

# 1,3-Dipolar Cycloaddition of Furfuryl Nitrones with Acrylates. A Convenient Approach to Protected 4-Hydroxypyroglutamic Acids

Pedro Merino,\* Sonia Anoro, Santiago Franco, Francisco L. Merchan, Tomas Tejero,\* and Victoria Tuñon

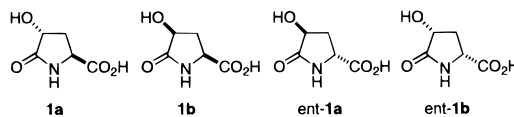
Departamento de Química Orgánica, ICMA, Facultad de Ciencias, Universidad de Zaragoza, E-50009 Zaragoza, Aragon, Spain

Received October 7, 1999

## Introduction

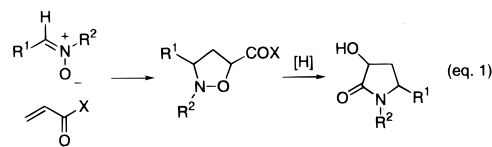
Enantiomerically pure highly functionalized pyrrolidines are basic building blocks for the synthesis of a large variety of biologically interesting nitrogen-containing products.<sup>1</sup> Several polyhydroxylated pyrrolidines also show activity as inhibitors of various glycosidases<sup>2</sup> and other pyrrolidine alkaloids, like preussin and anisomycin, are potent antifungal agents.<sup>3</sup> These findings have prompted significant interest in the synthesis of those and related compounds.<sup>4</sup> In particular, functionalized derivatives of pyroglutamic acid are of current interest because they have been employed as key intermediates in numerous syntheses.<sup>5</sup> Despite all of this activity in the area, there still does not exist a practical stereoselective

synthesis of differentially protected derivatives of 3-hydroxy-2-pyrrolidine-5-carboxylic acid (4-hydroxypyroglutamic acid) **1**.



The different stereoisomers of **1** are valuable chiral synthons of wide applicability whose potential has been scarcely explored due to the few synthetic procedures found in the literature. In this context, Lee and Kaneko<sup>6</sup> reported a method for obtaining the four optical isomers of  $\gamma$ -hydroxyglutamic acid (the open-chain form of 4-hydroxypyroglutamic acid) that relied on fractional crystallization of the corresponding brucine and/or strychnine salts. Koskinen et al.<sup>7</sup> reported the asymmetric synthesis of (4*S*)-4-hydroxy-L-glutamic acid via an asymmetric 1,3-dipolar cycloaddition of a nitron derived from glyoxylic acid with acrylamide derived from Oppolzer's chiral sultam. Nozoe et al.<sup>8</sup> have synthesized a protected derivative of **1a** by stereoselective hydroxylation of methyl *N*-Boc-L-pyroglutamate. More recently, a concise synthesis of racemic *cis*- and *trans*-4-hydroxypyroglutamic acids has been reported.<sup>9</sup>

Recent studies by us<sup>10</sup> and others<sup>11</sup> have shown that nitrones are attractive starting materials for the synthesis of 5-substituted 3-hydroxy-2-pyrrolidinones via 1,3-dipolar cycloadditions with acrylates and subsequent intramolecular cyclization after N–O bond reduction (eq 1).



With the goal of developing a simple route to protected derivatives of **1**, we envisioned that a similar synthetic strategy using furfuryl nitrones **2** could be used to construct the pyrrolidine ring. As we<sup>12</sup> and others<sup>13</sup> have

\* To whom correspondence should be addressed: Fax: +34 976 762075. E-mail: pmerino@posta.unizar.es.

(1) (a) Zhang, R.; Mamai, A.; Madalengoitia, J. S. *J. Org. Chem.* **1999**, *64*, 547–555. (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261–270. (c) Weir, C. A.; Taylor, C. M. *J. Org. Chem.* **1999**, *64*, 1554–1558. (d) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050–2056. (e) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M. C.; Haviari, G.; Célérier, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122–3131. (f) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541–1554. (g) de Koning, H.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N. *Eur. J. Org. Chem.* **1998**, *1729*, 9–1737. (h) van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801–3803. (i) Remuzon, P. *Tetrahedron* **1996**, *52*, 13803–13835.

(2) (a) Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem.* **1999**, *64*, 498–506. (b) Shibano, M.; Nakamura, S.; Motoya, N.; Kusano, G. *Chem. Pharm. Bull.* **1956**, *4*, 472–476. (c) Limbert, G.; Lundt, I.; Zavilla, J. *Synthesis* **1999**, 178–183. (d) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335–1336. (e) Blanco, M. J.; Sardina, F. J. *J. Org. Chem.* **1998**, *63*, 3411–3416. (f) Jager, V.; Muller, R.; Leibold, T.; Hein, M.; Schwarz, M.; Fegler, M.; Jaroskova, L.; Patzel, M.; Leroy, P.-Y. *Bull. Soc. Chim. Belg.* **1994**, *103*, 491–507.

(3) (a) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280–5291. (b) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383–1386. (c) Schwardt, O.; Veith, U.; Gaspard, C.; Jager, V. *Synthesis* **1999**, 1473–1490. (d) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651. (e) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581–590.

(4) (a) Katritzky, A. R.; Cui, X. L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979–1985. (b) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160–1165. (c) Schnell, B.; Bernardinelli, G.; Kundig, E. P. *Synlett* **1999**, 348–350. (d) Dudot, B.; Micouin, L.; Baussane, I.; Royer, J. *Synthesis* **1999**, 688–694. (e) Rasso, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333–1350. (f) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 575–579. (g) Pichon, M.; Frigadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964. (h) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872. (i) Steele, J. *Contemp. Org. Synth.* **1994**, *1*, 95–111. (j) Li, W.-R.; Han, S.-Y.; Jouliffe, M. M. *Heterocycles* **1993**, *36*, 359–388. (k) Galeazzi, R.; Mobbili, G.; Orena, M. In *Targets in Heterocyclic Systems*; Attanasi, O.; Spinelli, D., Eds.; Italian Chemical Society: Rome, 1997; Vol. 1, pp 355–400.

(5) Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303 and references therein.

(6) Lee, Y. K.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3494–3498.

(7) Gefflaut, T.; Bauer, U.; Ariola, K.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **1996**, *7*, 3099–3102.

(8) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329–332.

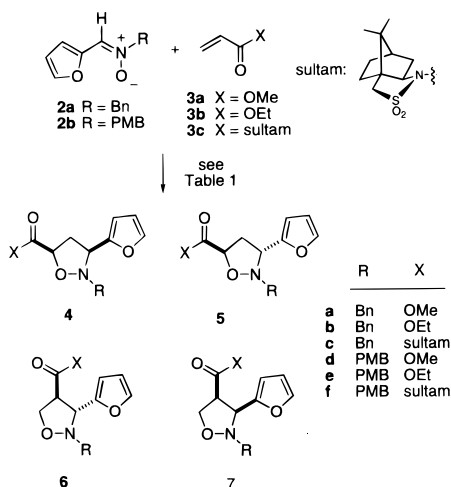
(9) Heinz, L. J.; Lunn, W. H. W.; Murff, R. E.; Paschal, J. W.; Spangle, L. A. *J. Org. Chem.* **1996**, *61*, 4838–4841.

(10) Tejero, T.; Dondoni, A.; Rojo, I.; Merchan, F. L.; Merino, P. *Tetrahedron* **1997**, *53*, 3301–3318.

(11) (a) Shimazaki, M.; Okazaki, F.; Nakasima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823–1836. (b) White, J. D.; Badger, R. A.; Kezar, H. J., III; Pallenberg, A. J.; Schieser, G. A. *Tetrahedron* **1989**, *45*, 6631–6644. (c) Burdisso, M.; Gamba, A.; Gandolfi, R. *Tetrahedron* **1988**, *44*, 3735–3548. (d) Herczegh, P.; Kovacs, I.; Szilagy, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211–1214. (e) Coutouli-Argyropoulou, E.; Malamidou-Xenikaki, E.; Stampelou, X. N.; Alexopoulou, I. N. *Tetrahedron* **1997**, *53*, 707–718.

(12) (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627–5630. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484–5496. (c) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497–5507. (d) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synthesis* **1994**, 1450–1454.

Scheme 1



previously demonstrated, the furan ring provides an excellent template for the efficient introduction of a masked carbonyl group. The presence of a surrogate of a carboxylic acid is crucial for obtaining the target compounds. It can be anticipated that a carboxyl group at C-3 of the isoxazolidine ring ( $R^1=COOR^2$ ) could lead to competitive cyclization with the emerging hydroxyl group after the reduction of the N–O bond. Hence, it seems more advisable to construct the pyrrolidine ring by *in situ* cyclization rather than from  $\gamma$ -hydroxyglutamic acid.

## Results and Discussion

Nitrones **2** were prepared according to our previously reported procedure.<sup>14</sup> The *Z* configuration of both nitrones were ascertained by NOE experiments and, in the case of *N*-benzyl nitrone **2a**, confirmed by X-ray analysis.<sup>15</sup> Our results in the cycloadditions of **2** with several acrylates are illustrated in Scheme 1 and Table 1. We initially investigated the reaction with achiral acrylates under a variety of conditions, some of which appear in Table 1 (entries 1–7 and 11–16). In all cases, mixtures of racemic diastereomeric cycloadducts **4**–**6** were obtained. The diastereoselectivities of these reactions were measured by <sup>1</sup>H NMR (300 MHz) on the crude reaction products. The obtained cycloadducts were separated by preparative, centrifugally accelerated, radial, thin-layer chromatography with a Chromatotron. The regiochemistry of the adducts was evident from analysis of their <sup>1</sup>H NMR spectra. The relative *trans* (endo) stereochemistry of **5** and **6** and the *cis* (exo) stereochemistry of **4** were readily deduced by means of NOE measurements. The high 3,5-regioselectivity and preference for the *endo* approach (leading to *trans* adducts) is comparable to that obtained in similar reactions involving other heterocyclic nitrones.<sup>10,11e,16</sup> In fact, the observed regioselectivity can

Table 1. 1,3-Dipolar Cycloaddition of Nitrones **2** with Alkenes **3**

entry	R	X	reaction conditions	product ratio <sup>a</sup>				yield <sup>b</sup> (%)
				4	5	6	7	
1	Bn	OMe	neat/reflux/5 h	17	70	13	0	80
2	Bn	OMe	CH <sub>2</sub> Cl <sub>2</sub> /reflux/48 h	40	54	6	0	60
3	Bn	OMe	1,2-DCE/reflux/16 h	28	58	14	0	96
4	Bn	OMe	toluene/reflux/12 h	22	58	20	0	68
5	Bn	OMe	CHCl <sub>3</sub> /reflux/24 h	36	50	14	0	93
6	Bn	OEt	1,2-DCE/reflux/16 h	16	67	13	0	75
7	Bn	OEt	toluene/reflux/12 h	27	73	0	0	68
8	Bn	sultam	CH <sub>2</sub> Cl <sub>2</sub> /reflux/48 h	15 <sup>c</sup>	85 <sup>c</sup>	0	0	90
9	Bn	sultam	1,2-DCE/reflux/24 h	16 <sup>c</sup>	84 <sup>c</sup>	0	0	85
10	Bn	sultam	toluene/reflux/16 h	39 <sup>c</sup>	61 <sup>c</sup>	0	0	76
11	PMB	OMe	toluene/reflux/12 h	22	61	17	0	96
12	PMB	OMe	1,2-DCE/reflux/16 h	19	64	17	0	91
13	PMB	OMe	CH <sub>2</sub> Cl <sub>2</sub> /reflux/9 d	20	60	20	0	85
14	PMB	OMe	neat/reflux/5h	10	82	8	0	91
15	PMB	OEt	toluene/reflux/16 h	27	63	10	0	56
16	PMB	OEt	CH <sub>2</sub> Cl <sub>2</sub> /reflux/9 d	20	69	11	0	85
17	PMB	sultam	CH <sub>2</sub> Cl <sub>2</sub> /reflux/48 h	22 <sup>c</sup>	78 <sup>c</sup>	0	0	88
18	PMB	sultam	1,2-DCE/reflux/24 h	25 <sup>c</sup>	75 <sup>c</sup>	0	0	85
19	PMB	sultam	toluene/reflux/16 h	45 <sup>c</sup>	55 <sup>c</sup>	0	0	78

<sup>a</sup> Measured by integration of the corresponding signals in the <sup>1</sup>H NMR spectra. <sup>b</sup> Isolated yield of mixture of isomers. <sup>c</sup> Only one diastereoisomer was observed at the limit of detection by NMR spectroscopy (diastereofacial selectivity >25:1).

be explained qualitatively by the FMO method. Comparing energy values (PM3) of nitrones with those of acrylates, the reaction results in controlled HOMO<sub>nitron</sub> – LUMO<sub>alkene</sub>, the predominant interaction being derived from the preferential combination between the atoms with larger orbital coefficients. Addition of Lewis acids such as MgBr<sub>2</sub>, Et<sub>2</sub>O, ZnBr<sub>2</sub>, or Et<sub>2</sub>AlCl only led to slow reactions that did not show significant differences in regio- and diastereoselectivities.

Next, our attention turned to the use chiral auxiliaries for the acryloyl moiety. Since we<sup>10</sup> and others<sup>7,17</sup> had observed satisfactory results with Oppolzer's chiral sultam in similar reactions, we chose *N*-acryloyl-(2*R*)-bornane-10,2-sultam **3c** as the dipolarophile. Thus, addition of **3c** to nitrones **2** gave the diastereomeric isoxazolidines **4/5** in the *cis/trans* ratios indicated in Table 1 (entries 8–10 and 17–19) and with a complete stereoface discrimination at the limit of detection by NMR (>95:5). This result is in marked contrast with our previous findings on thiazolyl nitrones that presented a complete control of regioselectivity and *cis/trans* diastereoselectivity but a lower level of asymmetric induction.<sup>10</sup> On the other hand, the result obtained with nitrones **2** is more consistent with previous 1,3-dipolar cycloadditions of dipolarophile **3c**.<sup>7,18</sup>

Indeed, the observed difference in selectivity is well reproduced by calculations of the transition states. We attempted an explanation of the selectivity on the basis of semiempirical calculations. These methods are more practical and allow the treatment of molecular structures of relevant size (such as sultam-containing adducts **4**–**7**),

(13) (a) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229–6234. (b) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280–1285. (c) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940. (d) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 7579–7582. (e) Mukaiyama, T.; Tsuzuki, R.; Kato, S. *Chem. Lett.* **1985**, 837–840.

(14) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537–2550.

(15) The authors have deposited atomic coordinates for the structure of **2a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(16) Malamidou-Xenikaki, E.; Stampelos, X. N.; Coutouli-Argyropoulou, E.; Cardin, C. J.; Teixeira, S.; Kavounis, C. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 949–957.

(17) (a) Kim, B. H.; Lee, J.-Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359–1370. (b) Kanemasa, S.; Onimura, K.; Wada, E.; Tanaka, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1185–1188. (c) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555–3558.

(18) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559–3562.

which precludes the use of high-level *ab initio* methods.<sup>19</sup> For comparison, all optimized structures were calculated at both AM1 and PM3 levels.<sup>20</sup> Single-point energy calculations were also carried out at the RHF/6-31G\* and B3LYP/6-31G\* levels using PM3 geometries.<sup>21</sup>

The optimized geometries of the nitron **2a** and alkene **3c** showed the expected bond lengths and angles. In fact, rather similar structural data were obtained when the optimized geometry of **2a** was compared with its X-ray structure. In a similar way, the optimized geometry of alkene **3c** was in good agreement with previously proposed conformations for that compound.<sup>17c</sup> The TSs for the four different approaches of **3c** to **2a** were located by the calculation of a reaction path profile starting from optimized geometries of the corresponding final adducts, followed by an optimization of the TS with respect of all structural variables. The TSs were characterized through the calculation of the force constant matrix by ensuring that they had one and only one imaginary harmonic vibrational frequency corresponding to the formation of new bonds. Both sides of the reaction path were also investigated starting from each transition state by using the internal reaction coordinate procedure. In all cases, it could be verified that the TSs proceed from the reactants and give rise to the products. The results are summarized in Table 2 and the TSs illustrated in Figure 1.

As expected for 1,3-dipolar cycloadditions, all TSs were asynchronous, the newly created C–O bond being formed to a greater extent than the C–C bond. Interestingly, whereas PM3, RHF/6-31G\*, and B3LYP/6-31G\* calculations correctly identify the favored products corresponding to approach of nitron by the *Re* face of dipolarophile **3c**, AM1 does not predict correctly the observed selectivity. For this reason, AM1 values will not be considered further in this work. The transition states **TS<sub>Re/endo</sub>** and **TS<sub>Re/exo</sub>** for *Re* attack are clearly more stable than attack from the opposite *Si* face, thus explaining the excellent diastereofacial selectivity observed for the reaction. The calculated TS energies for *endo* (**TS<sub>Re/endo</sub>**) and *exo* (**TS<sub>Re/exo</sub>**) approaches indicate that the reaction should lead to the formation of *cis/trans* mixtures of cycloadducts.

The lowest calculated TS energy is for the *endo* approach of the nitron to the *Re* face of the alkene, thus predicting the formation of (3*R*,5*R*) isomer preferentially. These results are in agreement with the experimental data observed for cycloadditions of nitrones **2a** and **2b**

**Table 2. Semiempirical and *ab Initio* Energies of Ground States, Transition Structures, and Adducts for Cycloadditions of **2a** with **3c**<sup>a</sup>**

structure	AM1 (kcal mol <sup>-1</sup> )	PM3 (kcal mol <sup>-1</sup> )	RHF/ 6-31G* <sup>c,d</sup> (hartrees)	B3LYP/ 6-31G* <sup>c,d</sup> (hartrees)
nitron <b>2a</b> <sup>b</sup>	27.460	9.049	-435.316 150 3	-437.948 927 6
alkene <b>3c</b>	-73.408	-92.631	-1179.773 702 3	-1185.333 677 6
TS <i>exo/Re</i>	-21.438 (24.51)	-47.748 (35.83)	-1615.033 071 7 (35.63)	-1623.256 391 8 (16.45)
TS <i>exo/Si</i>	-19.542 (26.41)	-41.547 (42.04)	-1615.010 269 1 (49.94)	-1623.237 849 4 (28.08)
TS <i>endo/Re</i>	-23.563 (22.39)	-49.563 (34.02)	-1615.035 656 7 (34.00)	-1623.258 832 0 (14.89)
TS <i>endo/Si</i>	-21.893 (24.06)	-44.585 (39.00)	-1615.011 421 2 (49.22)	-1623.240 147 4 (26.64)
(3 <i>S</i> ,5 <i>R</i> )- <b>4</b> <sup>e</sup>	-72.657	-111.248	-1615.125 300 3	-1623.302 079 4
(3 <i>R</i> ,5 <i>S</i> )- <b>4</b> <sup>f</sup>	-72.096	-106.662	-1615.122 071 6	-1623.298 255 2
(3 <i>R</i> ,5 <i>R</i> )- <b>5</b> <sup>g</sup>	-74.624	-111.876	-1615.126 896 7	-1623.303 061 6
(3 <i>S</i> ,5 <i>S</i> )- <b>5</b> <sup>h</sup>	-74.476	-106.054	-1615.124 792 1	-1623.300 314 5

<sup>a</sup> For TSs, potential energy barriers are given in parentheses. <sup>b</sup> For simplicity, the *N*-benzyl group of the nitron was replaced by a methyl group. <sup>c</sup> Single-point calculations using PM3 geometries. <sup>d</sup> Energy barriers given in kcal mol<sup>-1</sup>. <sup>e</sup> From TS *exo/Re*. <sup>f</sup> From TS *exo/Si*. <sup>g</sup> From TS *endo/Re*. <sup>h</sup> From TS *endo/Si*.

and accounts for both the *cis/trans* and diastereofacial selectivity of the reaction.

Returning to the synthetic methodology, inseparable mixtures of **4/5** were obtained in cycloaddition reactions of both **2a** and **2b**.<sup>22</sup> The isoxazolidine ring of cycloadducts **4** and **5** was subsequently transformed into a pyrrolidin-2-one ring by reduction (Zn/AcOH) of the N–O bond followed by *in situ* lactamization (Scheme 2). From this reaction, pyrrolidin-2-ones **8** and **9** could be easily separated by column chromatography, and the chiral auxiliary—the Oppolzer's sultam—was recovered in high yield (ca. 92%). Since better results in the cycloaddition reaction were obtained with *N*-benzyl nitron **2a**, we chose the corresponding pyrrolidines **8a** and **9a** for further transformations.

The relative *cis/trans* stereochemistry of chiral isoxazolidines **4c,f** and **5c,f** were assigned by comparing the optically pure pyrrolidin-2-ones **8/9** with the same compounds obtained previously in a racemic form. The absolute configuration and stereochemical integrity of the compounds **8** and **9** were determined by preparation of corresponding Mosher esters. Analysis of the 300 MHz NMR spectra of these esters showed the presence of only one diastereoisomer in each case, at the limit of detection, indicating enantiomeric purity >98%. Racemic products obtained from methyl/ethyl acrylate cycloaddition and further cyclization were used as reference materials.<sup>23</sup> The absolute configuration of **8** and **9** was ascertained by employing the Kakisawa method<sup>24</sup> on the Mosher esters derived from both racemic and optically pure compounds.<sup>23</sup>

To further illustrate the utility of compounds **8a** and **9a** as precursors of versatile building blocks, we undertook the preparation of differentially protected derivatives of 4-hydroxy pyroglutamic acids. The cyclization products **8a** and **9a** formed in the reduction of cycloadd-

(19) Several comparative studies have suggested semiempirical methods as a good choice for studying cycloaddition processes involving chiral substrates. See: (a) Sbai, A.; Branchadell, V.; Ortuño, R. M.; Oliva, A. *J. Org. Chem.* **1997**, *62*, 3049–3054. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1995**, *60*, 4697–4706.

(20) Semiempirical geometry optimizations for all systems were carried out at the AM1 and PM3 levels of theory as implemented in WINMOPAC 2.0. Fujitsu Limited, 1998. For simplicity, the *N*-benzyl group of the nitron **2a** was replaced with a methyl group.

(21) *Ab initio* single point energy calculations were performed using Gaussian 98, Revision A.3: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

(22) After tedious chromatographic separations enriched mixtures of diastereomers could be obtained in order to identify selected signals from the NMR spectra (see the Experimental Section). Nevertheless, subsequent reduction–cyclization to diastereomeric pyrrolidin-2-ones afforded separable mixtures of isomers.

(23) See the Supporting Information for the detailed discussion.  
(24) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.



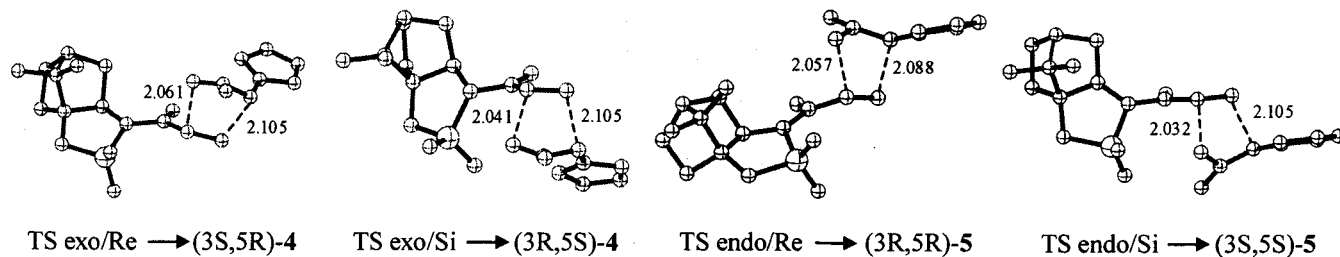
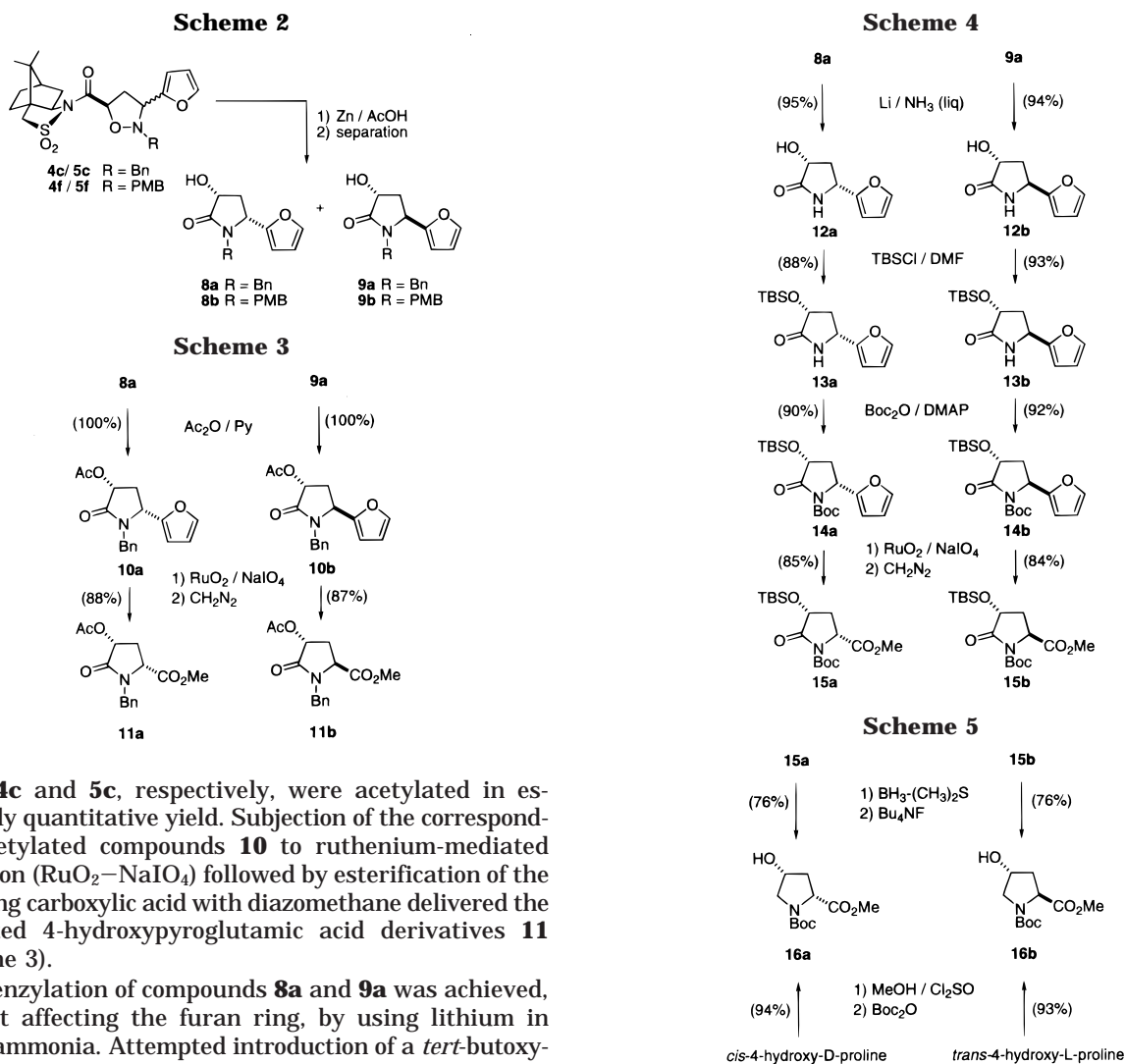


Figure 1. Transition-state structures for 1,3-dipolar cycloaddition of **2a** and **3c**.



ducts **4c** and **5c**, respectively, were acetylated in essentially quantitative yield. Subjection of the corresponding acetylated compounds **10** to ruthenium-mediated oxidation ( $\text{RuO}_2\text{-NaIO}_4$ ) followed by esterification of the resulting carboxylic acid with diazomethane delivered the protected 4-hydroxypyroglutamic acid derivatives **11** (Scheme 3).

Debenzylation of compounds **8a** and **9a** was achieved, without affecting the furan ring, by using lithium in liquid ammonia. Attempted introduction of a *tert*-butoxy-carbonyl group at the nitrogen atom with  $\text{Boc}_2\text{O}$  under a variety of conditions in compounds **12** returned only starting material. Other less common *N*-Boc protection conditions examined without success included  $\text{Boc-ON}$ , *tert*-butylchloroformate, and  $\text{BocONH}_2$ .<sup>25</sup> However, treatment of **12** with TBSCl in the presence of imidazole yielded silylated compounds **13**, which were amenable to protection with  $\text{Boc}_2\text{O}$  to provide **14** in good chemical yield. Oxidation of the furan ring as described above proceeded smoothly for both isomers to provide after esterification the protected derivatives **15** (Scheme 4).

Furthermore, additional confirmation of the absolute configuration of pyrrolidin-2-ones synthesized was achieved by reducing ( $\text{BH}_3\text{-DMS}$ )<sup>26</sup> and desilylating com-

pounds **15a** and **15b** to give protected *cis*-4-hydroxy-D-proline **16a** and *trans*-4-hydroxy-L-proline **16b**, respectively (Scheme 5). Comparison of the spectroscopic data ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) and optical rotation data with the reported literature values for **16a**<sup>27</sup> and **16b**<sup>28</sup> verified the previously assigned absolute configuration. In addition, and given the complexity of NMR spectra (due to the presence of rotamers), compounds **16a** and **16b** were also prepared from commercial *cis*-4-hydroxy-D-proline and *trans*-4-hydroxy-L-proline, respectively.

(26) Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett.* **1991**, 32, 3057–3058.

(27) Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, 34, 2787–2797.

(28) Schumaker, K. K.; Jiang, J.; Joullie, M. M. *Tetrahedron: Asymmetry* **1998**, 9, 47–53.

(25) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

### Summary

In summary, an asymmetric 1,3-dipolar cycloaddition with furfuryl nitrones has been used to synthesize protected derivatives of *cis*- and *trans*-4-hydroxy pyroglutamic acids by short and efficient sequences. These derivatives would appear to be particularly attractive for preparing a variety of nitrogenated compounds endowed with similar structures. Moreover, the sense of induction could be reversed by employing the antipodal dipolarophile in the cycloaddition step, thus being accessible all stereoisomers. The utilization of this chemistry in the context of natural products and related compounds synthesis is being explored in our laboratory.

### Experimental Section

**General Methods.** For general experimental information see ref 29. Furfuryl nitrones **2**<sup>14</sup> and *N*-acryloyl-(2*R*)-bornane-10,2-sultam **3c**<sup>17a</sup> were prepared as described.

**General Protocol for the Cycloaddition of Nitrones (2) with Acrylates (3).** To a solution of the appropriate nitrone **2** (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added the corresponding acrylate **3** (5 mmol), and the resulting mixture was heated at reflux under Ar atmosphere for 48 h. The solvent was evaporated, and the product ratio was established by <sup>1</sup>H NMR analysis. The residue was purified by preparative, centrifugally accelerated, radial, thin-layer chromatography (Chromatotron). Spectroscopic and analytical data for racemic compounds are given in the Supporting Information.

***N*-[[[(3*S*,5*R*)-2-Benzyl-3-(2-furyl)-5-isoxazolidinyl]carbonyl]-(2*R*)-bornane-10,2-sultam (4c) and *N*-[[[(3*R*,5*R*)-2-Benzyl-3-(2-furyl)-5-isoxazolidinyl]carbonyl]-(2*R*)-bornane-10,2-sultam (5c).** Nitrone **2a** (0.2 g, 1 mmol) and *N*-acryloyl-(2*R*)-bornane-10,2-sultam **3c** (1.35 g, 5 mmol) were allowed to react according to the general protocol detailed above. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 30:70) to separate the excess of dipolarophile and to afford 0.425 g (90%) of a 15:85 mixture of two diastereomers. Purification of this mixture with a Chromatotron using hexane/EtOAc, 20:80 as eluent gave an almost pure sample of **5c** (eluted first) and a mixed fraction of **4c** and **5c**. **4c** (selected signals): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C) δ 0.85 and 1.05 (2s, 6H), 1.85–1.94 (m, 4H), 2.00–2.08 (m, 2H), 2.11–2.15 (m, 1H), 2.83 (dt, 1H, *J* = 8.6, 12.6 Hz), 3.14 (ddd, 1H, *J* = 5.2, 8.6, 12.6 Hz), 3.28 and 3.45 (2d, 2H, *J* = 13.7 Hz), 3.75 (dd, 1H, *J* = 5.5, 7.5 Hz), 3.94 and 4.02 (2d, 2H, *J* = 13.8), 4.34 (t, 1H, *J* = 8.6), 5.00 (dd, 1H, *J* = 5.2, 8.6 Hz), 6.27 (m, 2H), 7.20–7.40 (m, 6H).

**5c** (selected signals): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C) δ 0.85 and 1.05 (2s, 6H), 1.78–1.92 (m, 4H), 2.02–2.06 (m, 2H), 2.10–2.14 (m, 1H), 2.88–2.95 (m, 2H), 3.26 and 3.35 (2d, 2H, *J* = 13.5 Hz), 3.85 (dd, 1H, *J* = 5.3, 7.3 Hz), 4.00 and 4.08 (2d, 2H, *J* = 13.9), 4.38 (t, 1H, *J* = 7.1), 5.15 (dd, 1H, *J* = 5.8, 8.0 Hz), 6.34 (m, 2H), 7.18–7.40 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 55 °C) δ 18.8, 19.4, 26.5, 28.3, 32.5, 35.8, 44.5, 49.0, 49.4, 52.7, 60.7, 62.3, 65.2, 75.8, 108.3, 110.4, 127.8, 128.2, 128.9, 137.4, 142.6, 150.9, 170.4.

***N*-[[[(3*S*,5*R*)-2-(*p*-Methoxybenzyl)-3-(2-furyl)-5-isoxazolidinyl]carbonyl]-(2*R*)-bornane-10,2-sultam (4f) and *N*-[[[(3*R*,5*R*)-2-(*p*-methoxybenzyl)-3-(2-furyl)-5-isoxazolidinyl]carbonyl]-(2*R*)-bornane-10,2-sultam (5f).** Nitrone **2b** (0.231 g, 1 mmol) and *N*-acryloyl-(2*R*)-bornane-10,2-sultam **3c** (1.35 g, 5 mmol) were allowed to react according to the general protocol detailed above. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 30:70) to separate the excess of dipolarophile and to afford 0.440 g (88%) of a 22:78 mixture of two diastereomers. Purification of this mixture with a Chromatotron using hexane/EtOAc, 25:75, as eluent afforded mixed fractions of **4f** and **5f**.

**4f** (selected signals): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C) δ 0.97 and 1.13 (2s, 6H), 1.72–1.90 (m, 4H), 2.00–2.12 (m, 3H), 2.60 (ddd, 1H, *J* = 5.6, 7.2, 12.8 Hz), 3.04 (ddd, 1H, *J* = 7.4, 9.1, 12.8 Hz), 3.35

(bs, 2H), 3.75 (s, 3H), 3.90 (dd, 1H, *J* = 5.8, 7.1 Hz), 3.94 and 4.08 (2d, 2H, *J* = 13.8), 4.19 (t, 1H, *J* = 7.3), 5.28 (dd, 1H, *J* = 5.6, 9.1 Hz), 6.30 (m, 2H), 6.82 (m, 2H), 7.31 (m, 2H), 7.37 (dd, 1H, *J* = 0.9, 1.7 Hz).

**5f** (selected signals): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C) δ 0.92 and 1.10 (2s, 6H), 1.71–1.86 (m, 4H), 1.90–2.02 (m, 2H), 2.08–2.12 (m, 1H), 2.82 (ddd, 1H, *J* = 6.9, 7.9, 12.7 Hz), 2.92 (dt, 1H, *J* = 6.9, 12.7 Hz), 3.25 and 3.31 (2d, 2H, *J* = 13.6 Hz), 3.72 (s, 3H), 3.83 (dd, 1H, *J* = 5.2, 7.2 Hz), 3.92 and 4.00 (2d, 2H, *J* = 13.8), 4.28 (t, 1H, *J* = 6.9), 5.11 (dd, 1H, *J* = 6.9, 7.9 Hz), 6.27 (m, 2H), 6.79 (m, 2H), 7.25 (m, 2H), 7.35 (bs, 1H).

**(3*R*,5*R*)-1-Benzyl-5-(2-furyl)-3-hydroxypyrrolidin-2-one (8a) and (3*R*,5*S*)-1-Benzyl-5-(2-furyl)-3-hydroxypyrrolidin-2-one (9a).** To a solution of a mixture of cycloadducts **4c** and **5c** (0.471 g, 1 mmol) in THF (10 mL) were added AcOH (20 mL) and H<sub>2</sub>O (10 mL). The resulting solution was treated with Zn dust (0.4 g, 6.1 mmol) and heated at 60 °C for 5 h. The reaction mixture was allowed to cool to room temperature and filtered; the filtrate was treated with saturated aqueous Na<sub>2</sub>SO<sub>4</sub>, and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. Column chromatography on silica gel (Et<sub>2</sub>O/EtOAc, 95:5) of the residue gave the pure pyrrolidin-2-ones. Eluted first was recovered (2*R*)-bornane-10,2-sultam (0.198 g, 92%).

Eluted second (**9a**): 0.033 g, 13%; white solid; mp 91–93 °C; [α]<sub>D</sub> +10.7 (c 1.10, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.22 (dt, 1H, *J* = 8.8, 13.0 Hz), 2.54 (ddd, 1H, *J* = 2.1, 8.8, 13.0 Hz), 3.66 and 4.97 (2d, 2H, *J* = 14.7 Hz), 4.30 (bs, 1H, ex. D<sub>2</sub>O), 4.48 (dd, 1H, *J* = 2.1, 8.8 Hz), 4.80 (t, 1H, *J* = 8.8 Hz), 6.16 (dd, 1H, *J* = 0.8, 3.3 Hz), 6.30 (dd, 1H, *J* = 1.8, 3.3 Hz), 7.30–7.18 (m, 5H), 7.39 (dd, 1H, *J* = 0.8, 1.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 33.8, 44.8, 51.5, 69.1, 108.5, 110.3, 127.7, 128.3, 128.7, 135.5, 143.0, 151.8, 175.1. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.28; H, 5.59; N, 5.27.

Eluted third (**8a**): 0.188 g, 73%; white solid; mp 134–136 °C; [α]<sub>D</sub> –7.6 (c 0.42, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.23 (dt, 1H, *J* = 8.6, 12.9 Hz), 2.67 (ddd, 1H, *J* = 6.8, 8.6, 12.9 Hz), 3.32 (bs, 1H, ex. D<sub>2</sub>O), 3.61 and 4.89 (2d, 2H, *J* = 14.7 Hz), 4.41 (t, 1H, *J* = 8.6 Hz), 4.43 (dd, 1H, *J* = 6.8, 8.6 Hz), 6.25 (dd, 1H, *J* = 0.7, 3.2 Hz), 6.34 (dd, 1H, *J* = 1.8, 3.2 Hz), 7.11–7.30 (m, 5H), 7.39 (dd, 1H, *J* = 0.7, 1.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 33.8, 44.8, 51.3, 69.4, 110.1, 110.4, 127.6, 128.3, 128.6, 136.0, 143.3, 150.6, 174.1. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 5.70; N, 5.61.

**(3*R*,5*R*)-1-(*p*-Methoxybenzyl)-5-(2-furyl)-3-hydroxypyrrolidin-2-one (8b) and (3*R*,5*S*)-1-(*p*-Methoxybenzyl)-5-(2-furyl)-3-hydroxypyrrolidin-2-one (9b).** The same procedure described above for the conversion of a mixture of **4c** and **5c** to **8a** and **9a** was applied to a mixture of cycloadducts **4f** and **5f** (0.500, 1 mmol). After column chromatography on silica gel (Et<sub>2</sub>O/EtOAc, 90:10) of the crude product, the pure pyrrolidin-2-ones **8b** and **9b** were obtained. Eluted first was recovered (2*R*)-bornane-10,2-sultam (0.194 g, 90%).

Eluted second (**9b**): 0.055 g, 19%; sticky foam; [α]<sub>D</sub> +23.4 (c 1.26, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.17 (dt, 1H, *J* = 8.3, 13.1 Hz), 2.50 (ddd, 1H, *J* = 2.1, 8.3, 13.1 Hz), 3.12 (bs, 1H, ex. D<sub>2</sub>O), 3.57 and 4.90 (2d, 2H, *J* = 14.6 Hz), 3.75 (s, 3H), 4.46 (dd, 1H, *J* = 2.1, 8.3 Hz), 4.75 (t, 1H, *J* = 8.3 Hz), 6.20 (dd, 1H, *J* = 0.9, 3.2 Hz), 6.31 (dd, 1H, *J* = 1.7, 3.2 Hz), 6.80 (m, 2H), 7.1 (m, 2H), 7.40 (dd, 1H, *J* = 0.9, 1.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 33.8, 44.1, 50.9, 55.1, 69.2, 108.4, 110.3, 114.0, 128.4, 129.5, 142.9, 151.8, 159.1, 174.8. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.74; H, 5.78; N, 4.95.

Eluted third (**8b**): 0.198 g, 69%; white solid; mp 91–93 °C; [α]<sub>D</sub> –10.1 (c 1.01, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.20 (dt, 1H, *J* = 8.8, 12.8 Hz), 2.65 (ddd, 1H, *J* = 6.8, 8.1, 12.8 Hz), 3.06 (bs, 1H, ex. D<sub>2</sub>O), 3.54 and 4.84 (2d, 2H, *J* = 14.5 Hz), 3.76 (s, 3H), 4.39 (dd, 1H, *J* = 8.1, 8.8 Hz), 4.40 (dd, 1H, *J* = 6.8, 8.8 Hz), 6.24 (dd, 1H, *J* = 0.7, 3.2 Hz), 6.35 (dd, 1H, *J* = 1.8, 3.2 Hz), 6.80 (m, 2H), 7.05 (m, 2H), 7.40 (dd, 1H, *J* = 0.7, 1.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 33.8, 44.1, 51.2, 55.2, 69.4, 109.9, 110.4, 113.9, 128.1, 129.7, 143.2, 150.8, 159.0, 174.2. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.95; H, 6.03; N, 4.97.

**(3*R*,5*R*)-3-Acetoxy-1-benzyl-5-(2-furyl)pyrrolidin-2-one (10a).** A solution of **8a** (0.257 g, 1 mmol) in pyridine (2 mL) was treated with Ac<sub>2</sub>O (2 mL) and DMAP (2.4 mg, 0.02 mmol). The resulting mixture was stirred at room temperature for 10 h, and

then  $\text{CH}_2\text{Cl}_2$  (20 mL) and  $\text{H}_2\text{O}$  (15 mL) were added. The organic layer was washed sequentially with saturated aqueous  $\text{CuSO}_4$  and brine, dried ( $\text{MgSO}_4$ ), and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}$ , 40:60) gave **10a** (0.300 g, 100%) as a sticky oil;  $[\alpha]_{\text{D}} -33.0$  ( $c$  0.98,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.05 (s, 3H), 2.10 (dt, 1H,  $J = 8.4$ , 13.2 Hz), 2.66 (ddd, 1H,  $J = 7.1$ , 8.4, 13.2 Hz), 3.56 and 4.79 (2d, 2H,  $J = 14.7$  Hz), 4.36 (dd, 1H,  $J = 7.1$ , 8.4 Hz), 5.32 (t, 1H,  $J = 8.4$  Hz), 6.23 (dd, 1H,  $J = 0.8$ , 3.2 Hz), 6.34 (dd, 1H,  $J = 1.8$ , 3.2 Hz), 6.98–7.25 (m, 5H), 7.30 (dd, 1H,  $J = 0.8$ , 1.8 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  22.6, 31.7, 44.7, 51.2, 70.0, 110.0, 110.3, 127.5, 128.3, 128.4, 135.6, 143.2, 150.2, 169.6, 170.1. Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_4$ : C, 68.21; H, 5.72; N, 4.68. Found: C, 68.44; H, 5.61; N, 4.80.

**(3R,5S)-3-Acetoxy-1-benzyl-5-(2-furyl)pyrrolidin-2-one (10b).** The same procedure described above for the conversion of **8a** to **10a** was applied to compound **9a** (0.077 g, 0.3 mmol). After column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}$ , 40:60) of the crude product, pure **10b** (0.090 g, 100%) was obtained as a sticky oil;  $[\alpha]_{\text{D}} -12.8$  ( $c$  0.52,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.13 (s, 3H), 2.17 (dt, 1H,  $J = 8.8$ , 13.3 Hz), 2.63 (ddd, 1H,  $J = 2.2$ , 8.8, 13.3 Hz), 3.60 and 5.01 (2d, 2H,  $J = 14.7$  Hz), 4.47 (dd, 1H,  $J = 2.2$ , 8.8 Hz), 5.64 (t, 1H,  $J = 8.8$  Hz), 6.17 (dd, 1H,  $J = 0.7$ , 3.2 Hz), 6.29 (dd, 1H,  $J = 1.8$ , 3.2 Hz), 7.15–7.35 (m, 6H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.9, 32.1, 44.8, 51.4, 70.6, 109.4, 110.9, 127.9, 128.4, 128.7, 135.4, 144.0, 152.0, 170.0, 171.2. Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_4$ : C, 68.21; H, 5.72; N, 4.68. Found: C, 68.00; H, 5.69; N, 4.76.

**(3R,5R)-3-Acetoxy-1-benzyl-5-(methoxycarbonyl)pyrrolidin-2-one (11a).** To a well-stirred mixture of  $\text{CH}_3\text{CN}$  (9.5 mL),  $\text{CCl}_4$  (6.3 mL), and  $\text{H}_2\text{O}$  (9.5 mL) were added sequentially  $\text{NaIO}_4$  (0.98 g, 4.6 mmol) and  $\text{RuO}_2 \cdot \text{H}_2\text{O}$  (12.2 mg, 0.092 mmol). The mixture was stirred vigorously at room temperature. After 30 min,  $\text{NaHCO}_3$  (1.9 g, 23 mmol) was added in one portion followed by 4.6 mL of  $\text{H}_2\text{O}$ . After 15 min, the resulting mixture was treated with a solution of **10a** (0.275 g, 0.92 mmol) in  $\text{CH}_3\text{CN}$  (0.7 mL). The solution turned black, and after 5 min enough  $\text{NaIO}_4$  (ca. 0.250 g) was added in small portions to turn the color light green. The mixture was diluted with water (10 mL) and extracted with  $\text{AcOEt}$  ( $3 \times 15$  mL). The aqueous layer was acidified with 1 N  $\text{HCl}$  to pH = 2–3 and reextracted with  $\text{AcOEt}$  ( $3 \times 20$  mL). The combined organic extracts were washed sequentially with 20% aqueous  $\text{NaHSO}_3$  until colorless and then with brine and dried ( $\text{MgSO}_4$ ), and the solvent was evaporated under reduced pressure. The crude acid was dissolved in  $\text{Et}_2\text{O}$  (20 mL), and the solution was cooled to 0 °C and treated with an ethereal solution of diazomethane until a slight yellow color persisted. The excess of diazomethane was eliminated by quenching with acetic acid. The resulting solution was concentrated under reduced pressure, and the crude ester was purified by column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}$ , 50:50) to give **11a** (0.236 g, 88%) as an oil;  $[\alpha]_{\text{D}} -16.2$  ( $c$  0.55,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.00 (dt, 1H,  $J = 6.4$ , 13.9 Hz), 2.07 (s, 3H), 2.77 (dt, 1H,  $J = 8.5$ , 13.9 Hz), 3.65 (s, 3H), 3.92 (dd, 1H,  $J = 6.4$ , 8.5 Hz), 4.13 and 5.13 (2d, 2H,  $J = 14.9$  Hz), 5.29 (dd, 1H,  $J = 6.4$ , 8.5), 7.10–7.30 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.6, 29.9, 45.8, 52.5, 55.4, 69.5, 128.0, 128.4, 128.7, 134.8, 170.0, 170.1, 170.8. Anal. Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$ : C, 61.85; H, 5.88; N, 4.81. Found: C, 61.93; H, 6.01; N, 4.72.

**(3R,5S)-3-Acetoxy-1-benzyl-5-(methoxycarbonyl)pyrrolidin-2-one (11b).** The same procedure described above for the conversion of **10a** to **11a** was applied to compound **10b** (0.075 g, 0.25 mmol). After column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}$ , 50:50) of the crude product, pure **11b** (0.063 g, 87%) was obtained as an oil;  $[\alpha]_{\text{D}} -6.7$  ( $c$  0.52,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.15 (dt, 1H,  $J = 8.9$ , 13.4 Hz), 2.15 (s, 3H), 2.64 (ddd, 1H,  $J = 1.5$ , 8.9, 13.4 Hz), 3.67 (s, 3H), 4.00 (dd, 1H,  $J = 1.5$ , 8.9 Hz), 4.06 and 4.98 (2d, 2H,  $J = 14.8$  Hz), 5.46 (t, 1H,  $J = 8.9$ ), 7.20–7.40 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.8, 30.6, 46.2, 52.7, 55.9, 69.7, 128.1, 128.7, 128.8, 134.7, 170.2, 170.5, 171.3. Anal. Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$ : C, 61.85; H, 5.88; N, 4.81. Found: C, 61.77; H, 5.72; N, 4.90.

**(3R,5R)-5-(2-Furyl)-3-hydroxypyrrolidin-2-one (12a).** To cold (–35 °C) stirred liquid ammonia (35 mL) were added a solution of **8a** (0.250 g, 0.97 mmol) in anhydrous THF (20 mL) and lithium (0.48 g, 69 mmol). The deep blue solution was stirred at –35 °C for 2 h while the blue color persisted. Ethanol (3 mL)

was added, and the ammonia was allowed to evaporate. The mixture was concentrated, and the residue was purified by column chromatography on silica gel ( $\text{EtOAc}$ ) to afford **12a** (0.154 g, 95%) as a white powder: mp 130–132 °C;  $[\alpha]_{\text{D}} -7.6$  ( $c$  0.11,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.02–2.10 (m, 1H), 2.74 (ddd, 1H,  $J = 6.5$ , 8.0, 12.6 Hz), 3.55 (bs, 1H, ex.  $\text{D}_2\text{O}$ ), 4.30 (dd, 1H,  $J = 8.0$ , 9.5 Hz), 4.68 (dd, 1H,  $J = 6.5$ , 9.2 Hz), 5.65 (bs, 1H), 6.28–6.38 (m, 2H), 7.28 (m, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  37.3, 47.9, 69.8, 107.4, 111.2, 143.4, 155.2, 176.9. Anal. Calcd for  $\text{C}_8\text{H}_9\text{NO}_3$ : C, 57.48; H, 5.43; N, 8.38. Found: C, 57.33; H, 5.21; N, 8.12.

**(3R,5S)-5-(2-Furyl)-3-hydroxypyrrolidin-2-one (12b).** The same procedure described above for the conversion of **8a** to **12a** was applied to compound **9a** (0.1 g, 0.39 mmol). After column chromatography on silica gel ( $\text{EtOAc}$ ) of the crude product, pure **12b** (0.061 g, 94%) was obtained as white solid: mp 68–70 °C;  $[\alpha]_{\text{D}} -10.5$  ( $c$  0.15,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.32 (dt, 1H,  $J = 8.3$ , 13.2 Hz), 2.49 (ddd, 1H,  $J = 2.2$ , 8.2, 13.2 Hz), 3.46 (bs, 1H, ex.  $\text{D}_2\text{O}$ ), 4.54 (t, 1H,  $J = 8.2$  Hz), 4.73 (dd, 1H,  $J = 2.2$ , 8.4 Hz), 5.65 (bs, 1H), 6.18 (bd, 1H,  $J = 3.3$  Hz), 6.22 (dd,  $J = 1.8$ , 3.3 Hz), 7.27 (bd, 1H,  $J = 1.8$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  35.3, 48.6, 68.3, 106.3, 110.2, 142.4, 153.7, 178.6. Anal. Calcd for  $\text{C}_8\text{H}_9\text{NO}_3$ : C, 57.48; H, 5.43; N, 8.38. Found: C, 57.39; H, 5.55; N, 8.24.

**(3R,5R)-3-(tert-Butyldimethylsiloxy)-5-(2-furyl)pyrrolidin-2-one (13a).** To a warmed (70 °C), stirred solution of **12a** (0.150 g, 0.90 mmol) and imidazole (0.368 g, 5.4 mmol) in anhydrous DMF (4 mL) was added *tert*-butyldimethylsilyl chloride (0.407 g, 2.7 mmol). The mixture was stirred at 70 °C for 18 h and then cooled to ambient temperature, treated with MeOH (1 mL), stirred for additional 15 min, diluted with  $\text{H}_2\text{O}$ , and extracted with  $\text{EtOAc}$ . The combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. Purification of the crude product by column chromatography on silica gel (hexane/ $\text{EtOAc}$ , 60:40) gave **13a** (0.223 g, 88%) as a white solid: mp 72–74 °C;  $[\alpha]_{\text{D}} +1.8$  ( $c$  0.23,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.09 and 0.11 (2s, 6H), 0.86 (s, 9H), 2.11 (dt, 1H,  $J = 8.8$ , 12.6 Hz), 2.66 (ddd, 1H,  $J = 6.7$ , 7.7, 12.6 Hz), 4.33 (dd, 1H,  $J = 7.7$ , 8.8 Hz), 4.56 (dd, 1H,  $J = 6.7$ , 8.8 Hz), 6.23 (bd, 1H,  $J = 3.2$  Hz), 6.26 (dd,  $J = 1.8$ , 3.2 Hz), 7.20 (bs, 1H), 7.30 (bd, 1H,  $J = 1.8$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  –5.1, –4.4, 18.3, 25.8, 37.5, 47.7, 70.4, 106.4, 110.4, 142.4, 154.0, 175.7. Anal. Calcd for  $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{Si}$ : C, 59.75; H, 8.24; N, 4.98. Found: C, 59.69; H, 8.11; N, 5.05.

**(3R,5S)-3-(tert-Butyldimethylsiloxy)-5-(2-furyl)pyrrolidin-2-one (13b).** The same procedure described above for the conversion of **12a** to **13a** was applied to compound **12b** (0.060 g, 0.36 mmol). After column chromatography on silica gel (hexane/ $\text{EtOAc}$ , 60:40) of the crude product, pure **13b** (0.094 g, 93%) was obtained as an oil;  $[\alpha]_{\text{D}} -3.6$  ( $c$  0.17,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.14 and 0.16 (2s, 6H), 0.91 (s, 9H), 2.33 (ddd, 1H,  $J = 6.4$ , 7.9, 13.0 Hz), 2.47 (ddd, 1H,  $J = 4.0$ , 7.4, 13.0 Hz), 4.43 (dd, 1H,  $J = 6.4$ , 7.4 Hz), 4.76 (dd, 1H,  $J = 4.0$ , 7.9 Hz), 5.80 (bs, 1H), 6.17 (dd, 1H,  $J = 0.8$ , 3.2 Hz), 6.29 (dd,  $J = 1.8$ , 3.2 Hz), 7.34 (dd, 1H,  $J = 0.8$ , 1.8 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  –5.1, –4.5, 18.3, 25.8, 37.4, 48.4, 69.5, 106.1, 110.3, 142.6, 154.4, 175.6. Anal. Calcd for  $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{Si}$ : C, 59.75; H, 8.24; N, 4.98. Found: C, 59.86; H, 8.38; N, 4.90.

**(3R,5R)-1-(tert-Butoxycarbonyl)-3-(tert-butyldimethylsiloxy)-5-(2-furyl)pyrrolidin-2-one (14a).** To a solution of **13a** (0.200 g, 0.71 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (25 mL) at 0 °C were added  $\text{Et}_3\text{N}$  (0.108 g, 1.06 mmol) and DMAP (13 mg, 0.11 mmol) with magnetic stirring. After 30 min, a solution of  $\text{Boc}_2\text{O}$  (0.186 g, 0.85 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) was added dropwise. The resulting reaction mixture was then allowed to warm to ambient temperature and stirred for additional 18 h. The mixture was then treated with 1 N aqueous  $\text{KHSO}_4$  (10 mL). The organic layer was separated and washed with 1 N aqueous  $\text{KHSO}_4$ , saturated aqueous  $\text{NaHCO}_3$ , and brine, dried ( $\text{MgSO}_4$ ), and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane/ $\text{Et}_2\text{O}$ , 80:20) afforded **14a** (0.244 g, 90%) as a white solid: mp 90–92 °C;  $[\alpha]_{\text{D}} +12.2$  ( $c$  0.35,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 55 °C)  $\delta$  0.11 and 0.17 (2s, 6H), 0.88 (s, 9H), 1.37 (s, 9H), 2.06 (dt, 1H,  $J = 7.4$ , 13.1 Hz), 2.56 (dt, 1H,  $J = 7.4$ , 13.1 Hz), 4.32 (t, 1H,  $J = 7.4$  Hz), 4.97 (t, 1H,  $J = 7.4$  Hz), 6.23 (dd, 1H,  $J = 1.1$ , 3.2 Hz), 6.31 (dd,  $J = 1.8$ , 3.2 Hz), 7.31 (dd, 1H,  $J = 1.1$ , 1.8 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ,



55 °C)  $\delta$  -5.4, -4.6, 18.1, 25.6, 29.7, 34.8, 52.0, 70.7, 83.0, 106.5, 110.4, 141.4, 154.0, 154.5, 172.2. Anal. Calcd for  $C_{19}H_{31}NO_5Si$ : C, 59.81; H, 8.19; N, 3.67. Found: C, 59.73; H, 8.24; N, 3.77.

**(3R,5S)-1-(tert-Butoxycarbonyl)-3-(tert-butylidimethylsiloxy)-5-(2-furyl)pyrrolidin-2-one (14b).** The same procedure described above for the conversion of **13a** to **14a** was applied to compound **13b** (0.090 g, 0.32 mmol). After column chromatography on silica gel (Hexane/Et<sub>2</sub>O, 80:20) of the crude product, pure **14b** (0.112 g, 92%) was obtained as an oil:  $[\alpha]_D$  -3.0 (c 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  0.12 and 0.17 (2s, 6H), 0.89 (s, 9H), 1.43 (s, 9H), 2.25 (ddd, 1H,  $J$  = 9.3, 10.5, 12.8 Hz), 2.46 (dt, 1H,  $J$  = 7.9, 12.8 Hz), 4.70 (dd, 1H,  $J$  = 7.9, 10.5 Hz), 5.16 (dd, 1H,  $J$  = 7.9, 9.3 Hz), 6.19 (dd, 1H,  $J$  = 1.0, 3.2 Hz), 6.29 (dd,  $J$  = 1.7, 3.2 Hz), 7.32 (dd, 1H,  $J$  = 1.0, 1.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  -5.2, -4.4, 18.3, 25.8, 28.0, 34.8, 50.9, 70.4, 83.2, 107.0, 110.4, 142.1, 153.5, 154.7, 172.4. Anal. Calcd for  $C_{19}H_{31}NO_5Si$ : C, 59.81; H, 8.19; N, 3.67. Found: C, 59.73; H, 8.24; N, 3.77.

**(3R,5R)-1-(tert-Butoxycarbonyl)-3-(tert-butylidimethylsiloxy)-5-(methoxycarbonyl)pyrrolidin-2-one (15a).** The same procedure described above for the conversion of **10a** to **11a** was applied to compound **14a** (0.220 g, 0.58 mmol). After column chromatography on silica gel (hexane/Et<sub>2</sub>O, 80:20) of the crude product, pure **15a** (0.184 g, 85%) was obtained as an oil:  $[\alpha]_D$  +24.4 (c 0.37, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  0.07 and 0.13 (2s, 6H), 0.85 (s, 9H), 1.46 (s, 9H), 1.94 (dt, 1H,  $J$  = 7.1, 12.9 Hz), 2.54 (dt, 1H,  $J$  = 7.7, 12.9 Hz), 3.73 (s, 3H), 4.24 (t, 1H,  $J$  = 7.4 Hz), 4.43 (t, 1H,  $J$  = 7.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  -5.4, -4.6, 18.1, 25.6, 27.9, 32.3, 52.5, 55.6, 70.6, 83.8, 149.4, 171.0, 171.4. Anal. Calcd for  $C_{17}H_{31}NO_6Si$ : C, 54.66; H, 8.37; N, 3.75. Found: C, 54.47; H, 8.31; N, 3.69.

**(3R,5S)-1-(tert-Butoxycarbonyl)-3-(tert-butylidimethylsiloxy)-5-(methoxycarbonyl)pyrrolidin-2-one (15b).** The same

procedure described above for the conversion of **10a** to **11a** was applied to compound **14b** (0.100 g, 0.26 mmol). After column chromatography on silica gel (hexane/Et<sub>2</sub>O, 80:20) of the crude product, pure **15b** (0.082 g, 84%) was obtained as an oil:  $[\alpha]_D$  +27.6 (c 0.27, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  0.10 and 0.15 (2s, 6H), 0.87 (s, 9H), 1.48 (s, 9H), 2.18 (ddd, 1H,  $J$  = 9.7, 10.2, 13.2 Hz), 2.23 (ddd, 1H,  $J$  = 1.7, 8.3, 13.2 Hz), 3.76 (s, 3H), 4.39 (t, 1H,  $J$  = 8.3, 10.2 Hz), 4.55 (dd, 1H,  $J$  = 1.7, 9.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 55 °C)  $\delta$  -5.3, -4.4, 18.2, 25.7, 27.9, 31.9, 52.7, 55.0, 76.6, 83.9, 149.5, 171.8, 172.0. Anal. Calcd for  $C_{17}H_{31}NO_6Si$ : C, 54.66; H, 8.37; N, 3.75. Found: C, 54.89; H, 8.24; N, 3.87.

**Acknowledgment.** We thank the MEC (Madrid, Spain) for financial support (DGES, Project PB97-1014) and for a predoctoral fellowship to one of us (V.T.).

**Supporting Information Available:** Spectroscopic data, <sup>1</sup>H NMR assignments, and NOE data for **4a,b,d,e**, **5a,b,d,e**, and **6a,b,d,e**. Experimental details for the preparation of **16a** and **16b** and characterization data of these compounds. Details on the determination of the absolute configuration and enantiomeric purity of pyrrolidin-2-ones **8a** and **9a** by <sup>1</sup>H NMR analysis and characterization data of the corresponding Mosher esters. ORTEP drawing and CIF file of the X-ray structure of **2a**. Cartesian coordinates of the transition states **TS<sub>Re/endo</sub>**, **TS<sub>Re/exo</sub>**, **TS<sub>Si/endo</sub>**, and **TS<sub>Si/exo</sub>** at the PM3 level of theory. Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of final products **11a,b** and **15a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO991560N