 mmol) in anhydrous THF (10 mL) at room temperature under argon was added a 2.0 M solution of LDA in heptane/THF/ethylbenzene (1.75 mL, 3.5 mmol). The mixture was stirred for 10 min at room temperature. A solution of compound **2** (443 mg, 1.0 mmol) in anhydrous THF (20 mL) was added, and the resulting mixture was stirred at room temperature until conversion was complete (TLC). The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure, and subsequently chromatographed to yield the corresponding alkene as an *E*/*Z* mixture of diastereoisomers.

(*E*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[(*N*-methoxy-*N*-methyl)carbamoylmethylene]-1-[(*S*)-1-phenylethyl]piperidine [(*E*)-3d]. From a 79:21 *E*/*Z* mixture isolated in 99% yield after purification by column chromatography (first eluent, Et_2O/hexanes 1:1; second eluent, Et_2O/hexanes 4:1): oil; IR absorptions (pure) ν_{max} 1658, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 6.7), 2.17 (1H, dd, J = 13.6, J = 7.6), 2.37−2.50 (2H, m), 2.56−2.59 (1H, m), 2.58−2.62 (1H, m), 2.94−3.03 (1H, m), 3.03−3.10 (1H, m), 3.12 (3H, s), 3.58 (3H, s), 3.63 (1H, dd, J = 10.9, J = 7.0), 3.87−3.94 (2H, m), 4.03 (1H, q, J = 6.7), 4.49 (1H, d, J = 12.1), 4.52 (1H, d, J = 12.1), 4.61 (1H, d, J = 11.7), 4.74 (1H, d, J = 11.7), 6.04 (1H, bs), 7.13−7.39 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (CH_3), 29.4 (CH_2), 30.2 (CH_3), 36.4 (CH_2), 43.8 (CH_2), 56.7 (CH), 58.8 (CH), 61.3 (CH_3), 70.9 (CH_2), 72.6 (CH_2), 73.3 (CH_2), 78.5 (CH), 112.4 (CH), 126.4 (CH), 127.3 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 138.2 (C), 138.8 (C), 144.6 (C), 157.1 (C), 167.5 (C); HRMS (FAB$^+$) calcd for $C_{33}H_{41}N_2O_4$ (MH^+) 529.3066, found 529.3081.

TABLE 3. Synthesis of (*R*)- and (*S*)-2-Substituted-4-alkylydenepiperidines from (*E*/*Z*)-3d

entry	R	reaction conditions[a]	dr **3**/**4**	dr[b] *E*/*Z*	yield[c] (%)
1	CH_3	I	>98:<2	77:23	quant.
2	CH_3	II	<2:>98	94:6	54
3	Bu	I	>98:<2	78:22	80
4	Bu	II	3:97	89:11	56
5	Ph	I	>98:<2	96:4	47
6	Ph	II	<2:>98	89:11	52

[a] I: reaction of (*E*/*Z*)-**3d** with the corresponding organolithium reagent. II: treatment for 7 days of the corresponding compound (*E*/*Z*)-**3e−g** with DBU (10 equiv) in the presence of LiCl. [b] *E*/*Z* ratio of major isomer determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield after column chromatography on silica gel.

Representative Procedure for the Synthesis of (*E*/*Z*)-(*R*)-2-Substituted-4-alkylidenepiperidines 3e−f from Compound 3d. To a solution of a 79:21 *E*/*Z* mixture of compound **3d** (200 mg, 0.38 mmol) in anhydrous THF (8 mL) at −78 °C under argon was added dropwise a commercial solution of the corresponding organolithium reagent (0.57 mmol). The mixture was stirred at −78 °C until conversion was complete (TLC). The reaction was quenched by slow addition of saturated aqueous NH_4Cl (10 mL) at 0 °C and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure and subsequently chromatographed, only if necessary, to yield the corresponding alkene as an *E*/*Z* mixture of diastereoisomers.

(*E*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-(2-oxo)propylidene-1-[(*S*)-1-phenylethyl]piperidine [(*E*)-3e]. From a 77:23 *E*/*Z* mixture: oil; IR absorptions (pure) ν_{max} 1682, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, J = 6.6), 2.01 (3H, s), 2.09 (1H, dd, J = 14.0, J = 6.9), 2.38−2.52 (3H, m), 2.55−2.62 (1H, m), 2.83−2.91 (1H, m), 2.98−3.05 (1H, m), 3.56 (1H, dd, J = 10.8, J = 7.0), 3.77−3.82 (2H, m), 3.96 (1H, q, J = 6.6), 4.43 (1H, d, J = 12.0), 4.47 (1H, d, J = 12.0), 4.54 (1H, d, J = 11.9), 4.69 (1H, d, J = 11.9), 5.90 (1H, bs), 7.10−7.32 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 29.6 (CH_2), 31.7 (CH_3), 35.7 (CH_2), 43.3 (CH_2), 57.2 (CH), 58.8 (CH), 71.1 (CH_2), 72.8 (CH_2), 73.4 (CH_2), 79.1 (CH), 122.3 (CH), 126.6 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 138.3 (C), 138.9 (C), 144.6 (C), 159.0 (C), 198.7 (C); HRMS (FAB$^+$) calcd for $C_{32}H_{38}NO_3$ (MH^+) 484.2851, found 484.2866.

(*E*/*Z*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-(2-oxo-2-phenyl)ethylidene-1-[(*S*)-1-phenylethyl]piperidine [(*E*/*Z*)-3g]. To a 1.9 M solution of phenyllithium in dibutyl ether (0.60 mL, 1.14 mmol) diluted with anhydrous THF (4 mL) at −78 °C under argon was added dropwise a solution of a 79:21 *E*/*Z* mixture of compound **3d** (200 mg, 0.38 mmol) in anhydrous THF (8 mL). The mixture was stirred for 14 h at −78 °C until conversion was complete (TLC). The reaction was quenched by slow addition of saturated aqueous NH_4Cl (10 mL) at 0 °C and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure, and subsequently chromatographed (eluent, Et_2O/hexanes 1:4) to yield 97 mg (47%) of a 96:4 mixture of (*E*)-**3g**/(*Z*)-**3g**. Data for (*E*)-**3g** from a 96:4 *E*/*Z* mixture: oil; IR absorptions (pure) ν_{max} 1705, 1656; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 6.7), 2.25 (1H, dd, J = 13.8, J = 6.8), 2.41−2.50 (1H, m), 2.51 (1H, bdd, J = 14.7, J = 4.0), 2.53−2.63 (1H, m), 2.64 (1H, bdd, J = 13.8, J = 4.5), 2.86−2.94 (1H, m), 3.06−3.12 (1H, m), 3.61 (1H, dd, J = 10.8, J = 7.0), 3.83−3.89 (2H, m), 3.99 (1H, q, J = 6.7), 4.45 (1H, d, J = 12.1), 4.49 (1H, d, J = 12.1), 4.57 (1H, d, J = 11.9), 4.71 (1H, d, J = 11.9), 6.58 (1H, bs), 7.08−7.40 (15H, m), 7.40−7.47 (2H, m), 7.50−7.55 (1H, m), 7.77−7.82 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 30.4 (CH_2), 36.4 (CH_2), 43.5 (CH_2), 57.1 (CH), 58.9 (CH), 71.1 (CH_2), 72.8 (CH_2), 73.5 (CH_2), 78.9 (CH), 119.4 (CH), 126.6 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 132.3 (CH), 138.2 (C), 138.8 (C), 139.1 (C), 144.6 (C), 160.6 (C), 191.4 (C); HRMS (FAB$^+$) calcd for $C_{37}H_{40}NO_3$ (MH^+) 546.3008, found 546.3019.

Representative Procedures for the Synthesis of (*E*/*Z*)-(*S*)-2-Substituted-4-alkylidenepiperidines 4. Method A (Wadsworth−Emmons Reaction). To a suspension of anhydrous lithium chloride [148 mg, 3.5 mmol for the synthesis of (*E*/*Z*)-**4a**,**c**,**d** or 210 mg, 5.0 mmol for the synthesis of (*E*/*Z*)-**4b**] in anhydrous CH_3CN (10 mL) at room temperature under argon was added the corresponding diethylphosphonate [3.5 mmol for the synthesis of (*E*/*Z*)-**4a**,**c**,**d** or 5.0 mmol for the synthesis of (*E*/*Z*)-**4b**] and DBU (1.52 g, 10 mmol). The mixture was stirred for 10 min at room temperature. A solution of compound **2** (443 mg, 1.0 mmol) in anhydrous CH_3CN (20 mL) was added, and the resulting mixture was stirred at room temperature for 7 days. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure, and subsequently chromatographed to yield the corresponding alkenes **4a**−**d** as *E*/*Z* mixtures of diastereoisomers.

(*E*)-(*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[(*N*-methoxy-*N*-methyl)carbamoylmethylene]-1-[(*S*)-1-phenylethyl]piperidine [(*E*)-4d]. From a 73:27 *E*/*Z* mixture isolated in 78% yield after purification by column chromatography (first eluent, Et_2O/hexanes 2:1; second eluent, Et_2O) of crude obtained according to method A: oil; IR absorptions (pure) ν_{max} 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 6.7), 1.76−1.96 (2H, m), 2.58−2.70 (2H, m), 2.87−2.94 (1H, m), 2.96−3.04 (1H, m), 3.08 (3H, s), 3.35−3.40 (1H, m), 3.51 (1H, dd, J = 10.7, J = 7.6), 3.56 (3H, s), 3.70 (1H, dd, J = 10.7, J = 2.0), 3.77 (1H, ddd, J = 7.6, J = 4.3, J = 2.0), 3.88 (1H, q, J = 6.7), 4.38 (1H, d, J = 12.1), 4.43 (1H, d, J = 12.1), 4.56 (1H, d, J = 12.0), 4.65 (1H, d, J = 12.0), 5.53 (1H, bs), 7.06−7.35 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3), 26.9 (CH_2), 30.2 (CH_3), 40.9 (CH_2), 45.4 (CH_2), 56.9 (CH), 57.8 (CH), 60.4 (CH_3), 72.3 (CH_2), 72.8 (CH_2), 73.2 (CH_2), 79.7 (CH), 123.8 (CH), 126.4 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 132.4 (C), 138.7 (C), 139.0 (C), 144.8 (C), 164.4 (C); HRMS (FAB$^+$) calcd for $C_{33}H_{41}N_2O_4$ (MH^+) 529.3066, found 529.3081.

Method B (from Olefins of 2*R* Configuration). To a suspension of anhydrous lithium chloride (148 mg, 3.5 mmol) in anhydrous CH_3CN (10 mL) at room temperature under argon were added successively DBU (1.52 g, 10 mmol) and a solution of the corresponding compound (*E*/*Z*)-**3a**−**g** (1.0 mmol) in anhydrous CH_3CN (20 mL). The mixture was stirred at room temperature for 7 days. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure, and subsequently chromatographed to yield the corresponding alkenes **4a**−**g** as *E*/*Z* mixtures of diastereoisomers.

(*E*)-(*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-(2-oxo)propylidene-1-[(*S*)-1-phenylethyl]piperidine [(*E*)-4e]. Purification by column chromatography (first eluent, Et_2O/hexanes 2:1, second eluent, Et_2O/hexanes 4:1; third eluent, Et_2O) of crude obtained according to method B yielded 260 mg (54%) of a 94:6 mixture of (*E*)-**4e**/(*Z*)-**4e** from which an analytically pure sample of the *E* isomer was isolated by column chromatography using the same system of eluents: oil; IR absorptions (pure) ν_{max} 1716, 1655; $[\alpha]^{25}_D$ = +50.4 (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 6.6), 1.73−1.78 (2H, m), 2.20 (3H, s), 2.53−2.67 (2H, m), 2.92−3.04 (2H, m), 3.36−3.42 (1H, m), 3.50 (1H, dd, J = 10.6, J = 7.4), 3.71 (1H, dd, J = 10.6, J = 2.0), 3.80 (1H, ddd, J = 7.4, J = 4.3, J = 2.0), 3.88 (1H, q, J = 6.6), 4.40 (1H, d, J = 12.1), 4.45 (1H, d, J = 12.1), 4.57 (1H, d, J = 11.9), 4.68 (1H, d, J = 11.9), 5.57 (1H, bs), 7.10−7.34 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 27.0 (CH_2), 29.1 (CH_3), 40.9 (CH_2), 52.7 (CH_2), 56.9 (CH), 58.0 (CH), 72.2 (CH_2), 73.0 (CH_2), 73.3 (CH_2), 79.6 (CH), 125.1 (CH), 126.6 (CH), 127.4 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 132.2 (C), 138.5 (C), 139.0 (C), 144.6 (C), 207.0 (C); HRMS (FAB$^+$) calcd for $C_{32}H_{38}NO_3$ (MH^+) 484.2851, found 484.2840.

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Supporting Information Available: General statement describing materials and methods, spectroscopic data, and full experimental procedure for compound **2**, physical and spectral data for compounds (*E*)-**3a**−**c**, (*E*)-**3f**, (*E*)-**4a**, (*Z*)-**4a**, (*E*)-**4b**, (*E*)-**4c**, (*Z*)-**4c**, (*E*)-**4f**, and (*E*)-**4g**, as well as copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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