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Synthesis of Highly Substituted Enantiopure Piperazines and Ketopiperazines from Vicinal *N*-Sulfinyl Diamines

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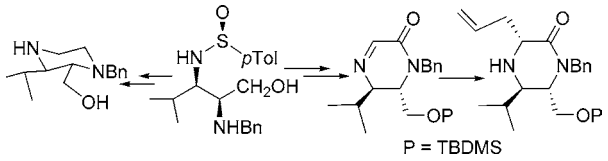
Received October 4, 2005



Enantiopure 1-benzyl-2,3-disubstituted piperazines (**4**) have been synthesized by treatment of *N*-sulfinyl-*N*-benzyldiamino alcohols (**1**) with diethyl oxalate and sodium methoxide followed by reduction with borane. Alternatively, the sulfinamido group was preserved by an *N*-acylation/cyclization protocol using α-chloroacetyl chloride that led to the synthesis of *N*-sulfinyl ketopiperazines (**11**). Ensuing elimination of the sulfinyl group with NaH produced imino ketopiperazines (**9**) that are suitably functionalized for nucleophilic addition to the imino moiety. Stereoselective and high yielding allylation of imino ketopiperazines (**9c**) was achieved under Barbier conditions using $CeCl_3 \cdot 7H_2O$ as the additive.

Introduction

The piperazine ring is truly ubiquitous in molecules involved in the regulation of a wide variety of biological processes. Indeed, the piperazine scaffold is considered a privileged structure in drug discovery,[1] and it has served for the development of therapeutically valuable compounds such as Indinavir, an HIV-protease inhibitor,[2] Glivec, a potent antiproliferative agent,[3] and different compounds acting at receptors in the CNS such as arylpiperazines, powerful 5-HT_{1A} ligands.[4] In addition, a number of natural products with a broad spectrum of biological activities such as ectenaiscidin 743,[5] TAN-1251A,[6] and dragmacines[7] contain a chiral piperazine ring as a part of their structure. On the other hand, the structurally related mono- and diketopiperazines have gained importance as farnesyl transferase inhibitors,[8] as conformationally restricted peptidomimetics,[9] and also as fragments of natural products of diverse structural complexity and biological activities.[10] Furthermore, during the

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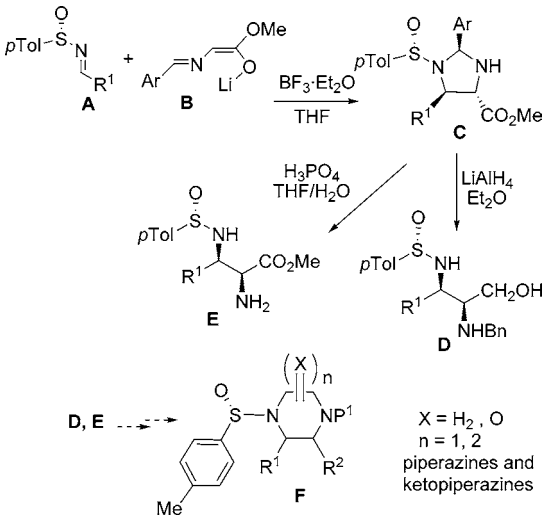
10.1021/jo052077h CCC: $33.50
Published on Web 01/14/2006

past years, several groups have examined the role of piperazines and diketopiperazines as efficient chiral ligands in enantioselective catalysis.[11]

The increasing interest in these compounds entails the search of efficient routes toward piperazines. The existing methods to prepare chiral piperazines are scarce[12] and not fully applicable to the straightforward synthesis of highly substituted derivatives since many of these routes rely on the condensation of natural α-amino acids. The previous limitation is particularly true for nonsymmetrical 2,3-disubstituted piperazines for which the simplest route entails reduction of 2,3-disubstituted diketopiperazines in turn prepared from the corresponding vicinal diamines. In fact, the synthesis of suitably substituted enantiopure vicinal diamines may be quite challenging,[13] and this severely limits the viability of this approach.

Within a program directed to the discovery of new therapeutically valuable piperazine derivatives,[14] we envisioned that *N*-sulfinyl piperazines would be practical intermediates for the synthesis of enantiopure highly substituted piperazines. Besides, the chiral sulfinamide moiety could be an additional handle for subsequent asymmetric transformations of these molecules. In past years, we have gained experience in the asymmetric synthesis of nonsymmetrical vicinal diamine derivatives.[15] We have reported the asymmetric synthesis of enantiopure 1,3-imidazolidines **C** through the diastereoselective stepwise condensation between readily available *p*-toluenesulfinimines **A**[16] and glycine iminoester enolates **B** in the presence of boron trifluoride (Scheme 1). Under these conditions, enantiopure *p*-toluenesulfinimines display a moderate to high facial selectivity rendering the corresponding *N*-sulfinylimidazolidines in good to excellent diastereomeric excess. Ensuing reductive cleavage of the aminal moiety expediently transforms our *N*-sulfinylimidazolidines **C** into differentially protected vicinal diamino alcohols **D** in good yields. Alternatively, we have found conditions to effect the selective cleavage of the aminal moiety in *N*-sulfinylimidazolidines **C** to yield efficiently *N*-sulfinyldiamino esters **E**. The availability of these substrates **D** and **E**, along with the aforementioned relevance of piperazines, prompted us to examine the transformation of a series of vicinal diamines into enantiopure *N*-sulfinylpiperazines **F** and eventually to explore subsequent asymmetric transformations on these molecules. Herein, we describe in detail our results in this field.[15b]

SCHEME 1. Route to *N*-Sulfinylpiperazines from *p*-Toluenesulfinimines



Results and Discussion

Our work to obtain enantiopure diketopiperazines was focused on substrates **1a**−**f**[15a] originally obtained from glycine-derived enolates (Scheme 2). Initially, we tested different experimental conditions using oxalyl chloride or 1,1′-oxalyldiimidazole in THF as acylating agents; however, we did not isolate the expected diketopiperazines. After some experimentation, we found that the treatment of **1a** (R^1 = Et) with diethyl oxalate in CH_2Cl_2 afforded 2,3-diketopiperazine **2a** in moderate yields (60%), along with a small amount of morpholinedione **3a** derived from the N/O ring closure. After chromatographic separation, we observed that **3a** slowly converted into **2a** upon standing in a solution of MeOH (5 days) and that a catalytic amount of NaOMe promoted this conversion in only 1 h. Similarly, *N*-sulfinyldiamino alcohols **1b** (R^1 = CH_2CH_2Ph) and **1c** (R^1 = *i*Pr) paralleled this behavior after removal of the

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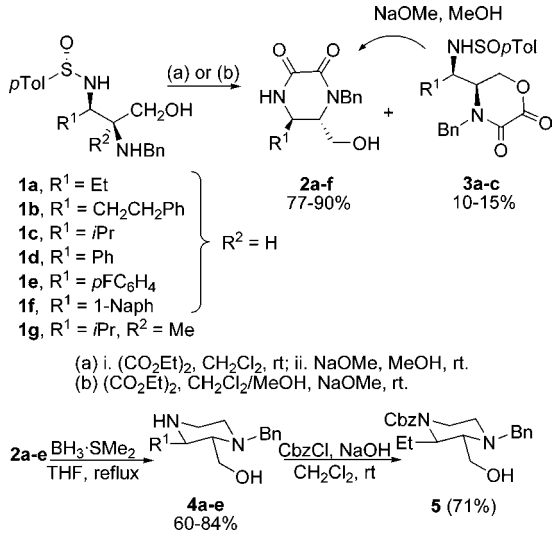
SCHEME 2. Synthesis of Enantiopure Hydroxymethyl Diketopiperazines and Piperazines

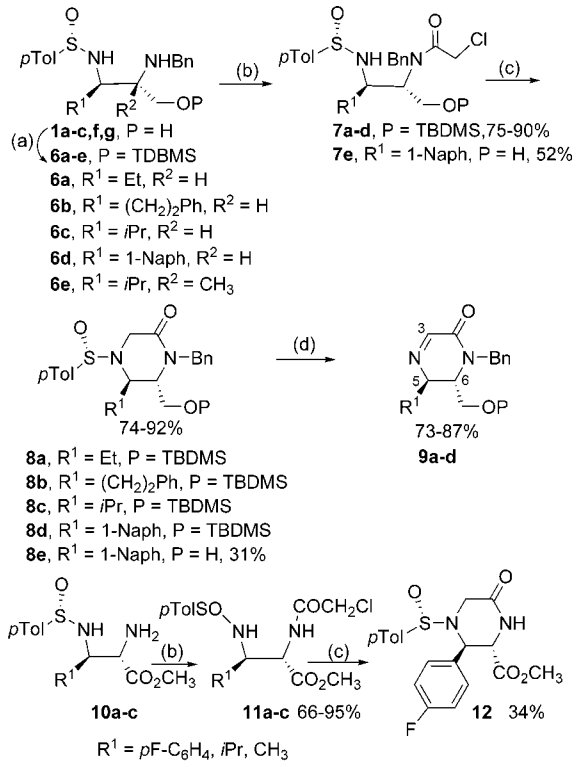


diketopiperazines **2b** and **2c** by filtration. Seeking to increase the efficiency of the process, we added a solution of NaOMe in MeOH to the reaction mixture, and we found a complete conversion to hydroxymethyl diketopiperazines. This procedure was also satisfactorily extended to aromatic substrates (**1d**−**f**) to produce diketopiperazines **2d**−**f**. From these results, we hypothesized that the addition of NaOMe catalyzes ester cleavage in morpholinediones **3** and also simultaneously promotes in situ nucleophilic displacement at sulfur, rendering methyl *p*-toluenesulfinate along with the desired diketopiperazine in excellent yields.

Despite the loss of the sulfinamide group, the remarkably efficient access to enantiopure 2,3-diketopiperazines prompted us to address the reduction to 2-hydroxymethylpiperazines. Initial attempts performed with $LiAlH_4$ as reducing agents gave the expected piperazines in poor yields;[17] however, diketopiperazines **2a**−**e** were efficiently transformed into the corresponding enantiopure 2,3-disubstituted piperazines **4a**−**e** in good yields (60−84%), upon treatment with a borane dimethyl sulfide complex. These 2-hydroxymethylpiperazines are amenable to selective protection at the secondary nitrogen as benzyloxycarbonyl derivatives as illustrated by the preparation of hydroxymethyl piperazine **5**. To broaden the scope of these procedures, we considered vicinal diamine **1g**, originally obtained from alanine (Scheme 1).[15a] Unfortunately, the presence of a quaternary carbon in its skeleton prevented any cyclization from taking place. Thus, when compound **1g** was treated with diethyl oxalate, cyclic derivatives **2** or **3** were not observed, even in the presence of NaOMe; instead, labile open-chain acylated intermediates were detected. The generality of these findings remains to be tested.

At this point, we focused our attention on preserving the sulfinamide moiety attached to the piperazine skeleton. We envisioned that *N*-sulfinyl monoketopiperazines could be prepared from our substrates and α-chloroacetyl chloride by sequential *N*-acylation and cyclization in basic media.[18] Thus, the primary alcohol of **1a**−**c** and **1f** was protected uneventfully

SCHEME 3. Synthetic Route to *N*-Sulfinyl Ketopiperazines and Imino Ketopiperazines



Reagents and conditions:

(a) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 64-88%; (b) $ClCH_2COCl$, EtOAc:$NaHCO_3$ aq (50 : 50), 0 °C to rt; (c) Cs_2CO_3, DMF, 65 °C; (d) NaH, THF, 0 °C to reflux.

as a silyl ether in excellent yields, affording **6a**−**d**, respectively (Scheme 3). Not unexpectedly, **6e** did not undergo *N*-acylation with $ClCH_2COCl$ under mild conditions, presumably due to the quaternary carbon hindering the amino moiety, and no further efforts were conducted on this substrate. In contrast, **6a**−**d** underwent smooth *N*-acylation to give chloroacetamides **7a**−**d** that cyclized to *N*-sulfinyl-*N*-benzyl ketopiperazines **8a**−**d** in excellent yields in the presence of Cs_2CO_3. In addition, we have examined the *N*-acylation/cyclization protocol for hydroxymethyl sulfinamide **1f** (R^1 = 1-Naph) to avoid protection/deprotection steps, and although we have found lower yields for the sequence, in this particular case, a selective *N*-acylation took place with $ClCH_2COCl$ giving **7e**, followed by a selective cyclization of the sulfinamide moiety onto the chloride to afford *N*-sulfinyl ketopiperazine **8e**. These results suggest that suitable reaction conditions could be found to perform the cyclization to piperazines avoiding the protecting silyl group for the other substrates. The spectroscopic structural assignment of the previous products was further confirmed by chemical means. Thus, *N*-sulfinyl ketopiperazine **8d** was submitted to desilylation conditions with TBAF to render hydroxymethyl derivative **8e** (yield: 97%), and more interestingly, treatment of silyloxy chloroacetamide **7d** with TBAF simultaneously produced desilylation and cyclization to hydroxymethyl *N*-sulfinyl ketopiperazine **8e** in good yield (87%).

Additionally, we have observed that after treatment of **7a** with Cs_2CO_3, *N*-sulfinyl ketopiperazine **8a** was often accompanied by small amounts of a desulfinylated product in the crude mixtures, tentatively assigned as imine **9a** and presumably derived from **8a** by enolate formation and elimination of the

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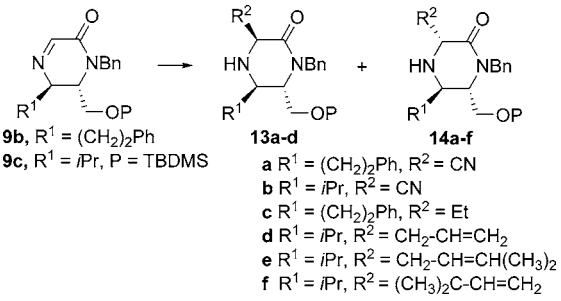
TABLE 1. Nucleophilic Additions to Imino Ketopiperazines 9



entry	sub	conditions	**13**[a]	**14**[a]	yield[b]
1	**9b**	KCN, HOAc	**13a** (69)	**14a** (31)	40[c]
2	**9c**	KCN, HOAc	**13b** (64)	**14b** (36)	63[d]
3	**9b**	Et_2Zn, TMSCl	**13c** (78)	**14c** (22)	42[e]
4	**9c**	allylSiMe$_3$ $SnCl_4$	**13d** (76)	**14d** (24)	74
5	**9c**	allylSnBu$_3$ $TiCl_4$	**13d** (43)	**14d** (57)	77
6	**9c**	allylMgBr $BF_3{\cdot}Et_2O$	**13d** (24)	**14d** (76)	64[f]
7	**9c**	allylMgBr $CeCl_3$		**14d**	28[g]
8	**9c**	allylBr, Zn			
9	**9c**	allylBr Zn, $CeCl_3{\cdot}7H_2O$		**14d**	87
10	**9c**	$Me_2C{=}CHCH_2B$ r Zn, $CeCl_3{\cdot}7H_2O$		**14e** (65) **14f** (35)	71

[a] Ratio measured in the ^{1}H NMR spectra of the crude substance. [b] Combined yield of **13** and **14**. [c] 21% of starting material was recovered. [d] 10% of starting material was recovered. [e] 52% of starting material was recovered. [f] 18% of starting material was recovered. [g] 53% of starting material was recovered.

sulfur moiety. To further prove this hypothesis, **8a** was submitted to treatment with NaH in refluxing THF affording an excellent yield of imine **9a** that was fully characterized (Scheme 3). Elimination of the sulfinyl group was successfully conducted for *N*-sulfinyl ketopiperazines **8b**−**d**, rendering enantiopure imino ketopiperazines **9b**−**d** in good yields.

Subsequently, we addressed the transformation of *N*-sulfinyl diaminoesters **10a**−**c**, available through selective imidazolidine hydrolysis,[15c] into *N*-sulfinyl ketopiperazines. Unfortunately, although the *N*-acylation step gave good yields of the expected α-chloroacetamides **11a**−**c**, in most cases, we failed in finding suitable conditions to effect the cyclization step, and only 34% of *p*-fluorophenyl piperazine **12** could be isolated upon reaction of **11a** with Cs_2CO_3.[19]

Ketopiperazine derivatives **8** and **9** hold considerable potential for further selective manipulations at C-5 and C-6, and little has been published concerning the reactivity of imino keto piperazines.[9a,20] Therefore, we examined the addition of nucleophiles to imino ketopiperazines **9** under different experimental conditions to introduce different substituents at C-3 (Table 1).[21]

Thus, ketopiperazines **9b** and **9c** can be easily transformed into the corresponding mixtures of amino nitriles **13a** and **14a** (69:31) and **13b** and **14b** (64:36) by treatment with KCN in HOAc (Table 1, entries 1 and 2). The synthesis of enantiopure amino nitriles **13a**,**b** and **14a**,**b** is remarkable due to their similarity to the bioactive piperazine core of saframycin A and phthalascidin-650, compounds with valuable antiproliferative properties.[5]

In addition, we have found that trimethylsilyl chloride promoted the nucleophilic addition of diethylzinc to **9b** rendering an inseparable mixture of adducts **13c** and **14c** with moderate stereoselectivity (78:22, Table 1, entry 3).[22] Subsequently, we examined the addition of an allyl group upon different experimental conditions (Table 1, entries 4−9).[23] Initially, the addition of allyltrimethylsilane and $SnCl_4$ to **9c** led to a 76:24 mixture of **13d** and **14d**. In the presence of $TiCl_4$, the addition of allyltributylstannane produced a decrease in selectivity affording a mixture of **13d** and **14d** (43:57) in good yield. In contrast, the stereoselectivity was notably improved using allylmagnesium bromide as nucleophile and upon activation with boron trifluoride as a Lewis acid but in an opposite sense (24:76, **13d**/**14d**). Furthermore, this stereoselectivity was complete when allylmagnesium bromide was added in the presence of anhydrous $CeCl_3$ (**13d**/**14d**, 0:100, entry 7), but 53% of the starting material was recovered despite forcing conditions. While introduction of an allyl group under classical Barbier conditions $CH_2{=}CHCH_2$-Br/Zn led to complete recovery of the starting material, the presence of cerium salts ($CeCl_3{\cdot}7H_2O$) produced a dramatic increase of both reactivity and selectivity rendering **14d** as a single diastereomer in 87% yield.[24] Finally, a complete control of the stereoselectivity relative to the piperazine ring was observed for the reaction of 1-bromo-3-methylbut-2-ene under the previous conditions (entry 10); however, a 65:35 mixture of regioisomers (**14e**/**14f**) was produced in this experiment due to the nonsymmetric structure of the allylic moiety.

The remarkable increase in reactivity produced by the cerium salt under Barbier conditions could be attributed to its role as Lewis acid, activating the carbon−nitrogen double bond and promoting formation of the allylzinc species.[23e] This high diastereoselectivity can be rationalized by the initial attack of the allylmetal species to the less hindered face of the imino group, opposite to the axial isopropyl group [$J(H_5-H_6)$ is ∼0.0 Hz for **9a**−**c**][25] and potential inhibition of secondary retroallylation processes by release of small amounts of water from

(19) We have speculated about secondary processes caused by the acidity of the amide (CONH) and the carbon α-to the ester; however, the precise origin of the failure of these cyclizations remains unclear.

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(24) The structural assignment for **13d**, **14d**, and **14e** was based on their spectral data. The stereochemistry at C-3 was confirmed by DNOE experiments (i.e., **14d**: H-3/CH (*i*Pr): 5.9%). The tentative stereochemical assignment of C-3 for **13a**−**c** and **14a**−**c** is based on the comparison of their ^{1}H NMR spectra with those of **13d** and **14d**; small differences of chemical shifts for benzylic, C$\underline{H}_2$O and C$\underline{H}i$Pr protons were observed (see Supporting Information).

(25) Small values of J H_5/H_6 (0−2 Hz) indicated a pseudoaxial arrangement of adjacent substituents (R^1, CH_2OP, and Bn) for *N*-sulfinyl ketopiperazines **8** and imino ketopiperazines **9** that was confirmed by DNOE experiments (see Experimental Procedures). For a related example, see: (a) Knapp, S.; Morriello, G. J.; Doss, G. A. *Tetrahedron Lett.* **2003**, *44*, 2645−2647.

the hydrated cerium salt.[23e,f] Independent treatment of **14d** and **13d** with NaH in THF did not afford any epimerization at C-3, ruling out base-mediated epimerization of the final products. Nevertheless, enolization processes induced by the presence of Lewis acids that could potentially explain the stereochemical results cannot be ruled out.

In summary, readily available enantiopure *N*-sulfinyl-*N*-benzyl diamino alcohols have been expediently transformed into a variety of enantiopure 2,3-disubstituted piperazines with adequate functionalization for subsequent transformations. In addition, a simple entry to more functionalized *N*-sulfinyl monoketopiperazines from the same precursors has been examined. Subsequent elimination of the sulfinamide under basic conditions led to imino ketopiperazines readily functionalized by a variety of nucleophilic additions. The diastereoselective allylation of these substrates brings to light their potential versatility for the synthesis of highly substituted piperazines. Further applications of these methodologies will be pursued in our laboratory.

Experimental Procedures

General Procedure for Reaction with Diethyl Oxalate. Method A: to a solution of *N*-sulfinyldiamino alcohol **1** in anhydrous CH_2Cl_2 (6 mL/mmol) at room temperature, 6 equiv of diethyl oxalate was added, and the mixture was stirred until formation of morpholinedione **3** was observed by TLC. Then, 2 equiv of NaOMe (from a 0.25 M solution in MeOH) was added, and the mixture was stirred until the disappearance of starting materials (TLC). At that point, water (10 mL/mmol) was added, and the solvents ($MeOH/CH_2Cl_2$) were evaporated in vacuo. The residue was diluted with water (10 mL/mmol) and extracted with CH_2Cl_2 (3 times, 5 mL/mmol). The combined organic extracts were dried over Na_2SO_4 and filtered to give, after evaporation of the solvent, a crude product that was purified by column chromatography on silica gel using the appropriate mixture of solvents. Usually piperazin-2,3-diones **2** precipitate in CH_2Cl_2 and Et_2O; therefore, they could be purified by washing repeatedly the crude solid product with 90% Et_2O−hexane. Method B: to a solution of diamino alcohol **1** at room temperature in anhydrous CH_2Cl_2 (6 mL/mmol), 6 equiv of diethyl oxalate was added. The mixture was stirred until the formation of morpholinedione **3** and piperazin-2,3-dione **2** was observed by TLC. Then, the solvent was removed under reduced pressure, and piperazin-2,3-dione was isolated by washing thoroughly the crude product with CH_2Cl_2 or by column chromatography using the appropriate mixture of solvents. The mother liquors or the chromatographic fraction containing the morpholinedione **3** was treated with 2 equiv of NaOMe (from a 0.25 M solution in MeOH) until no starting material was detected by TLC. Isolation and purification of piperazin-2,3-diones **2** was carried out as described in method A. Compound **3a** was the only morpholinedione fully characterized.

(+)-(5*R*,6*S*)-1-Benzyl-6-hydroxymethyl-5-(2-phenylethyl)piperazin-2,3-dione, 2b. From **1b** (267 mg, 0.603 mmol) and diethyl oxalate (0.47 mL, 3.618 mmol), following general procedure B (40 h), a mixture of diketopiperazine **2b** and morpholinedione **3b** was obtained. Purification by chromatography afforded 96 mg (0.284 mmol, 47%) of **2b** as a white foam and 140 mg (0.282 mmol, 47%) of **3b** as a white foam. Subsequently, a solution of NaOMe in MeOH (0.24 M, 0.60 mL, 0.14 mmol) was added to a solution of **3b** in methanol (10 mL/mmol) following the general procedure (1 h 30 min). After purification by chromatography (50% $Et_2O-CH_2Cl_2$, then 2−10% $MeOH-CH_2Cl_2$), 64 mg of **2b** was obtained (0.189 mmol, 31%) as a white foam that was recrystallized from Et_2O. The global yield was 78%. Data for **2b**: mp: 150−152 °C (Et_2O). $R_f = 0.23$ (10% $MeOH-CH_2Cl_2$). $[\alpha]_D^{20}$ +177.8 ($c = 1.11$). ^{1}H NMR (300 MHz) δ 1.41 (m, 1 H), 1.64 (m, 1 H), 2.07 (m, 1 H), 2.24 (m, 1 H), 3.37 (ap t, 1 H, $J = 5.6$ Hz), 3.56 (m, 1 H), 3.77 (AB system, 2 H), 3.94 (d, 1 H, $J = 14.2$ Hz), 5.34 (d, 1 H, $J = 14.3$ Hz), 6.81 (d, 2 H, $J = 6.5$ Hz), 7.10 (m, 3 H), 7.29 (m, 5 H), 8.29 (d, 1 H, $J = 5.2$ Hz). ^{13}C NMR (50 MHz) δ 31.4, 35.9, 49.2, 49.8, 57.1, 61.1, 125.8 (2 C), 128.1 (2 C), 128.2 (2 C), 128.5 (2 C), 128.9 (2 C), 135.6, 140.3, 157.9, 158.4. IR (KBr): $\nu = 3435$, 2920, 2855, 1714, 1666, 1453, 700 cm^{-1}. MS (ES): 699 $[2M + Na]^+$, 361 $[M + Na]^+$, 339 $[M + 1]^+$ (100%). Anal. Calcd for $C_{20}H_{22}N_2O_3S$ (338.2): C, 70.97; H, 6.56; N, 8.28; found: C, 70.85; H, 6.80; N, 8.22. Partial data for **3b**: $R_f = 0.40$ (5% $MeOH-CH_2Cl_2$). ^{1}H NMR (200 MHz) δ 1.44 (m, 1 H), 1.65 (m, 1 H), 2.16 (t, 2 H, $J = 7.7$ Hz), 2.41 (s, 3 H), 3.38 (m, 1 H), 3.53 (m, 2 H), 3.82 (d, 1 H, $J = 14.1$ Hz), 3.97 (m, 2 H), 5.28 (d, 1 H, $J = 14.1$ Hz), 6.86 (dd, 2 H, $J = 7.9$, 2.0 Hz), 7.10−7.34 (m, 10 H), 7.50 (d, 2 H, $J = 8.2$ Hz).

General Procedure of Reduction with BH_3·SMe_2. To a solution of diketopiperazine in dry THF (10 mL/mmol) under reflux was added dropwise 9 equiv of a 2 M solution of BH_3·SMe_2 in THF. The mixture was refluxed for 7 h, the solvent was evaporated under reduced pressure, and 4 equiv of a 0.2−0.4 M HCl solution was added. The mixture was stirred for 30 min at 100 °C, and then it was cooled at 0 °C, and 6 equiv of a 0.2−0.4 M solution of NaOH was added and was stirred for 1 h 30 min. The aqueous mixture was saturated with solid K_2CO_3 and extracted with CH_2Cl_2 (3−4 times, 5 mL/mmol), and the combined organic extracts were dried over Na_2SO_4 and filtered to give, after evaporation of the solvent, a crude product that was purified by chromatography on silica gel using the appropriate mixture of solvents.

(−)-(2*S*,3*R*)-1-Benzyl-2-hydroxymethyl-3-*i*-propylpiperazine, 4c. From **2c** (110 mg, 0.398 mmol) and BH_3·SMe_2 (2 M, 1.79 mL, 3.582 mmol) following the general procedure (7 h), piperazine **4c** was obtained. Purification by chromatography (0−30% MeOH-Et_2O) and a second chromatography (30% $MeOH-CH_2Cl_2$) afforded (60 mg, 0.242 mmol, 61%) **4c** as a colorless oil. Data for **4c**: $R_f = 0.10$ (20% $MeOH-Et_2O$). $[\alpha]_D^{20}$ −19.6 ($c = 0.91$). ^{1}H NMR (400 MHz) δ 0.87 (d, 3 H, $J = 1.8$ Hz), 0.89 (d, 3 H, $J = 1.8$ Hz), 2.39 (m, 2 H), 2.48 (ap quint, 1 H, $J = 2.6$ Hz), 2.61 (dd, 1 H, $J = 6.7$, 5.1 Hz), 2.68 (dd, 1 H, $J = 7.9$, 5.8 Hz), 2.98 (ap q, 2 H, $J = 7.9$ Hz), 3.04 (br s, 2 H), 3.48 (d, 1 H, $J = 13.3$ Hz), 3.66 (dd, 1 H, $J = 11.5$, 2.6 Hz), 3.91 (d, 1 H, $J = 13.4$ Hz), 4.15 (dd, 1 H, $J = 11.6$, 2.7 Hz), 7.23 (m, 1 H), 7.29 (m, 4 H). ^{13}C NMR (50 MHz) δ 17.0, 20.6, 25.9, 41.8, 49.9, 58.6, 58.8, 61.0, 61.5, 127.0, 128.3 (2 C), 128.7 (2 C), 138.9. IR (film): $\nu = 3325$, 3028, 2955, 2869, 1602, 1452, 1363, 1071, 742, 698 cm^{-1}. MS (ES): 249 $[M + 1]^+$ (100%). Anal. Calcd for $C_{15}H_{24}N_2O$ (248.4): C, 72.54; H, 9.74; N, 11.28; O, 6.44; found: C, 72.29; H, 9.55; N, 11.32.

(−)-(2*S*,3*R*)-1-Benzyl-3-*p*-fluorophenyl-2-hydroxymethylpiperazine, 4e. Piperazine **4e** was obtained from **2e** (65 mg, 0.198 mmol) and BH_3·SMe_2 (2 M, 0.90 mL, 1.782 mmol) following the general procedure (7 h). Purification by chromatography (0−20% MeOH-Et_2O) followed by crystallization as hydrochloride [obtained by bubbling HCl (g) through an ethereal solution of **4e**] rendered pure **4e** as a salt. Finally, standard basic treatment produced **4e**, 50 mg (0.166 mmol, 84%), as a free base. Data for **4e**: $R_f = 0.30$ (20% $MeOH-Et_2O$). $[\alpha]_D^{20}$ −50.5 ($c = 0.40$). ^{1}H NMR (300 MHz) δ 2.01 (br s, 2 H), 2.37−2.45 (m, 2 H), 2.84−2.90 (m, 3 H), 3.19 (d, 1 H, $J = 11.7$ Hz), 3.21 (d, 1 H, $J = 13.4$ Hz), 3.81 (dd, 1 H, $J = 11.7$, 3.2 Hz), 3.93 (d, 1 H, $J = 9.5$ Hz), 4.18 (d, 1 H, $J = 13.2$ Hz), 6.99 (ap t, 2 H, $J = 8.7$ Hz), 7.30 (m, 5 H), 7.37−7.42 (m, 2 H). ^{13}C NMR (50 MHz) δ 45.8, 52.0, 58.0 (2 C), 61.0, 66.9, 115.3 (d, 2 C, $J_oC-F = 21.0$ Hz), 127.2, 128.4 (2 C), 128.9 (2 C), 130.0 (d, 2 C, $J_mC-F = 8.0$ Hz), 137.8, 137.9 (d, 1 C, $J_pC-F = 3.4$ Hz), 162.3 (d, 1 C, $J_{ipso}C-F = 246.1$ Hz). IR (film): $\nu = 3308$, 3028, 2942, 2832, 1604, 1510, 1451, 1223, 1067, 836, 740, 700 cm^{-1}. MS (ES): 301 $[M + 1]^+$ (100%).

General Procedure for Synthesis of Chloroacetamides. To a cold (0 °C) suspension of **6** or **10** in EtOAc (10 mL/mmol) and a saturated solution of $NaHCO_3$ (10 mL/mmol), 1.2−2 equiv of

freshly distilled chloroacetyl chloride was added. The mixture was stirred and allowed to warm to room temperature until disappearance of the starting material (TLC). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL/mmol). The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, and filtered to give, after evaporation of the solvents, a crude product that was purified by chromatography on silica gel to afford chloroacetamide **7** or **11**.

(+)-*N*-Benzyl-*N*-[(1*S*,2*R*,*S*$_S$)-1-(*t*-butyldimethylsilyloxymethyl)-4-phenyl-2-(*p*-tolylsulfinylamino)but-1-yl] 2-chloroacetamide, 7b. 7b (76 mg, 0.831 mmol, 83%) was obtained as a white solid from **6b** (80 mg, 0.149 mmol) following the general procedure (24 h) and after purification by column chromatography (20−40% Et_2O−hexane) and crystallization (CH_2Cl_2-hexane). Data for **7b**: R_f = 0.18 (60% Et_2O−hexane). mp: 110−112 °C. $[\alpha]_D^{20}$ +356.3 (c = 1.00). ^{1}H NMR (400 MHz) δ −0.44 (s, 3 H), −0.20 (s, 3 H), 0.71 (s, 9 H), 1.55 (m, 2 H), 2.35−2.41 (m, 1 H), 2.38 (s, 3 H), 2.46−2.59 (m, 1 H), 3.71−3.87 (m, 4 H), 4.02 (d, 1 H, J = 13.7 Hz), 4.27 (d, 1 H, J = 13.9 Hz), 4.60 (br s, 1 H), 4.85 (d, 1 H, J = 17.0 Hz), 4.96 (d, 1 H, J = 18.1 Hz), 7.02−7.08 (m, 4 H), 7.14−7.34 (m, 8 H), 7.60 (d, 2 H, J = 8.1 Hz). ^{13}C NMR (75 MHz) δ −6.4 (2 C), 18.0, 21.4, 25.6 (3 C), 30.8, 35.0, 42.9, 49.4, 52.2, 58.7, 61.3, 125.6 (2 C), 125.8 (2 C), 127.4, 128.3 (3 C), 128.4 (2 C), 128.9 (2 C), 129.5 (2 C), 137.5, 141.5, 141.6, 141.9, 169.9. IR (KBr): ν = 3435, 3028, 2954, 2928, 2856, 1634, 1495, 1452, 1257, 1092, 1070, 986, 836, 813, 778, 727, 699 cm^{-1}. MS (ES): 1249 [2M + Na]$^+$, 615 [M + 3]$^+$, 613 [M + 1]$^+$ (100%), 481 [M −(OTBDMS)]$^+$. Anal. Calcd for $C_{33}H_{45}ClN_2O_3SSi$ (613.3): C, 64.62; H, 7.40; N, 4.57; found: C, 64.97; H, 7.77; N, 4.36.

General Procedure for Synthesis of Ketopiperazines. A solution of chloroacetamide **7** or **11** in DMF (10 mL/mmol) and 1.8 equiv of solid Cs_2CO_3 were stirred at 65 °C until the starting material disappearance was monitored by TLC. The mixture was cooled to room temperature and was diluted with CH_2Cl_2 (10 mL/mmol) and H_2O (10 mL/mmol). The layers were separated, and the organic phase was washed with cold water (3 × 10 mL/mmol) and a saturated solution of $NaHCO_3$ (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by gradient column chromatography.

(+)-(5*R*,6*S*,*S*$_S$)-1-Benzyl-6-[(*t*-butyldimethylsilyloxy)methyl]-5-(*i*-propyl)-4-(*p*-tolylsulfinyl)piperazin-2-one, 8c. 8c (38 mg, 0.074 mmol, 77%) was obtained from **7c** (53 mg, 0.096 mmol) as a white foam following the general procedure (2 h 30 min) and after chromatography on silica gel (30−40% Et_2O−hexane). Data for **8c**: R_f = 0.21 (80% Et_2O−hexane). $[\alpha]_D^{20}$ +6.2 (c = 1.40). ^{1}H NMR (300 MHz) δ 0.06 (s, 3 H), 0.10 (s, 3 H), 0.36 (d, 3 H, J = 6.6 Hz), 0.91 (s, 9 H), 1.09 (d, 3 H, J = 6.6 Hz), 1.55−1.68 (m, 1 H), 2.39 (s, 3 H), 3.31 (d, 1 H, J = 18.1 Hz), 3.36 (ddd, 1 H, J = 8.6, 5.3, 1.3 Hz), 3.43 (dd, 1 H, J = 10.8, 1.3 Hz), 3.49 (ap t, 1 H, J = 8.6 Hz), 3.63 (dd, 1 H, J = 10.0, 5.3 Hz), 3.71 (d, 1 H, J = 18.3 Hz), 3.83 (d, 1 H, J = 14.4 Hz), 5.25 (d, 1 H, J = 14.4 Hz), 7.22−7.31 (m, 7 H), 7.54 (d, 2 H, J = 8.3 Hz). DNOE between CH_3 (1.09)/CH_3 (0.36): 5.8%; CH_3 (1.09)/CH (*i*Pr): 11.0%; CH_3 (1.09)/H-5: 4.6%; CH_3 (1.09)/H-3 (3.71): 3.0%; CH (*i*Pr)/H-3 (3.71): 3%; CH (*i*Pr)/ H-5: 1.2%; CH (*i*Pr)/H-6: 1.2. ^{13}C NMR (75 MHz) δ −5.3 (2 C), 18.1, 19.7, 21.0, 21.3, 25.8 (3 C), 26.8, 40.6, 48.7, 57.5, 62.3, 63.6, 125.4 (2 C), 128.1, 128.8 (2 C), 129.1 (2 C), 129.6 (2 C), 136.6, 139.9, 141.8, 165.3. IR (film): ν = 3028, 2954, 2927, 2855, 1658, 1470, 1457, 1374, 1254, 1152, 1089, 955, 837, 777, 701 cm^{-1}. MS (ES): 537 [M + Na]$^+$, 515 [M + 1]$^+$ (100%), 375 [M − (*p*TolSO)]$^+$. Anal. Calcd for $C_{28}H_{42}N_2O_3SSi$ (514.8): C, 65.33; H, 8.22; N, 5.44; S, 6.23; Si, 5.46; found: C, 65.45; H, 8.07; N, 5.28.

General Procedure for Synthesis of Imino Ketopiperazines 9. A solution of **8** in THF (5 mL/mmol) was added dropwise to a cold (0 °C) suspension of 4 equiv of NaH (60% in mineral oil) in anhydrous THF (5 mL/mmol of NaH), and the reaction mixture was stirred at room temperature (1 h) and at reflux (1 h) until the disappearance of the starting material was observed by TLC. The mixture was cooled to room temperature and water (5 mL/mmol of NaH), and CH_2Cl_2 (5 mL/mmol) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL/mmol). The combined organic extracts were washed with a saturated solution of NaCl (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel.

(+)-(5*R*,6*S*)-1-Benzyl-6-(*t*-butyldimethylsilyloxymethyl)-5-(2-phenylethyl)-5,6-dihydro-1*H*-pyrazin-2-one, 9b. 9b (27 mg, 0.062 mmol, 87%) was obtained as a yellow oil from **8b** (41 mg, 0.071 mmol) according to the general procedure (2 h 30 min) and after purification by column chromatography (20−40% Et_2O−hexane). Data for **9b**: R_f = 0.28 (70% Et_2O−hexane). $[\alpha]_D^{20}$ +243.5 (c = 2.20). ^{1}H NMR (300 MHz) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.85 (s, 9 H), 1.18−1.32 (m, 1 H), 1.64−1.76 (m, 1 H), 2.28 (t, 2 H, J = 7.8 Hz), 3.32 (ap t, 1 H, J = 6.3 Hz), 3.52 (dd, 1 H, J = 10.2, 7.0 Hz), 3.61 (dd, 1 H, J = 10.3, 5.9 Hz), 3.91 (ap t, 1 H, J = 7.1 Hz), 3.94 (d, 1 H, J = 14.2 Hz), 5.34 (d, 1 H, J = 14.2 Hz), 6.90 (d, 2 H, J = 8.1 Hz), 7.11−7.23 (m, 3 H), 7.29−7.36 (m, 5 H), 7.74 (d, 1 H, J = 1.2 Hz). ^{13}C NMR (75 MHz) δ −5.6 (2 C), 18.1, 25.8 (3 C), 31.8, 34.3, 48.4, 55.8, 56.9, 62.9, 126.0, 128.1, 128.3 (4 C), 128.9 (2 C), 129.1 (2 C), 136.2, 140.7, 154.9, 155.3. IR (film): ν = 3086, 3063, 3028, 2951, 2929, 2857, 1951, 1674, 1627, 1604, 1585, 1496, 1470, 1454, 1390, 1361, 1313, 1257, 1155, 1119, 1030, 1006, 938, 924, 838, 814, 778, 748, 699, 667 cm^{-1}. MS (ES): 438 [M + 2]$^+$, 437 [M + 1]$^+$ (100%). Anal. Calcd for $C_{26}H_{36}N_2O_2Si$ (436.7): C, 71.51; H, 8.31; N, 6.42; O, 7.33; Si, 6.43; found: C, 71.57; H, 8.62; N, 6.53.

(+)-(5*R*,6*S*)-1-Benzyl-6-(*t*-butyldimethylsilyloxymethyl)-5-(*i*-propyl)-5,6-dihydro-1*H*-pyrazin-2-one, 9c. **9c** (20 mg, 0.053 mmol, 84%) was obtained as a colorless oil from **8c** (33 mg, 0.064 mmol) according to the general procedure (3 h 45 min) and after purification by column chromatography (20−30% Et_2O−hexane). Data for **9c**: R_f = 0.22 (60% Et_2O−hexane). $[\alpha]_D^{20}$ +189.5 (c = 0.60). ^{1}H NMR (300 MHz) δ 0.00−0.09 (m, 6 H), 0.41 (d, 3 H, J = 6.8 Hz), 0.85 (d, 3 H, J = 6.8 Hz), 0.86 (s, 9 H), 1.38−1.48 (m, 1 H), 3.38 (ap t, 1 H, J = 6.1 Hz), 3.50 (dd, 1 H, J = 10.1, 6.7 Hz), 3.56 (dd, 1 H, J = 10.3, 5.6 Hz), 3.62 (ap d, 1 H, J = 7.8 Hz), 4.01 (d, 1 H, J = 14.4 Hz), 5.21 (d, 1 H, J = 14.2 Hz), 7.30 (m, 5 H), 7.79 (d, 1 H, J = 1.5 Hz). ^{13}C NMR (75 MHz) δ −5.6, −5.5, 18.1, 19.0, 19.2, 25.8 (3 C), 32.0, 48.5, 54.4, 63.2, 63.7, 128.1 (2 C), 128.8, 129.3 (2 C), 136.1, 155.0, 155.1. IR (film): ν = 3028, 2949, 2929, 2855, 1676, 1632, 1470, 1257, 1103, 837, 778 cm^{-1}. MS (ES): 397 [M + Na]$^+$, 375 [M + 1]$^+$ (100%). Anal. Calcd for $C_{21}H_{34}N_2O_2Si$ (374.6): C, 67.33; H, 9.15; N, 7.48; O, 8.54; Si, 7.50; found: C, 67.55; H, 9.02; N, 7.23.

Procedure for Addition of Allyltributylstannane and $TiCl_4$. A solution of **9c** (28 mg, 0.075 mmol) in CH_2Cl_2 (5 mL/mmol) and 1 equiv of $TiCl_4$ (14 mg, 8 μL, 0.075 mmol) was stirred at −78 °C for 3 h, and then 2 equiv of allyltributylstannane (50 mg, 46 μL, 0.150 mmol) was added. After 1 h, the mixture was warmed to room temperature and monitored by TLC (48 h). Then, the mixture was hydrolyzed with 2 N aqueous NaOH (10 mL/mmol). The solvent was evaporated in vacuo, and the residue was extracted with CH_2Cl_2 (4 × 10 mL/mmol). The organic extracts were washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **13d** and **14d** as a 43:57 mixture. The combined yield of the mixture after purification by column chromatography (5−10% EtOAc−hexane) was 77% (24 mg, 0.058 mmol). Small amounts of **13d** and **14d** were separated after careful chromatography on silica gel.

Procedure for Zinc-Mediated Barbier Allylation.[23d] To a suspension of Zn powder (2 equiv), (12 mg, 0.176 mmol) in THF (1.5 mL/mmol) at 0 °C, was added $CeCl_3 \cdot 7H_2O$ (0.1 equiv, 3 mg, 0.009 mmol) and a solution of **9c** (1 equiv) and 1.5 equiv of allyl bromide in THF (3.0 mL/mmol **9c**). The mixture was stirred from 0 °C to room temperature monitored by TLC (23−24 h) and then was quenched with NH_4Cl (6 mL/mmol). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL/

mmol). The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the final products (**14**) after purification by column chromatography. The same procedure was applied in the absence of the $CeCl_3 \cdot 7H_2O$ with complete recovery of the starting material.

(+)-(3*R*,5*R*,6*S*)-3-Allyl-1-benzyl-6-[(*t*-butyldimethylsilyloxy)-methyl]-5-(*i*-propyl)piperazin-2-one, 14d. From **9c** (33 mg, 0.088 mmol) and 1.5 equiv of allyl bromide (11 μL, 0.132 mmol) was obtained after chromatography (5−10% EtOAc−hexane) **14d** (32 mg, 0.077 mmol, 87%) as a colorless oil. Data for **14d**: $R_f = 0.34$ (20% EtOAc−hexane). $[\alpha]_D^{20}$ +77.0 ($c = 1.33$). ^{1}H NMR (400 MHz) δ 0.04 (s, 6 H), 0.34 (d, 3 H, $J = 6.6$ Hz), 0.85 (d, 3 H, $J = 6.6$ Hz), 0.87 (s, 9 H), 1.58 (m, 1 H), 1.73 (br s, 1 H), 2.40 (ap d, 1 H, $J = 9.3$ Hz), 2.45 (ap t, 1 H, $J = 7.7$ Hz), 2.68 (m, 1 H), 3.24 (ddd, 1 H, $J = 7.7$, 4.8, 1.1 Hz), 3.49 (dd, 1 H, $J = 8.1$, 3.3 Hz), 3.73 (dd, 1 H, $J = 9.9$, 4.8 Hz), 3.81 (dd, 1 H, $J = 9.9$, 7.7 Hz), 3.82 (d, 1 H, $J = 14.3$ Hz), 5.11 (dd, 1 H, $J = 10.1$, 1.1 Hz), 5.16 (dd, 1 H, $J = 17.0$, 1.4 Hz), 5.44 (d, 1 H, $J = 14.3$ Hz), 5.77 (ddt, 1 H, $J = 17.0$, 10.1, 7.3 Hz), 7.25−7.29 (m, 5 H). DNOE between H-3/H-2 allyl: 1.4%; H-3/1 H CH_2 allyl: 3.5%; H-3/1 H CH_2 allyl: 2.0%; H-3/CH *i*Pr: 5.9%; CH *i*Pr/H-3: 1.8%; CH *i*Pr/H-6: 2.4%; H-6/1 H CH_2Ph: 1%; H-6/1 H CH_2Ph: 5%; H-6/1 H CH_2O: 4%. ^{13}C NMR (75 MHz) δ −5.4, −5.3, 18.2, 19.2, 19.5, 25.4, 25.9, 37.7, 48.7, 53.1, 56.8, 57.2, 63.8, 118.2, 128.5 (2 C), 128.8 (2 C), 134.9, 137.6, 170.3. IR (film): $\nu = 3300$, 3065, 2955, 2847, 1647, 1471, 1439, 1385, 1360, 1253, 1099, 917, 837, 777, 701 cm^{-1}. MS (ES): 417 $[M + 1]^+$ (100%). Anal. Calcd for $C_{24}H_{40}N_2O_2Si$ (416.3): C, 69.18; H, 9.68; N, 6.72; S, 6.74; found: C, 68.97; H, 9.98; N, 6.49; S, 6.63.

(−)-(3*S*,5*R*,6*S*)-3-Allyl-1-benzyl-6-[(*t*-butyldimethylsilyloxy)-methyl]-5-(*i*-propyl)piperazin-2-one, 13d. Data for **13d**: $R_f = 0.32$ (20% EtOAc−hexane). $[\alpha]_D^{20}$ −11.8 ($c = 0.11$). ^{1}H NMR (400 MHz) δ 0.00−0.05 (m, 6 H), 0.74 (d, 6 H, $J = 6.6$ Hz), 0.87 (s, 9 H), 1.55 (br s, 1 H), 1.60 (m, 1 H), 2.43 (m, 1 H), 2.78 (m, 1 H), 2.81 (t, 1 H, $J = 5.2$ Hz), 3.16 (dt, 1 H, $J = 6.0$, 3.8 Hz), 3.31 (dd, 1 H, $J = 8.3$, 3.9 Hz), 3.45 (dd, 1 H, $J = 10.7$, 3.6 Hz), 3.67 (dd, 1 H, $J = 10.6$, 4.0 Hz), 4.00 (d, 1 H, $J = 14.8$ Hz), 5.10 (ap d, 1 H, $J = 10.2$ Hz), 5.16 (ap d, 1 H, $J = 17.0$ Hz), 5.33 (d, 1 H, $J = 15.0$ Hz), 5.87 (ddt, 1 H, $J = 17.0$, 10.2, 6.9 Hz), 7.21−7.31 (m, 5 H). DNOE between H-3/1 H CH_2 allyl: 4.8%; H-3/1 H CH_2 allyl: 1.8%; H-6/CH *i*Pr: 1.5%; H-6/1 H CH_2O: 1.9%; H-6/CH_3: 3.9%; H-6/1 H CH_2Ph: 0.5%; CH *i*Pr/H-6: 0.7%; CH *i*Pr/H-5: 0.8%; CH *i*Pr/CH_3: 4.0%. ^{13}C NMR (100 MHz) δ −5.6, −5.5, 17.4, 18.2, 19.3, 25.8 (3 C), 31.2, 36.0, 47.4, 56.5, 58.4, 59.0, 63.3, 117.7, 127.3, 128.2 (2 C), 128.5 (2 C), 135.6, 137.5, 173.2. IR (film): $\nu = 3375$, 2925, 2855, 1736, 1658, 1462, 1374, 1258, 1107, 836, 778, 700 cm^{-1}. MS (ES): 417 $[M + 1]^+$ (100%). Anal. Calcd for $C_{24}H_{40}N_2O_2Si$ (416.3): C, 69.18; H, 9.68; N, 6.72; S, 6.74; found: C, 69.09; H, 9.79; N, 6.82; S, 6.54.

Acknowledgment. This research was supported by CAM (GR/SAL/0823/2004) and DGICYT (BQU2003-02921). We thank JANSSEN-CILAG for generous additional support and MEC and CAM for a doctoral fellowship to M.T. and A.F.

Supporting Information Available: Experimental procedures and analytical and spectral characterization data for **1f**, **6a**−**e**, **2f**, **3a**−**c**, **5**, **4a**−**e**, **7a**−**e**, **8a**−**e**, **9a**−**d**, **11a**−**c**, **12**, **13a**−**d**, and **14a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052077H