JOC*Note*

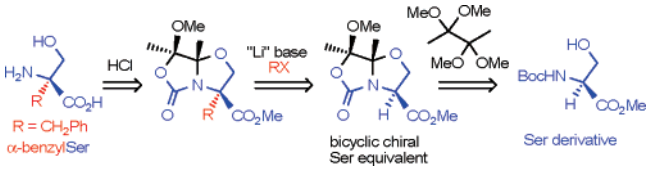
Role of the Countercation in Diastereoselective Alkylations of Pyramidalized Bicyclic Serine Enolates. An Easy Approach to α-Benzylserine†

Gonzalo Jiménez-Osés, Carlos Aydillo, Jesús H. Busto, María M. Zurbano,* Jesús M. Peregrina, and Alberto Avenoza*

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, UA-CSIC, 26006 Logroño, Spain

alberto.avenoza@unirioja.es

Received April 4, 2007

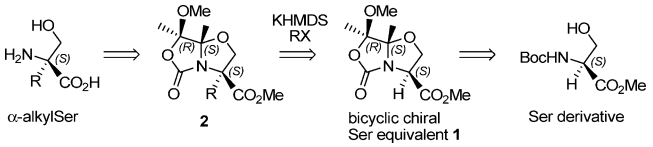


The use of a chiral serine equivalent as an excellent chiral building block has been demonstrated in the synthesis of α-benzylserine through a diastereoselective lithium enolate alkylation reaction and subsequent acid hydrolysis. The role of a coordinating countercation (lithium) in the alkylation reaction has been investigated. Theoretical studies have been performed in order to elucidate the stereochemical outcome of the alkylation process, which occurs with total retention of configuration.

The current interest in α,α-dialkyl-α-amino acids[1] relates to the important effects they have on the biological activity of peptides that incorporate these quaternary amino acids, because they introduce alterations in the conformations of the backbone. Among these compounds, chiral α-alkylserines have been extensively studied owing to their important roles in synthetic and biological chemistry.[1]

In the course of our studies aimed at finding synthetic routes for α,α-disubstituted α-amino acids based on the use of five-membered cyclic *N*,*O*-acetals[2] (Garner aldehyde derivatives), we became interested in diastereoselective alkylations of chiral serine equivalents. In this context, we envisioned the design of other, more stable chiral five-membered cyclic *N*,*O*-acetal serine derivatives by incorporating a new ring in the structure. Consequently, we recently reported the synthesis and reactivity of a novel class of bicyclic *N*,*O*-acetal (**1**) derived from serine (Scheme 1).[3] More specifically, we assessed the diastereoselective alkylation of this system oriented toward the large-scale preparation of α-alkylserines (Scheme 1).

SCHEME 1. Retrosynthesis of α-Alkylserines from Bicyclic Chiral Serine Equivalent 1



As a result of our theoretical investigations into the high diastereoselectivity obtained experimentally (dr >20:1), we proposed a highly pyramidalized ester enolate as the true source of this stereodifferentiation. In fact, the inversion barrier of this enolate was calculated to be greater than any other process occurring under the reaction conditions.[3] This proposal was made on the basis of a "naked" enolate, because a base with a noncoordinating cation—like potassium hexamethyldisilazane (KHMDS)—was used in the experiments. Clearly, it was necessary to test the validity of this hypothesis under other reaction conditions. Moreover, we needed to minimize a competitive retro-*O*-Michael reaction (often referred to as a *β*-elimination), which reduced the yields of *C*-alkylation by producing variable amounts of acrylate **3** with KHMDS as the base (Table 1 graphic). The notable influence that the base countercation has on alkylation processes is well-known, leading to dramatic changes in regio- and stereoselectivities.[4] The more coordinating character of metalic ions like Li^+ favors their tighter association with the enolate moiety (mainly with oxygen atoms), leading to complex structures like oligomers,[5] chelates,[6] and highly solvated adducts. In fact, the determination of the major species in these reactants[7] in solution is a challenging task to rationalize the observed results in this kind of reaction.

Bearing these facts in mind, and with the aim of further exploring the scope of the reaction, we decided to test the use

* To whom correspondence should be addressed. Fax: +34 941 299655.

† Dedicated to Prof. Vicente Gotor on the occasion of his 60th birthday.

(1) (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (c) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732. (d) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406−430. (e) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389−397. (f) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342−351. (g) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569−623.

(2) (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220−8225. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653−4661. (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195−2204. (d) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949−957. (e) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 399−405. (f) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 719−724. (g) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Synthesis* **2005**, 575−578.

(3) Aydillo, C.; Jiménez-Osés, G.; Busto, J. H.; Peregrina, J. M.; Zurbano, M. M.; Avenoza, A. *Chem. Eur. J.* **2007**, *13*, 4840−4848.

(4) (a) Hu, Y.; Bishop, R. L.; Luxenburger, A.; Dong, S.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2735−2737. (b) Boeckman, R. K., Jr.; Boehmler, D. J.; Musselman, R. A. *Org. Lett.* **2001**, *3*, 3777−3780. (c) Alvarez-Ibarra, C.; Csakÿ, A. G.; Maroto, R.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 7934−7940.

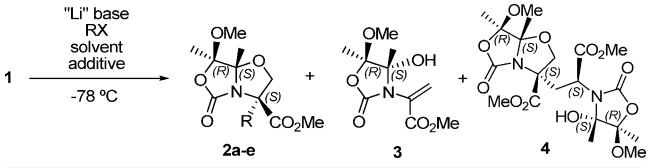
(5) (a) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462−468. (b) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345−3346. (c) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622−2626.

(6) (a) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602−8604. (b) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539−5541. (c) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829−7830. (d) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

(7) (a) Abbotto, A.; Leung, S. S.-W.; Streitwieser, A.; Kilway, K. V. *J. Am. Chem. Soc.* **1998**, *120*, 10807−10813. (b) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255−11268.

10.1021/jo070656b CCC: $37.00
Published on Web 06/08/2007

TABLE 1. Diastereoselective Alkylation of Building Block 1 with Li-Derived Bases



entry	RX	"Li" base	solvent	additive	**2a**−**e**/**3**/**4**[a]	product, yield[b] (%)
1	MeI	LDA	THF	none	−/−/100	**4**,[c] 46
2	MeI	LHDMS	THF	HMPA	100/−/−	**2a**,[d] 90
3	MeI	LHDMS	THF	HMPT	−/2/98	**4**, 43
4	MeI	LHDMS	THF	TMEDA	−/3/97	**4**, 56
5	MeI	LHDMS	THF	12-crown-4	−/2/98	**4**, 38
6	MeOTf	LHDMS	THF	none	100/−/−	**2a**, 96
7	MeOTf	LHDMS	Et_2O	none	62/−/38	**2a**, 54
8	EtOTf	LHDMS	THF	none	40/−/60	**4**, 54
9	EtOTf	LHDMS	THF	HMPA	100/−/−	**2b**,[e] 94
10	BnBr	LHDMS	THF	HMPA	53/−/47	**2c**,[d] 45
11	BnI	LHDMS	THF	HMPA	93/7/−	**2c**, 74
12	allylBr	LHDMS	THF	HMPA	52/−/48	**2d**,[e] 40
13	allylI	LHDMS	THF	HMPA	100/−/−	**2d**, 92
14	*n*-HexI	LHDMS	THF	HMPA	−/37/63	**4**, 51
15	none	LHDMS	THF	none	−/9/91	**4**, 87

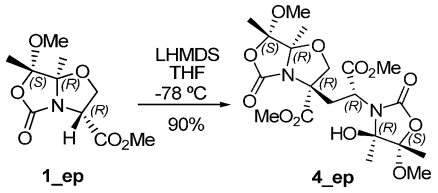
[a] Ratio **2a**−**e**/**3**/**4** determined by ^{1}H NMR analysis of the reaction mixture. [b] Yield of the major product isolated after column chromatography. [c] Stereochemistry determined by X-ray analysis (this work). [d] Stereochemistry predicted by NOE (ref 3). [e] Stereochemistry determined by X-ray analysis (ref 3).

of lithium diisopropylamide (LDA) and lithium hexamethyldisilazane (LHDMS) as bases in the alkylation of building block **1**. The influence of the leaving group was also studied by using different commercially available alkyl halides and trifluoromethanesulfonates (ROTf). For less reactive alkyl groups or poor leaving groups, several additives like hexamethylphosphoramide (HMPA), tris(dimethylamino)phosphine (HMPT), *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA), and 12-crown-4 were used. Bearing in mind that different ethereal solvents are often said to have different coordinating properties, causing a profound effect on aggregation and therefore on the reactivity of lithium enolates,[8] two ethereal solvents, tetrahydrofuran (THF) and diethyl ether (Et_2O), were also tested. The results obtained are summarized in Table 1. Alkylation reaction did not occur using LDA as a base (entry 1). The same feature was observed when the base LHMDS was combined with additives different from HMPA (entries 2−5). From the observation of entries 6 and 7, THF was selected as solvent instead Et_2O.

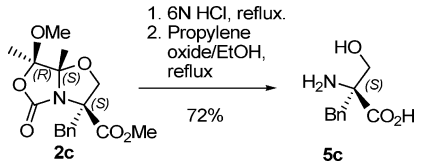
As can be seen, the best results in terms of alkylation were obtained with LHMDS as a base and MeOTf (without additives) and EtOTf (in the presence of HMPA) as alkylating agents (entries 6 and 9). These new conditions allowed us to improve on the yield previously obtained in ref 3 with the total suppression of secondary reactions. The alkylation products were obtained with the same absolute configuration and diastereomeric purity (dr >20:1) achieved in ref 3, as demonstrated by comparison of the NMR data and optical activity with the previously reported values. Therefore, the change in the base countercation from K^+ to Li^+ had a negligible effect on the diastereoselectivity of the alkylation reaction.

Interestingly, the retro-*O*-Michael product **3** was not observed under almost any conditions, except as a minor product in entries

SCHEME 2. Synthesis of 4_ep from Building Block 1_ep



SCHEME 3. Synthesis of (*S*)-α-Benzylserine 5c



3, 4, 5, 11, 14, and 15, with the formation of bis-adduct **4** being the alternative competitive pathway. This kind of "dimerization" has been previously reported[9] and is produced by the quick in situ alkylation of the enolate of **1** with acceptor **3** in a *C*-Michael-type reaction. This process proceeds with a high diastereoselectivity (dr >20:1 as demonstrated by ^{1}H NMR), and the absolute configuration of **4**, which contains six chiral carbons, was unambiguously determined by X-ray diffraction analysis[10] of monocrystals obtained by slow evaporation of a solution in a mixture of hexane/ethyl acetate. Starting from the enantiomer of bicycle **1 (1_ep)**, which could be obtained from commercially available (*R*)-*N*-Boc-serine methyl ester,[3] this protocol allows the preparation of "dimer" **4_ep** (Scheme 2), which is an enantiomer of **4**, as demonstrated by NMR, X-ray diffraction analysis,[10] and comparison of the optical activities of the two compounds (see the Supporting Information).

In an effort to expand this methodology to the preparation of α-alkylserines, we carried out the synthesis of (*S*)-α-benzylserine **5c** from the precursor **2c**. Hydrolysis of the alkylation substrate **2c** in an acidic medium gave the required amino acid **5c** as an hydrochloride derivative with a 97% yield (Scheme 3). An aliquot of this compound was treated with propylene oxide in order to obtain the free amino acid **5c** with a 73% yield. The structural and optical properties of this compound were identical to those reported in the literature ($[\alpha]^{25}_D = +16.8$).[11] It is important to note that although several synthetic methods have been reported for other chiral α-alkylserines, there are only four reports on the asymmetric synthesis of enantiomerically pure (*S*)- or (*R*)-α-benzylserine, also commonly named (*S*)- or (*R*)-α-hydroxymethylphenylalanine.[11] The interest in α-benzylserine has been illustrated in peptide chemistry[12] since several analogs of bioactive peptides (e.g.,

(8) Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J. K. *Org. Lett.* **2000**, *2*, 3739−3741.

(9) (a) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Palomero, M. A.; Polara, A.; Rodríguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3618−3627. (b) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53−80.

(10) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.

(11) (a) Horikawa, M.; Nakajima, T.; Ohfune, Y. *Synlett* **1997**, 253−254. (b) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345−6352. (c) Jew, S.-s; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382−2385. (d) Vassiliou, S.; Yiotakis, A.; Magriotis, P. A. *Tetrahedron Lett.* **2006**, *47*, 7339−7341.

(12) (a) Lempicka, E.; Slaninova, J.; Olma, A.; Lammek, B. *J. Peptide Res.* **1999**, *53*, 554−559. (b) Olma, A.; Tourwé, D. *Lett. Pept. Sci.* **2000**, *7*, 93−96. (c) Olma, A.; Chung, N. N.; Schiller, P. W.; Zabrocki, J. *Acta Biochim. Pol.* **2001**, *48*, 1121−1124. (d) Olma, A.; Lachwa, M.; Lipkowski, A. W. *J. Peptide Res.* **2003**, *62*, 45−52.

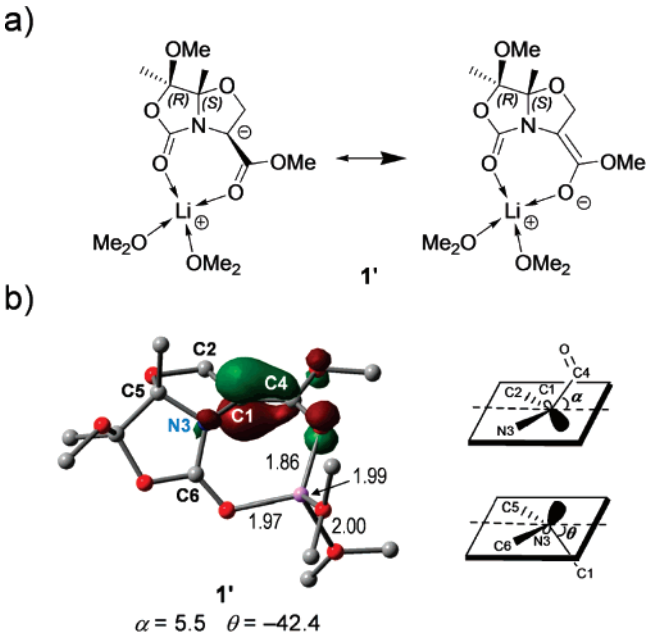


FIGURE 1. (a) Resonance forms of lithium enolate **1′** showing the higher contribution of the enol form. (b) Minimum energy structure together with HOMO of enolate **1′**, calculated at the B3LYP/6-31+G-(d) level. Distances are given in angstroms and angles α and θ in degrees.

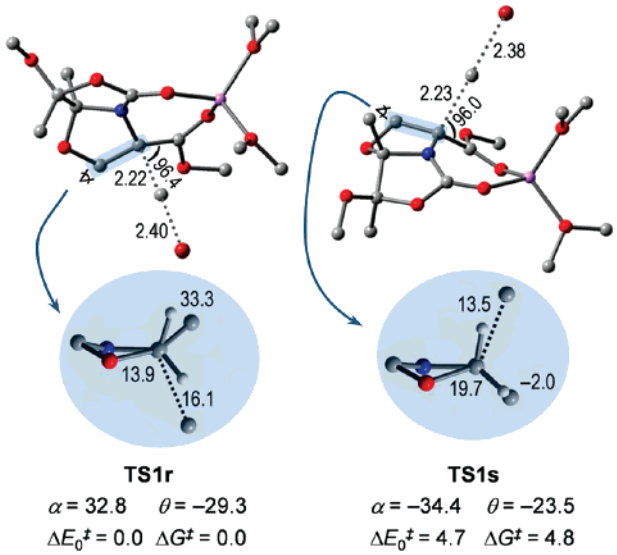


FIGURE 2. Transition structures for the reaction pathways evaluated from enolate **1′**, calculated at the B3LYP/6-31+G(d) level. Newman projections from C2 (front) to C1 (back) and related torsion angles are also displayed. Distances are given in Å, torsion and dihedral angles α and θ in degrees, and relative activation energies in kcal mol^{-1}.

μ-selective opioid peptide agonist DALDA, endomorphin-2, arginine vasopressin, deltorphin I) containing this quaternary amino acid have been synthesized and the biological consequences of replacing natural amino acids with (*S*)- or (*R*)-α-benzylserine have been studied, with many examples showing an increase in activity.

The aforementioned experimental findings encouraged us to carry out a theoretical study of the *C*-alkylation process starting from the enolate of bicycle **1** (see the Supporting Information). Bromomethane (MeBr) was chosen as the alkylating agent for the calculations, and discrete molecules of dimethyl ether (Me_2O) were used to explicitly solvate the lithium atom attached to the enolate moiety. In addition, bulk solvent effects were included in the estimation of energies in order to better reproduce the experimental conditions (see the Supporting Information).

After the exhaustive evaluation of a large number of coordination and solvation possibilities (see the Supporting Information for further details), the structure of the most stable lithium enolate was found to be the seven-membered chelate **1′** by far (Figure 1a). One significant feature found in these preliminary studies was the slightly nonplanar character of this lithium enolate. According to Seebach et al.,[13] this deviation from planarity (pyramidalization) was measured in terms of the out-of-plane angle (signed) between the bond vector C1−C4 and the plane C1−C2−N3 (denoted as α), which ranges from 0° in a pure sp^2 center to 54.7° in a typical sp^3 center. Subsequently, the calculated value of α (around 6°), together with the slightly asymmetric character at the nodal plane observed for the HOMO along the C1−C4 bond (Figure 1b), point toward retention of configuration of the stereocenter after deprotonation, probably due to stereoelectronic factors inherent in the structure of the bicyclic substrate.

In line with our previous observations,[3] one of the most remarkable geometrical features found in the calculated structure of enolate **1′** is the high nonplanar character of the bridgehead carbamate *N*-atom, measured in terms of the out-of-plane angle (signed) between the bond vector N3−C1 and the plane N3−C5−C6 (denoted as θ). This high level of pyramidalization is most likely the result of the conformational restraints imposed by the bicyclic structure and makes N3 formally chiral,[14] showing *S*-configuration. Therefore, and in order to minimize the stereoelectronic repulsions between the N3 lone pair and the π bond between C1 and C4 in **1′**, the pyramidalization of the enolate (α) would be a consequence of this high level of pyramidalization observed in N3 (θ).

The sources of stereoselectivity were then analyzed by calculating the transition structures corresponding to approach at the *Re* and *Si* faces (**TS1r** and **TS1s**, respectively), which were properly located and characterized. The most remarkable geometrical features are shown in Figure 2 along with the relative energies of the calculated geometries. As can be seen from these plots, the incipient C1−C7 and breaking C7−Br bonds, together with the approach angles of the electrophile, are very similar in both TS.

The energy barrier of the enolate alkylation by the *Re* face (**TS1r**) is ca. 5 kcal mol^{-1} lower than by the *Si* face (**TS1s**), which implies total diastereoselectivity (>99:1) in the reaction. This situation is in total agreement with the experimentally observed retention of configuration.

(13) Seebach, D.; Maetzke, T.; Petter, W.; Klötzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781−1786.

(14) (a) Calcagni, A.; Gavuzzo, E.; Lucente, G.; Mazza, F.; Morera, E.; Paglialunga Paradisi, M.; Rossi, D. *Biopolymers* **2000**, *54*, 379−387. (b) Kakuda, H.; Suzuki, T.; Takeuchi, Y.; Shiro, M. *Chem. Commun.* **1997**, 85−86. (c) Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K.; Yamaguchi, K. *Tetrahedron Lett.* **1998**, *39*, 865−868. (d) Ohwada, T.; Okamoto, I.; Shudo, K.; Yamaguchi, K. *Tetrahedron Lett.* **1998**, *39*, 7877−7880. (e) Srivastava, A.; Srivastava, V.; Verma, S. M. *J. Org. Chem.* **1994**, *59*, 3560−3563.

Once the calculated energy barriers had reproduced the experimental selectivity, we located the factors responsible for this high level of stereocontrol in the *C*-alkylation. The rehybridization of C1 to sp^3 in **TS1s** and **TS1r** diminishes the high pyramidalization of N3 in enolate **1′** in order to maintain the seven-membered chelate (Figures 1 and 2). This planarization (lower values of θ) and the subsequent strain on the bicyclic system are greater (by ca. 6°) in **TS1s**. Additionally, **TS1r** has a more staggered arrangement (and consequently lower torsional strain) than **TS1s** according to the Newman projections of the C1−C2 bonds (Figure 2). These distinct torsional effects occurring on each TS are in agreement with the stereoselectivity observed for this reaction.

In summary, a short and general strategy for the preparation of (*S*)-α-benzylserine **5c** from chiral serine-derived building block **1** has been developed. The synthetic route involves alkylation of **1** followed by acid hydrolysis. We first investigated the role of the countercation (lithium) in the diastereoselective alkylation of this building block, which occurs with retention of configuration—as it does when a base with a noncoordinating cation (potassium) is used.[3] Therefore, the change of the base countercation from K^+ to Li^+ has a negligible effect on the diastereoselectivity of the alkylation reaction, but this change increases the yield of the reaction, minimizing the formation of side-products. Additionally, the mechanism involved in this alkylation process has been studied from a theoretical point of view, including solvation effects.

Experimental Section

(*S*)-α-Benzylserine (5c). Compound **1** (2.06 g, 8.40 mmol) was dissolved in dry THF (100 mL) under an argon atmosphere, and HMPA (6.02 g, 33.60 mmol) was added by syringe. The solution was stirred at −78 °C, and benzyl iodide (5.49 g, 25.20 mmol) and a 1 M solution of LHMDS in THF (16.80 mL, 16.80 mmol) were added by syringe (LHMDS was added slowly). After being stirred for 5 min, the reaction was quenched with saturated NH_4Cl solution (100 mL). The mixture was warmed to rt and vigorously stirred. The mixture was diluted with diethyl ether, and the aqueous phase was separated and extracted with diethyl ether. The organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to give 2.08 g of compound **2c**, 74% yield. Analytical and spectroscopic data for this compound agree with those reported in the literature.[3] Compound **2c** (483 mg, 1.44 mmol) was charged into a round-bottomed flask with 6 N aqueous HCl (10 mL). The mixture was stirred and heated under reflux overnight. The solvent was removed in vacuo and the residue was partitioned between water and ethyl acetate. The aqueous phase was evaporated to give 323 mg of the corresponding hydrochloride derivative of (*S*)-α-benzylserine, 97% yield. An aliquot of this material (102 mg) was treated with (1:1) ethanol/propylene oxide (3 mL) under reflux for 2 h to give (*S*)-α-benzylserine **5c** (62 mg, 0.32 mmol) as a white solid, 73% yield: $[\alpha]^{25}_D$ +16.0 (*c* 1.00, H_2O). NMR data agree with the published data[11] (see the Supporting Information). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.45; H, 6.73; N, 7.23.

Acknowledgment. We thank the Ministerio de Educación y Ciencia and FEDER (project CTQ2006-05825/BQU and Ramón y Cajal contract to J.H.B.).

Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, crystal structure data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070656B