JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# The Aza-Wharton Reaction: Syntheses of Cyclic Allylic Amines and Vicinal Hydroxyamines from the Respective Acylaziridines

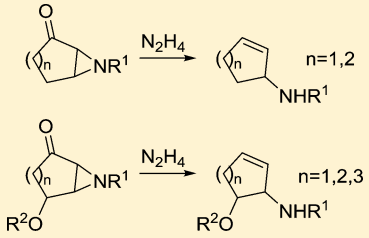
Saúl Silva,[†] Paula Rodrigues,[†] Isabel Bento,[†] and Christopher D. Maycock*[,†,‡]

[†]Instituto de Tecnologia Química e Biológica: António Xavier, Universidade Nova de Lisboa, Av. da República, 2780-157 Oeiras, Portugal

[‡]Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

Supporting Information

**ABSTRACT:** The Wharton reaction, initially described for acyl epoxides, has been studied using the structurally similar aziridines. By this reaction, a range of cyclic allylic amines and vicinal amino alcohols have been prepared stereoselectively and, in some cases, enantiomerically pure.

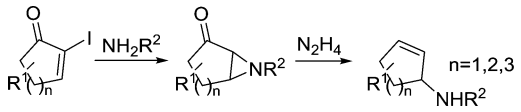



## INTRODUCTION

The original Wharton reaction[1] comprises a reductive rearrangement of $\alpha,\beta$-epoxyketones into allylic alcohols using hydrazine, and it has been used in several complex syntheses.[2] An obvious extension of this process is the analogous reductive rearrangement of cyclic acylaziridines (2-oxoazabicyclo[*x*.1.0]-alkanes) to produce allylic amines, important ligands and building blocks for organic chemistry.[3] Little work on this subject has been reported, one of the most notable being by Yudin,[4] who studied the reaction in linear benzoyl aziridines, but the formation of pyrazoles as secondary products was unavoidable. Another important work was carried out by Jørgensen,[5] who studied the reaction with a series of cyclic *N*-tosylaziridines exclusively.

With cyclic acylaziridines[6] containing a wide range of N-substituents in hand, the goal of the work reported here was to study the Wharton reaction (Scheme 1) on these substrates, in this way demonstrating the scope of this reaction for the preparation of cyclic allylic amines.

**Scheme 1. Aziridination and the Wharton Reaction**




## RESULTS AND DISCUSSION

Several acylaziridines (Scheme 1) were subjected to the Wharton conditions in order to study the effect of the groups attached to the nitrogen atom. Two methods were used to carry out the reaction: the classical[1] acidic conditions and the more recently studied[7] basic conditions. Although the reaction was much faster under acidic conditions, the yields in some cases were greater under basic ones. The results are summarized in Table 1, and in each case, several conditions were applied. The full range of conditions used is reported in the Supporting Information.

With *para*-substituted *N*-benzylaziridines it was possible to see the effect of having a remote electron-withdrawing (**1a**) or electron-donating (**1b**) group in the aromatic ring. The free amine **2a** was easily isolated in good yield, but the electron-rich amine **2b** was isolated as its acetamide since it was unstable and darkened rapidly in the air. The facile air oxidation of electron-rich benzylamines compared with electron-poor ones has already been described.[8] The acetamides of these products were easier to purify and manipulate, but this made the NMR characterization more difficult because of the presence of signals due to amide rotamers. In the case of benzylaziridines, there was no difference in yield under basic or acidic conditions. For the preparation of **2b**, basic conditions were preferred since they permitted the subsequent acetylation of the amino group in the same flask.

*N*-Benzyl-, *N*-aryl-, *N*-allyl-, and *N*-alkylaziridines (**1a–f**)[9] (Scheme 1, $n = 2$) were tested, and the *N*-alkylaziridines, for example **1d** and **1e**, were the ones that gave the best results. Acylaziridines with powerful electron-withdrawing groups (**1g** and **1h**) were found to be some of the worst substrates. Nevertheless the versatility of the Wharton reaction was demonstrated. It was not possible to prepare aniline **2f** under the acidic conditions, since the only product isolated was methoxyaniline, formed apparently by elimination.

Substrates having a five-membered ring (**1j** and **1k**) (Scheme 1, $n = 1$) were also studied and afforded good yields of the corresponding allylic amines. Interestingly it was not possible to isolate acetamide **2j** because the amide group was eliminated, probably through a pericyclic mechanism (Scheme 2), and the

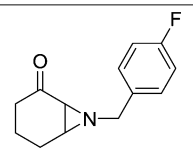
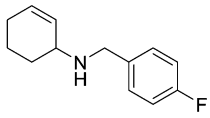
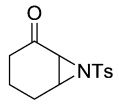
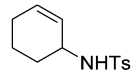
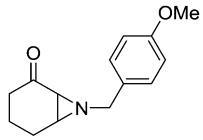
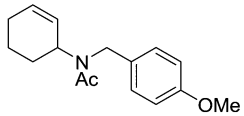
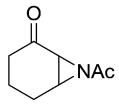
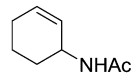
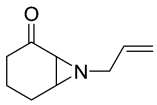
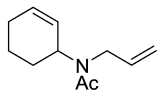
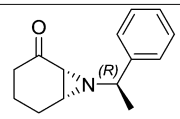
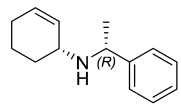
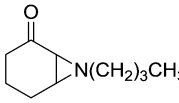
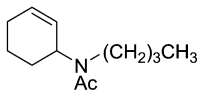
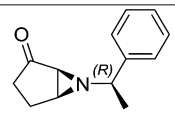
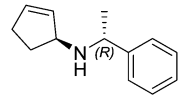
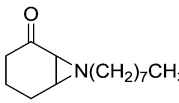
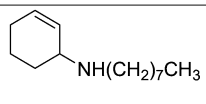
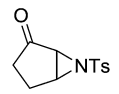
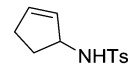
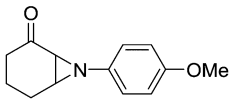
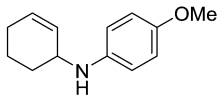
**Received:** December 29, 2014
**Published:** February 25, 2015





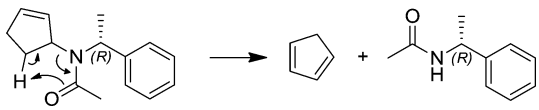
DOI: 10.1021/jo5029387
*J. Org. Chem.* 2015, 80, 3067−3074

**Table 1. Synthesis of Allylic Amines by the Wharton Reaction[10]**

| Substrate | Product | Yield | Substrate | Product | Yield |
|---|---|---|---|---|---|
|  (±)-1a |  (±)-2a | 83%[a] |  (±)-1g |  (±)-2g | 49%[a] |
|  (±)-1b |  (±)-2b | 60%[b] |  (±)-1h |  (±)-2h | 40%[a] |
|  (±)-1c |  (±)-2c | 84%[b] |  (+)-(1*R*,6*R*)-1i |  (+)-2i | 58%[a] |
|  (±)-1d |  (±)-2d | 94%[b] |  (-)-(1*S*,5*S*)-1j |  (+)-2j | 44%[c] |
|  (±)-1e |  (±)-2e | 93%[c] |  (±)-1k |  (±)-2k | 65%[a] |
|  (±)-1f |  (±)-2f | 54%[c] | | | |

[a]$N_2H_4·H_2O$, AcOH, MeOH. [b](1) $N_2H_4$, $Et_3N$, MeCN; (2) $Ac_2O$, $Et_3N$. [c]$N_2H_4$, $Et_3N$, MeCN.

**Scheme 2. Possible Mechanism for Amide Elimination from Acetylated 2j**



only product obtained was *N*-(1-phenylethyl)acetamide. Toluenesulfonamide **2k** was isolated without elimination of tosylamide, further consolidating the proposed mechanism for the elimination of acetamide from acetylated **2j**.

The enantiomerically pure amines **2i** and **2j** were prepared from the respective enantiopure aziridines (**1i,j**). (1*R*,6*R*)-**1i** and (1*S*,5*S*)-**1j** were obtained by separation of the two diastereoisomers formed by aziridination using enantiomerically pure (+)-*R*-*α*-methylbenzylamine. Their absolute configurations were determined by X-ray diffraction, and the structures obtained are reported in the Supporting Information.

Optically active tosylamide **2g** was previously prepared by Jørgensen using an aza-Wharton reaction[5] on **1g** formed by enantioselective organocatalytic aziridination of the corresponding cyclohexenone. The preparation of **2i** and **2j** represents a good alternative for the synthesis of optically pure allylic amines. Enantiomerically pure *α*-alkylbenzylamines are readily available, making the process cheap and easy.

*α*-Amino alcohols are important synthetic targets since they are present in diverse products of interest such as natural products and synthetic drugs.[11] They are also important for catalysis, acting as ligands and auxiliaries in enantioselective reactions.[12]

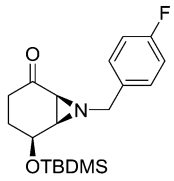
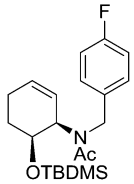
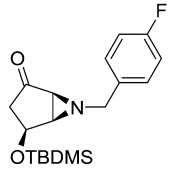
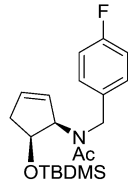
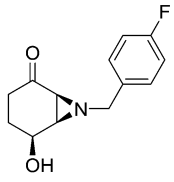
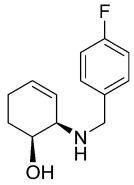
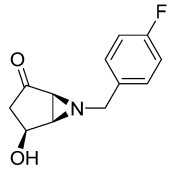
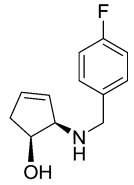
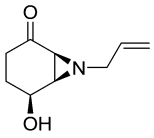
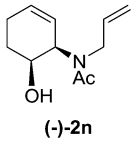
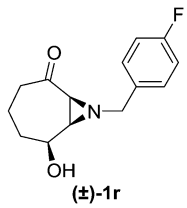
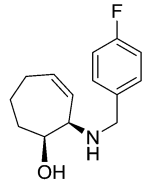
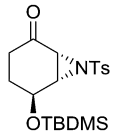
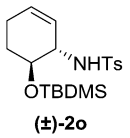
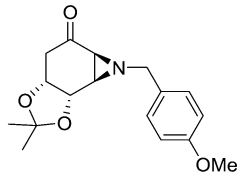
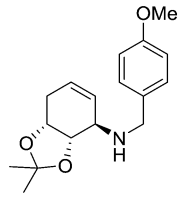
The major products obtained by aziridination of protected or free 4-hydroxy-2-iodocyclohex-2-enone using primary amines were the *cis*-hydroxyazidirines **1l−n**. On the other hand, when the aziridination was carried out with tosylamide, the major aziridination product was the *trans* isomer **1o**. Applying the Wharton conditions to aziridines **1l−n** produced *cis*-amino alcohols **2l−n**,[13] and similarly, *trans*-amino alcohol **2o** could be prepared in good yield from aziridine **1o** (Table 2).

Cyclopentene *cis*-amino alcohols **2p** and **2q** were also prepared, and it was possible to isolate acetamide **2p** without



DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067−3074

**Table 2. Synthesis of Amino Alcohols by the Wharton Reaction**

| Substrate | Product | Yield | Substrate | Product | Yield |
|---|---|---|---|---|---|
|  (±)-1l |  (±)-2l | 46%[a] |  (±)-1p |  (±)-2p | 29%[a] |
|  (±)-1m |  (±)-2m | 61%[b] |  (±)-1q |  (±)-2q | 41%[b] |
|  (-)-1n |  (-)-2n | 84%[a] |  (±)-1r |  (±)-2r | 77%[b] |
|  (±)-1o |  (±)-2o | 67%[b] |  (-)-1s |  (+)-2s | 68%[b] |

[a](1) $N_2H_4$, $Et_3N$, MeCN; (2) $Ac_2O$, $Et_3N$. [b]$N_2H_4{\cdot}H_2O$, AcOH, MeOH.

elimination of the amide group. This observation also supports the pericyclic mechanism for the unsubstituted cyclopentane (Scheme 2), since the substitution at position 4 of the ring is *cis* to the acetamido group. The *cis*-substituted cycloheptene **2r** was also formed in good yield from alcohol **1r.** The protected aminodiol **2s** was produced enantiomerically pure in a reasonable yield from aziridine **1s**.[14]

## CONCLUSION

The aza-Wharton reaction using a range of azabicyclic compounds has been studied and shown to be a viable method for the production of cyclic allylic amines. *N*-Alkylated azabicyclo[4.1.0] compounds were found to be the best substrates for this reaction. For the azabicyclo[3.1.0] compounds, the *N*-tosyl substrate was found to be the best. The choice between acidic or basic conditions depended upon the N-substituent, and clear trends were not observed. The potential for the rapid stereoselective production of cyclic amino alcohols by this method is noteworthy. Molecules with this type of functionality have the potential for use as chelating agents for metal-catalyzed reactions, as organocatalysts, and as intermediates for the synthesis of compounds such as aminocyclitols[15] and sialic acid mimics such as oseltamivir.[16]

## EXPERIMENTAL SECTION

**General.** All chemicals used were of reagent grade. All solvents were dried by established methods.[17] Flash chromatography was performed on Kieselgel 60, particle size 0.032−0.063 mm. Preparative TLC employed silica gel Merck 60 $GF_{254}$. Analytical TLC used aluminum-backed silica gel Merck 60 $F_{254}$. Infrared (IR) spectra were obtained using a commercial FT-IR spectrophotometer, and peak positions are given in $cm^{-1}$. Specific rotations were measured using an automatic polarimeter and are reported as follows: $[\alpha]_D^T$ ($c$ = g/100 mL; solvent), where $T$ is the temperature in °C. Melting points were determined with a capillary apparatus and are uncorrected. HRMS spectra were recorded on a commercial apparatus (ESI source). NMR spectra were obtained on a commercial instrument at 400 MHz ($^1$H NMR) or 100 MHz ($^{13}$C NMR) using $CDCl_3$ as the solvent. Chemical shifts ($\delta$) are reported in parts per million relative to TMS, and coupling constants ($J$) are reported in hertz. The chemical shift assignments of all compounds were carried out with the help of 2D NMR experiments such as COSY, HMQC, and HMBC.

**X-ray Crystallography.** Single-crystal X-ray data for compounds **1i** ($C_{14}H_{17}NO$) and **1j** ($C_{13}H_{15}NO$) were collected on a diffractometer with graphite-monochromatized Mo K$\alpha$ radiation ($\lambda$ = 0.71069 Å). The selected crystals of each compound were positioned 40 mm from the CCD detector and exposed for 10 s per frame. Data reduction of each data set was carried out with a multiscan absorption correction (SADABS). The structures were solved with SHELXS[18] by direct methods and refined on $F^2$ using full-matrix least-squares with



DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067−3074

SHELXL[18] included in the WINGX version 1.70.01 package of programs.[19] All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were placed in agreement with the electron density difference maps.

**General Procedure for the Synthesis of Aziridines 1a–s.** In a flask under argon, a mixture of iodoenone (1.35 mmol), anhydrous cesium carbonate (480 mg, 1.1 equiv), 1,10-phenanthroline (240 mg, 1.0 equiv), primary amine (1.5 equiv), and dry dichloromethane (10 mL) was stirred at room temperature. After complete reaction (TLC, about 4 h), the reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography afforded the pure aziridine. Small changes to the procedure in individual experiments are reported in the corresponding data paragraphs below.

*(±)-7-[(4-Fluorophenyl)methyl]-7-azabicyclo[4.1.0]heptan-2-one (**1a**).* By means of the general procedure, 264 mg (89% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 7.28 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.5; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.01 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 3.70 (1H, d, $^2J$ = 13.6; $CH_2$ –Ar); 3.37 (1H, d, $^2J$ = 13.6; $CH_2$ –Ar); 2.50–2.45 (1H, m, H-3); 2.32–2.29 (1H, m, H-6); 2.11 (1H, d, $J_{1,6}$ = 5.9; H-1); 2.07–1.98 (3H, m, H-3, H-4, H-5); 1.79–1.71 (1H, m, H-5); 1.64–1.57 (1H, m, H-4). $^{13}$C NMR $\delta$: 207.4 (C-2); 162.0 (d, $^1J_{C,F}$ = 245; Ar($p$) (C–F)); 134.2 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.1 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.3 (d, $^2J_{C,F}$ = 21; Ar($m$)); 62.6 ($CH_2$–Ar); 46.3 (C-1); 43.7 (C-6); 37.1 (C-3); 23.2 (C-5); 18.7 (C-4). $R_f$ = 0.33 (hexane/ethyl acetate 8:2).

*(±)-7-[(4-Methoxyphenyl)methyl]-7-azabicyclo[4.1.0]heptan-2-one (**1b**).* By means of the general procedure, 272 mg (87% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 7.23 (2H, d, $^3J$ = 8.6; Ar($o$)); 6.86 (2H, d, $^3J$ = 8.6; Ar($m$)); 3.80 (3H, s, –OMe); 3.71 (1H, d, $^2J$ = 13.4; $CH_2$–Ar); 3.32 (1H, d, $^2J$ = 13.4; $CH_2$–Ar); 2.50–2.44 (1H, m, H-3); 2.32–2.29 (1H, m, H-6); 2.10 (1H, d, $J_{1,6}$ = 6.0; H-1); 2.09–1.96 (3H, m, H-3, H-4, H-5); 1.77–1.70 (1H, m, H-5); 1.62–1.57 (1H, m, H-4). $^{13}$C NMR $\delta$: 207.7 (C-2); 158.8 (Ar($p$) (C–OMe)); 130.6 (Ar $C_q$); 128.9 (Ar($o$)); 113.8 (Ar($m$)); 62.8 ($CH_2$–Ar); 55.3 (–OMe); 46.3 (C-1); 43.7 (C-6); 37.1 (C-3); 23.2 (C-5); 18.8 (C-4). $R_f$ = 0.30 (hexane/ethyl acetate 8:2).

*(±)-7-(Prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one (**1c**).* By means of the general procedure, 202 mg (99% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 5.89 (1H, ddt, $J_{2',3'}$ = 16.7; $J_{2',3'}$ = 10.6; $J_{2',1'}$ = 5.4; H-2′); 5.23 (1H, d, $J_{3',2'}$ = 17.2; H-3′); 5.14 (1H, d, $J_{3',2'}$ = 10.4; H-3′); 3.10 (1H, dd, $^2J$ = 14.4; $J_{1',2'}$ = 5.1; H-1′); 2.90 (1H, dd, $^2J$ = 14.4; $J_{1',2'}$ = 5.5; H-1′); 2.51–2.41 (1H, m, H-3); 2.21 (1H, dt, $J_{6,1}$ = 5.9; $J_{6,5}$ = 2.9; H-6); 2.15–2.08 (1H, m, H-5); 2.05–1.92 (3H, m, H-2, H-3, H-4); 1.80–1.72 (1H, m, H-5); 1.68–1.56 (1H, m, H-4). $^{13}$C NMR $\delta$: 207.6 (C-2); 134.5 (C-2′); 130.6 (C-3′); 62.1 (C-1′); 46.0 (C-1); 43.6 (C-6); 37.0 (C-3); 23.2 (C-5); 18.8 (C-4). IR (NaCl): 1705 (C=O st.). $R_f$ = 0.54 (hexane/ethyl acetate 8:2).

*(±)-7-Butyl-7-azabicyclo[4.1.0]heptan-2-one (**1d**).* By means of the general procedure, 206 mg (91% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 2.47–2.37 (2H, m, H-3, H-1′); 2.29 (1H, dt, $^2J$ = 11.5; $J_{1',2'}$ = 7.1; H-1′); 2.21 (1H, dt, $J_{6,1}$ = 5.5; $J_{6,5}$ = 2.7; H-6); 2.08 (1H, dtd, $^2J$ = 13.4; $J_{5,4}$ = 4.5; $J_{5,6}$ = 2.2; H-5); 2.01–1.92 (2H, m, H-3, H-4); 1.90 (1H, d, $J_{1,6}$ = 5.9; H-1); 1.77–1.69 (1H, m, H-5); 1.63–1.49 (3H, m, H-4, H-2′); 1.41–1.31 (2H, m, H-3′); 0.91 (3H, t, $J_{4',3'}$ = 7.3; H-4′). $^{13}$C NMR $\delta$: 208.1 (C-2); 60.2 (C-1′); 46.3 (C-1); 43.8 (C-6); 37.0 (C-3); 31.8 (C-2′); 23.3 (C-5); 20.4 (C-3′); 18.9 (C-4); 14.0 (C-4′). IR (NaCl): 1707 (C=O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{10}H_{18}NO$ 168.1383; found 168.1376. $R_f$ = 0.62 (hexane/ethyl acetate 8:2).

*(±)-7-Octyl-7-azabicyclo[4.1.0]heptan-2-one (**1e**).* By means of the general procedure, 257 mg (100% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 2.47–2.37 (2H, m, H-3, H-1′); 2.26 (1H, dt, $^2J$ = 11.5; $J_{1',2'}$ = 7.2; H-1′); 2.14 (1H, dt, $J_{6,1}$ = 5.4; $J_{6,5}$ = 2.6; H-6); 2.08 (1H, dtd, $^2J$ = 13.3; $J_{5,4}$ = 4.5; $J_{5,6}$ = 2.1; H-5); 2.01–1.92 (2H, m, H-3, H-4); 1.90 (1H, d, $J_{1,6}$ = 5.9; H-1); 1.77–1.68 (1H, m, H-5); 1.62–1.49 (3H, m, H-4, H-2′); 1.36–1.24 (10H, m, H-3′–H-7′); 0.88 (3H, t, $J_{8',7'}$ = 6.7; H-8′). $^{13}$C NMR $\delta$: 208.1 (C-2); 60.6 (C-1′); 46.3 (C-1); 43.9 (C-6); 37.0 (C-3); 31.8, 29.7, 29.2, 27.3, 22.6 (C-3′–C-7′); 29.5 (C-2); 23.3 (C-5); 18.9 (C-4); 14.0 (C-8′). IR (NaCl): 1709 (C=O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{26}NO$ 224.2009; found 224.2009. $R_f$ = 0.65 (hexane/ethyl acetate 8:2).

*(±)-7-(4-Methoxyphenyl)-7-azabicyclo[4.1.0]heptan-2-one (**1f**).* By means of the general procedure, with a reaction time of 17 h, 109 mg (37% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:1).

$^1$H NMR $\delta$: 6.92 (2H, d, $^3J$ = 8.9; Ar($o$)); 6.78 (2H, d, $^3J$ = 8.9; Ar($m$)); 3.75 (3H, s, –OMe); 2.85–2.81 (1H, m, H-6); 2.00 (1H, d, $J_{1,6}$ = 6.0; H-1); 2.58–2.51 (1H, m, H-3); 2.34–2.28 (1H, m, H-5); 2.13–2.01 (2H, m, H-3, H-4); 1.93–1.84 (1H, m, H-5); 1.78–1.65 (1H, m, H-4). $^{13}$C NMR $\delta$: 206.6 (C-2); 155.6 (Ar($p$) (C–OMe)); 145.9 (Ar $C_q$); 121.1 (Ar($o$)); 114.4 (Ar($m$)); 55.6 (–OMe); 46.7 (C-1); 43.1 (C-6); 37.1 (C-3); 23.4 (C-5); 18.3 (C-4). IR (NaCl): 1704 (C=O st.); 1240 (C–O–C st.). Mp = 63–65 °C. Anal. Calcd for $C_{13}H_{15}NO_2$: C 71.87; H 6.96; N 6.45. Found: C 71.89; H 6.83; N 6.60. $R_f$ = 0.62 (hexane/ethyl acetate 2:1).

*(±)-7-[(4-Methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]heptan-2-one (**1g**).* The general procedure was followed except that 1,10-phenanthroline was not added and 3 equiv of tosylamide was used instead of the normal 1.5 equiv. After purification by flash column chromatography, eluting with hexane/ethyl acetate (8:2), 244 mg (68% yield) of pure **1g** was obtained as a white solid.

$^1$H NMR $\delta$: 7.81 (2H, d, $^2J$ = 8.0; Ar( $o$)); 7.35 (2H, d, $^2J$ = 8.0; Ar($m$)); 3.47–3.44 (1H, m, H-6); 3.15 (1H, d, $J_{1,6}$ = 6.4; H-6); 2.46–2.39 (4H, m, H-3, Me Ts); 2.20–2.15 (1H, m, H-5); 2.07–1.99 (1H, m, H-3); 1.95–1.81 (2H, m, H-4, H-5); 1.70–1.64 (1H, m, H-4). $^{13}$C NMR $\delta$: 201.3 (C-2); 145.0 (Ar C–$SO_2$ Ts); 134.4 (Ar($p$)); 129.9 (Ar($m$)); 127.9 (Ar($o$)); 43.9 (C-6); 40.9 (C-1); 37.0 (C-3); 21.7 (C-5); 21.6 (Me Ts); 17.0 (C-4). IR (NaCl): 1718 (C=O st.); 1161 ($SO_2$ st.). Mp = 73–73.5 °C. Anal. Calcd for $C_{13}H_{15}NO_3S$: C 58.85; H 5.70; N 5.28; S 12.09. Found: C 58.94; H 5.73; N 5.17; S 11.89. $R_f$ = 0.55 (hexane/ethyl acetate 6:4).

*(±)-7-Acetyl-7-azabicyclo[4.1.0]heptan-2-one (**1h**).* The general procedure was used, but instead of a primary amine, the reaction mixture was continuously saturated with ammonia gas for 4 h. Argon was then passed through the solution to eliminate excess ammonia. Acetic anhydride (2 equiv) was added at 0 °C, and the reaction mixture was left to stir for an additional hour at room temperature. The reaction mixture was treated as described in the typical procedure, and 108 mg (52% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (2:1).

$^1$H NMR $\delta$: 3.17 (1H, dt, $J_{6,1}$ = 5.6; $J_{6,5}$ = 2.8; H-6); 2.90 (1H, d, $J_{1,6}$ = 5.6; H-1); 2.51 (1H, dt, $^2J$ = 17.7; $J_{3,4}$ = 4.1; H-3); 2.26 (1H, dq, $^2J$ = 13.9; $J_{5,4}$ = $J_{5,6}$ = 3.2; H-5); 2.17 (3H, s, $CH_3$ Ac); 2.09 (1H, ddd, $^2J$ = 17.6; $J_{3,4}$ = 11.4; $J_{3,4}$ = 5.9; H-3); 2.01–1.80 (2H, m, H-4, H-5); 1.74–1.66 (1H, m, H-4). $^{13}$C NMR $\delta$: 203.5 (C-2); 181.3 (C=O Ac); 42.0 (C-1); 39.6 (C-6); 37.1 (C-3); 23.5 ($CH_3$ Ac); 22.8 (C-5); 17.0 (C-4). IR (NaCl): 1712 (C=O st.). Mp = 41–42 °C. Anal. Calcd for $C_8H_{11}NO_2$: C 62.73; H 7.24; N 9.14. Found: C 62.84; H 7.19; N 8.77. $R_f$ = 0.45 (hexane/ethyl acetate 1:1).

*(±)-7-[(1R)-1-Phenylethyl]-7-azabicyclo[4.1.0]heptan-2-one (**1i**).* By means of the general procedure, two diastereoisomers were obtained and separated by flash column chromatography, eluting with dichloromethane/hexane (1:1), affording 140 mg (48% yield) of pure (1*S*,6*S*)-**1i** as a colorless oil and 136 mg (47% yield) of pure (1*R*,6*R*)-**1i** as a white solid.

*(–)-(1S,6S)-7-[(1R)-1-Phenylethyl]-7-azabicyclo[4.1.0]heptan-2-one [(1S,6S)-**1i**].* $^1$H NMR $\delta$: 7.31–7.19 (5H, m, Ar); 2.70 (1H, q, $^3J$ =



DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067–3074

6.5; CH−Ar); 2.50 (1H, dt, $^2J$ = 17.0; $J_{3,4}$ = 5.1; H-3); 2.37−2.34 (1H, m, H-6); 2.17−2.04 (2H, m, H-4, H-5); 2.01−1.93 (2H, m, H-1, H-3); 1.85−1.77 (1H, m, H-5); 1.67−1.56 (1H, m, H-4); 1.41 (3H, d, $^3J$ = 6.5; Me). $^{13}$C NMR $\delta$: 207.6 (C-2); 143.8 (Ar $C_q$); 128.4 (Ar(*m*)); 127.1 (Ar(*p*)); 126.4 (Ar(*o*)); 68.8 (CH−Ar); 46.2 (C-1); 44.0 (C-6); 37.0 (C-3); 23.9 (Me); 23.7 (C-5); 19.5 (C-4). IR (NaCl): 1702 (C═O st.). $[\alpha]_D^{20}$ = −10 (*c* = 1.6; $CH_2Cl_2$). Anal. Calcd for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 78.24; H 8.16; N 6.45. $R_f$ = 0.68 (dichloromethane).

*(+)-(1R,6R)-7-[(1R)-1-Phenylethyl]-7-azabicyclo[4.1.0]heptan-2-one [(1R,6R)-**1i**].* $^1$H NMR $\delta$: 7.36 (2H, d, $^3J$ = 6.9; Ar( *o*)); 7.33 (2H, t, $^3J$ = 7.8; Ar(*m*)); 7.26 (1H, t, $^3J$ = 6.9; Ar(*p*)); 2.68 (1H, q, $^3J$ = 6.5; CH−Ar); 2.55−2.48 (1H, m, H-3); 2.20 (1H, dt, $J_{6,1}$ = 5.9; $J_{6,5}$ = 2.7; H-6); 2.11 (1H, d, $J_{1,6}$ = 6.0, H-1); 2.09−1.91 (3H, m, H-3, H-4, H-5); 1.67−1.56 (2H, m, H-4, H-5); 1.39 (3H, d, $^3J$ = 6.5; Me). $^{13}$C NMR $\delta$: 207.8 (C-2); 144.5 (Ar $C_q$); 128.4 (Ar(*m*)); 127.1 (Ar(*p*)); 126.4 (Ar(*o*)); 69.1 (CH−Ar); 46.4 (C-1); 42.9 (C-6); 37.2 (C-3); 23.7 (Me); 23.1 (C-5); 18.6 (C-4). IR (NaCl): 1702 (C═O st.). $[\alpha]_D^{20}$ = +79 (*c* = 1.3; $CH_2Cl_2$). Mp = 62.5−63.5 °C. Anal. Calcd for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 78.04; H 8.05; N 6.67. $R_f$ = 0.56 ($CH_2Cl_2$).

*(±)-6-[(1R)-1-Phenylethyl]-6-azabicyclo[3.1.0]hexan-2-one (**1j**).* By means of the general procedure, two diastereoisomers were obtained and separated by flash column chromatography, eluting with hexane/ethyl acetate (9:1). This afforded 95 mg (35% yield) of pure (1*R*,5*R*)-**1j** as a white solid and 122 mg (45% yield) of pure (1*S*,5*S*)-**1j** as a colorless oil.

*(−)-(1S,5S)-6-[(1R)-1-Phenylethyl]-6-azabicyclo[3.1.0]hexan-2-one [(1S,5S)-**1j**].* $^1$H NMR $\delta$: 7.30−7.20 (5H, m, Ar); 2.75 (1H, t, $J_{5,1}$ = $J_{5,4}$ = 3.5; H-5); (1H, q, $^3$ *J* = 6.5; CH−Ar); 2.44−2.22 (2H, m, H-3, H-4); 2.06 (1H, d, $J_{1,5}$ = 4.1; H-1); 2.04−1.93 (2H, m, H-3, H-4); 1.46 (3H, d, $^3J$ = 6.5; Me). $^{13}$C NMR $\delta$: 212.1 (C-2); 143.6 (Ar $C_q$); 128.4 (Ar(*m*)); 127.2 (Ar(*p*)); 126.4 (Ar(*o*)); 67.1 (CH−Ar); 46.6 (C-1); 46.4 (C-5); 33.0 (C-3); 24.4 (C-4); 23.9 (Me). IR (NaCl): 1735 (C═O st.). $[\alpha]_D^{20}$ = −13 (*c* = 0.6; $CH_2Cl_2$). Anal. Calcd for $C_{13}H_{15}NO$: C 77.58; H 7.51; N 6.96. Found: C 77.70; H 7.19; N 6.57. $R_f$ = 0.36 (hexane/ethyl acetate 8:2).

*(+)-(1R,5R)-6-[(1R)-1-Phenylethyl]-6-azabicyclo[3.1.0]hexan-2-one [(1R,5R)-**1j**].* $^1$H NMR $\delta$: 7.39 (2H, d, $^3J$ = 6.8; Ar( *o*)); 7.34 (2H, t, $^3J$ = 7.4; Ar(*m*)); 7.27 (1H, t, $^3J$ = 7.0; Ar(*p*)); 2.66 (1H, q, $^3J$ = 6.5; CH−Ar); 2.57 (1H, t, $J_{5,1}$ = $J_{5,4}$ = 3.7; H-5); 2.38 (1H, dt, $^2J$ = 17.9; $J_{3,4}$ = 9.0; H-3); 2.25 (1H, d, $J_{1,5}$ = 4.1, H-1); 2.08 (1H, ddd, $^2J$ = 13.0; $J_{4,3}$ = 9.1; $J_{4,3}$ = 1.0; H-4); 1.97 (1H, dd, $^2J$ = 17.9; $J_{3,4}$ = 9.7; H-3); 1.85 (1H, dtd, $^2J$ = 12.9; $J_{4,3}$ = 9.3; $J_{4,5}$ = 2.4; H-4); 1.41 (3H, d, $^3J$ = 6.5; Me). $^{13}$C NMR $\delta$: 212.5 (C-2); 144.2 (Ar $C_q$); 128.5 (Ar(*m*)); 127.2 (Ar(*p*)); 126.5 (Ar(*o*)); 67.1 (CH−Ar); 47.4 (C-1); 45.4 (C-5); 33.1 (C-3); 24.1 (C-4); 23.5 (Me). IR (NaCl): 1733 (C═O st.). $[\alpha]_D^{20}$ = +41 (*c* = 1.4; $CH_2Cl_2$). Mp = 74−75 °C. Anal. Calcd for $C_{13}H_{15}NO$: C 77.58; H 7.51; N 6.96. Found: C 77.40; H 7.29; N 6.84. $R_f$ = 0.49 (hexane/ethyl acetate 8:2).

*(±)-6-[(4-Methylphenyl)sulfonyl]-6-azabicyclo[3.1.0]hexan-2-one (**1k**).* By means of the experimental procedure used for **1g**, 185 mg (85% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (2:1).

$^1$H NMR $\delta$: 7.82 (2H, d, $^2J$ = 8.4, Ar( *o*)), 7.36 (2H, d, $^2J$ = 8.0; Ar(*m*)); 3.79−3.77 (1H, m, H-5); 3.26 (1H, d, $J_{1,5}$ = 4.8; H-1); 2.46 (3H, s, Me Ts); 2.33−2.21 (2H, m, H-3, H-4); 2.16−2.04 (2H, m, H-3, H-4). $^{13}$C NMR $\delta$: 206.8 (C-2); 145.2 (Ar C−$SO_2$ Ts); 134.4 (Ar(*p*)); 129.9 (Ar(*m*)); 127.9 (Ar(*o*)); 45.4 (C-1); 44.2 (C-5); 31.8 (C-3); 23.1 (C-4); 21.6 (Me Ts). IR (NaCl): 1753 (C═O st.); 1157 ($SO_2$ st.). Mp = 110.5−111 °C. Anal. Calcd for $C_{12}H_{13}NO_3S$: C 57.35; H 5.21; N 5.57; S 12.76. Found: C 57.53; H 5.29; N 5.45; S 12.42. $R_f$ = 0.59 (hexane/ethyl acetate 1:1).

*(±)-(1S,5S,6R)-5-[(tert-Butyldimethylsilyl)oxy]-7-[(4-fluorophenyl)methyl]-7-azabicyclo[4.1.0]heptan-2-one (**1l**).* By means of the general procedure, 370 mg (78% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (95:5).

$^1$H NMR $\delta$: 7.38 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.8; $J_{Ar(o),F}$ = 5.6; Ar(*o*)); 6.99 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.8; Ar(*m*)); 4.12 (1H, ddd, $J_{5,4}$ = 10.8; $J_{5,4}$ = 5.2; $J_{5,6}$ = 1.6; H-5); 3.91 (1H, d, $^2J$ = 14.0; $CH_2$−Ar); 3.26 (1H, d, $^2J$ = 14.0; $CH_2$−Ar); 2.43 (1H, ddd, $^2J$ = 18.0; $J_{3,4}$ = 5.4; $J_{3,4}$ = 2.0; H-3); 2.29 (1H, br d, $J_{6,1}$ = 6.0; H-6); 2.25−2.22 (2H, m, H-1, H-4); 2.07 (1H, ddd, $^2J$ = 18.4; $J_{3,4}$ = 12.4; $J_{3,4}$ = 6.0; H-3); 1.67−1.60 (1H, m, H-4); 0.86 (9H, s, $^t$Bu TBDMS); 0.08 (3H, s, Me TBDMS); 0.04 (3H, s, Me TBDMS). $^{13}$C NMR $\delta$: 205.4 (C-2); 162.0 (d, $^1J_{C,F}$ = 243; Ar(*p*) (C−F)); 133.9 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.1 (d, $^3J_{C,F}$ = 8; Ar(*o*)); 115.1 (d, $^2J_{C,F}$ = 21; Ar(*m*)); 67.8 (C-5); 62.1 ($CH_2$−Ar); 48.1 (C-6); 46.8 (C-1); 35.3 (C-3); 25.8 (C-4); 25.7 (3 × Me $^t$Bu); 18.0 ($C_q$ $^t$Bu); −4.7 (Me TBDMS); −4.8 (Me TBDMS). IR (NaCl): 1711 (C═O st.). Anal. Calcd for $C_{19}H_{28}FNO_2Si$: C 65.29; H 8.07; N 4.01. Found: C 65.29; H 7.90; N 3.92. $R_f$ = 0.43 (hexane/ethyl acetate 9:1).

*(±)-(1S,5S,6R)-7-[(4-Fluorophenyl)methyl]-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one (**1m**).* By means of the general procedure, 236 mg (74% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (2:1).

$^1$H NMR $\delta$: 7.31 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.3; $J_{Ar(o),F}$ = 5.5; Ar(*o*)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.6; Ar(*m*)); 4.15−4.09 (1H, m, H-5); 3.73 (1H, d, $^2J$ = 13.2; $CH_2$−Ar); 3.39 (1H, d, $^2J$ = 13.2; $CH_2$−Ar); 2.58 (1H, dd, $J_{6,1}$ = 5.7; $J_{6,5}$ = 3.5; H-6); 2.55−2.47 (1H, m, H-3); 2.31 (1H, d, $J_{1,6}$ = 5.9; H-1); 2.10−1.95 (3H, m, H-3, H-4, OH); 1.85−1.76 (1H, m, H-4). $^{13}$C NMR $\delta$: 207.8 (C-2); 162.3 (d, $^1J_{C,F}$ = 246; Ar(*p*) (C−F)); 133.6 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.7 (d, $^3J_{C,F}$ = 8; Ar(*o*)); 115.6 (d, $^2J_{C,F}$ = 21; Ar(*m*)); 64.8 (C-5); 62.6 ($CH_2$−Ar); 48.1 (C-6); 47.6 (C-1); 34.0 (C-3); 29.3 (C-4). IR (NaCl): 3390 (br, OH st.); 1698 (C═O st.). Mp = 69.5−71 °C. Anal. Calcd for $C_{13}H_{14}FNO_2$: C 66.37; H 5.95; N 6.00. Found: C 66.40; H 5.97; N 6.02. $R_f$ = 0.63 (hexane/ethyl acetate 1:1).

*(−)-(1S,5S,6R)-5-Hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]-heptan-2-one (**1n**).* By means of the general procedure, 198 mg (88% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:1).

$^1$H NMR $\delta$: 5.91 (1H, ddt, $J_{2',3'}$ = 17.0; $J_{2',3'}$ = 10.4; $J_{2',1'}$ = 5.9; H-2′); 5.26 (1H, dq, $J_{3',2'}$ = 17.2; $^2J$ = $J_{3',1'}$ = 1.5; H-3′); 5.19 (1H, dq, $J_{2',3'}$ = 10.3; $^2J$ = $J_{2',1'}$ = 1.2; H-3′); 4.17−4.14 (1H, m, H-5); 3.11 (1H, dd, $^2J$ = 13.8; $J_{1',2'}$ = 5.8; H-1′); 2.99 (1H, dd, $^2J$ = 13.8; $J_{1',2'}$ = 5.9; H-1′); 2.56−2.47 (2H, m, H-6, H-3); 2.41 (1H, s br, OH); 2.19 (1H, d, $J_{1,6}$ = 5.9; H-1); 2.09−1.96 (2H, m, H-3, H-4); 1.86−1.77 (1H, m, H-4). $^{13}$C NMR $\delta$: 206.2 (C-2); 133.9 (C-2′); 117.9 (C-3′); 64.5 (C-5); 62.1 (C-1′); 48.1 (C-6); 47.4 (C-1); 33.8 (C-3); 29.7 (C-4). IR: 3400 (OH st.); 1694 (C═O st.). $[\alpha]_D^{20}$ = −118 (*c* = 1.0; DCM). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{14}NO_2$ 168.1019; found 168.1015. $R_f$ = 0.31 (hexane/ethyl acetate 1:1).

*(±)-(1R,5S,6S)-5-[(tert-Butyldimethylsilyl)oxy]-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[4.1.0]heptan-2-one (**1o**).* By means of the same procedure as for **1g**, 386 mg (85% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 7.80 (2H, d, $^2J$ = 8.0; Ar(*o*)); 7.36 (2H, d, $^2J$ = 8.0; Ar(*m*)); 4.38 (1H, q, $J_{5,4}$ = $J_{5,6}$ = 3.1; H-5); 3.34 (1H, ddd, $J_{6,1}$ = 6.4; $J_{6,5}$ = 2.8; *J* = 1.2; H-6); 3.17 (1H, d, $J_{1,6}$ = 6.4; H-1); 2.45 (3H, s, Me Ts); 2.38 (1H, ddd, $^2J$ = 18.2; $J_{3,4}$ = 12.2; $J_{3,4}$ = 6.2; H-3); 2.20 (1H, ddd, $^2J$ = 18.4; $J_{3,4}$ = 5.2; $J_{3,4}$ = 3.2; H-3); 2.07−1.99 (1H, m, H-4); 1.71−1.63 (1H, m, H-4); 0.89 (9H, s, $^t$Bu TBDMS); 0.13 (3H, s, Me TBDMS); 0.09 (3H, s, Me TBDMS). $^{13}$C NMR $\delta$: 200.8 (C-2); 145.2 (Ar C−$SO_2$ Ts); 134.0 (Ar(*p*)); 129.9 (Ar(*m*)); 127.9 (Ar(*o*)); 63.6 (C-5); 43.7 (C-1); 43.5 (C-6); 31.9 (C-3); 25.6 (3 × Me $^t$Bu); 35.4 (C-4); 21.6 (Me Ts); 17.9 ($C_q$ $^t$Bu); −4.8 (Me TBDMS); −4.9 (Me TBDMS). IR (NaCl): 1722 (C═O st.); 1163 ($SO_2$ st.). Mp = 98.5−99 °C. Anal. Calcd for $C_{19}H_{29}NO_4SSi$: C 57.69; H 7.39; N 3.54; S 8.11. Found: C 57.90; H 7.54; N 3.58; S 7.90. $R_f$ = 0.39 (hexane/ethyl acetate 8:2).

*(±)-(1S,4S,5R)-4-[(tert-Butyldimethylsilyl)oxy]-6-[(4-fluorophenyl)methyl]-6-azabicyclo[3.1.0]hexan-2-one (**1p**).* By means of the general procedure, 374 mg (83% yield) of the pure product was


DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067−3074

obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (9:1).

$^1$H NMR $\delta$: 7.43 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.7; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 4.39 (1H, td, $J_{4,3}$ = 8.0; $J_{4,5}$ = 3.2; H-4); 3.94 (1H, d, $^2J$ = 14.1; $CH_2$–Ar); 3.18 (1H, d, $^2J$ = 14.1; $CH_2$–Ar); 2.74 (1H, t, $J_{5,1}$ = $J_{5,4}$ = 3.7; H-5); 2.47 (1H, dd, $^2J$ = 16.8; $J_{3,4}$ = 8.0; H-3); 2.37 (1H, d, $J_{1,5}$ = 4.2; H-1); 2.22 (1H, dd, $^2J$ = 16.8; $J_{3,4}$ = 8.0; H-3); 0.90 (9H, s, $^t$Bu TBDMS); 0.07 (3H, s, Me TBDMS); 0.06 (3H, s, Me TBDMS). $^{13}$C NMR $\delta$: 206.9 (C-2); 162.0 (d, $^1J_{C,F}$ = 245; Ar($p$) (C–F)); 133.7 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 128.9 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.2 (d, $^2J_{C,F}$ = 21; Ar($m$)); 68.2 (C-4); 60.1 ($CH_2$–Ar); 50.3 (C-5); 48.6 (C-1); 41.6 (C-3); 25.7 (3 × Me $^t$Bu); 18.1 ($C_q$ $^t$Bu); −4.7 (Me TBDMS); −4.8 (Me TBDMS). IR (NaCl): 1745 (C═O st.). Anal. Calcd for $C_{18}H_{26}FNO_2Si$: C 64.44; H 7.81; N 4.18. Found: C 64.48; H 8.00; N 4.10. $R_f$ = 0.57 (hexane/ethyl acetate 8:2).

*(±)-(1S,4S,5R)-6-[(4-Fluorophenyl)methyl]-4-hydroxy-6-aza-bicyclo[3.1.0]hexan-2-one (**1q**).* By means of the general procedure, 180 mg (60% yield) of the pure product was obtained as a white solid after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:1).

$^1$H NMR $\delta$: 7.32 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.4; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.6; Ar($m$)); 4.36 (1H, td, $J_{4,3}$ = 8.2; $J_{4,5}$ = 3.2; H-4); 3.62 (1H, d, $^2J$ = 13.4; $CH_2$–Ar); 3.46 (1H, d, $^2J$ = 13.4; $CH_2$–Ar); 2.96 (1H, t, $J_{5,1}$ = $J_{5,4}$ = 3.8; H-5); 2.47 (1H, d, $J_{1,5}$ = 4.2; H-1); 2.41 (1H, dd, $^2J$ = 17.9; $J_{3,4}$ = 8.4; H-3); 2.23 (1H, dd, $^2J$ = 17.9; $J_{3,4}$ = 6.9; H-3); 2.27–2.18 (1H, br s, OH). $^{13}$C NMR $\delta$: 206.7 (C-2); 162.3 (d, $^1J_{C,F}$ = 246; Ar($p$) (C–F)); 133.4 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.5 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.6 (d, $^2J_{C,F}$ = 21; Ar($m$)); 67.4 (C-4); 60.6 ($CH_2$–Ar); 50.0 (C-1); 49.7 (C-5); 42.0 (C-3). IR (NaCl): 3400 (OH st.); 1745 (C═O st.). Mp = 105–105.5 °C. Anal. Calcd for $C_{12}H_{12}FNO_2$: C 65.15; H 5.47; N 6.33. Found: C 65.24; H 5.55; N 6.24. $R_f$ = 0.31 (hexane/ethyl acetate 1:1).

*(±)-(1S,6S,7R)-8-[(4-Fluorophenyl)methyl]-6-hydroxy-8-aza-bicyclo[5.1.0]octan-2-one (**1r**).* By means of the general procedure, 201 mg (60% yield) of the pure product was obtained as a colorless oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:1).

$^1$H NMR $\delta$: 7.33 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.6; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 3.86 (1H, br d, $J$ = 9.8; H-4); 3.69 (1H, d, $^2J$ = 13.2; $CH_2$–Ar); 3.39 (1H, d, $^2J$ = 13.2; $CH_2$–Ar); 2.77 (1H, ddd, $^2J$ = 13.7; $J_{3,4}$ = 11.1; $J_{3,4}$ = 2.9; H-3); 2.33 (1H, dd, $J_{7,1}$ = 7.5; $J_{7,6}$ = 1.2; H-7); 2.30 (1H, d, $J_{1,7}$ = 7.5; H-1); 2.25–2.20 (1H, m, H-3); 1.96–1.78 (3H, m, H-4, H-5); 1.46 (1H, br s, OH); 1.28–1.15 (1H, m, H-4). $^{13}$C NMR $\delta$: 210.6 (C-2); 162.2 (d, $^1J_{C,F}$ = 246; Ar($p$) (C–F)); 134.0 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.6 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.5 (d, $^2J_{C,F}$ = 21; Ar($m$)); 71.6 (C-6); 63.4 ($CH_2$–Ar); 49.7 (C-1); 49.1 (C-7); 41.4 (C-3); 34.2 (C-5); 22.3 (C-4). IR (NaCl): 3400 (OH st.); 1687 (C═O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{17}FNO_2$ 250.1238; found 250.1240. $R_f$ = 0.57 (hexane/ethyl acetate 1:2).

**General Procedure for the Wharton Reaction of Aziridines 1a–s.** *Acidic Conditions.* A solution of aziridine (0.46 mmol), monohydrated hydrazine (44 μL, 2 equiv), and acetic acid (52 μL, 2 equiv) in distilled methanol (20 mL) was stirred at room temperature. After complete reaction (TLC, around 2 h), the reaction mixture was quenched with a saturated aqueous solution of sodium carbonate (10 mL), and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. Purification by chromatography (flash column or preparative plates) afforded the pure allylic amine or amide. Small changes to the procedure are reported below.

*Basic Conditions.* In a flask under argon, a mixture of hydrazine hydrochloride (170 mg, 3 equiv), triethylamine (170 mg, 3 equiv), and dry acetonitrile (2 mL) was sonicated for 2 h at room temperature. A solution of aziridine (0.43 mmol) in dry acetonitrile (1 mL) was added, and the reaction mixture was stirred at room temperature. After complete reaction (TLC, around 14 h), the reaction mixture was quenched with water (5 mL), and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. Purification by chromatography (flash column or preparative plates) afforded the pure allylic amine or amide. Small changes to the procedure are reported below.

*(±)-N-[(4-Fluorophenyl)methyl]cyclohex-2-en-1-amine (**2a**).* By means of the general procedure under acidic conditions, 78 mg (83% yield) of the pure product was obtained as a yellow oil after purification by flash column chromatography, eluting with chloroform/methanol (9:1).

$^1$H NMR $\delta$: 7.31 (2H, dd, $J_{Ar(o),Ar(m)}$ = 10.1; $J_{Ar(o),F}$ = 7.0; Ar($o$)); 7.00 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 5.79–5.75 (1H, m, H-3); 5.73–5.70 (1H, m, H-2); 3.80 (1H, d, $^2J$ = 12.7; $CH_2$–Ar); 3.76 (1H, d, $^2J$ = 12.7; $CH_2$–Ar); 3.23–3.19 (1H, m, H-1); 2.03–1.96 (2H, m, H-4); 1.93–1.86 (1H, m, H-6); 1.78–1.71 (1H, m, H-5); 1.66 (1H, br s, NH); 1.60–1.44 (2H, m, H-5, H-6). $^{13}$C NMR $\delta$: 161.9 (d, $^1J_{C,F}$ = 244; Ar($p$) (C–F)); 136.3 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 129.7 (d, $^3J_{C,F}$ = 8; Ar($o$)); 129.6 (C-2); 129.2 (C-3); 115.1 (d, $^2J_{C,F}$ = 21; Ar($m$)); 52.4 (C-1); 50.2 ($CH_2$–Ar); 29.4 (C-6); 25.3 (C-4); 20.2 (C-5). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{17}FN$ 206.1345; found 206.1340. $R_f$ = 0.69 (chloroform/methanol 8:2).

*(±)-N-(Cyclohex-2-en-1-yl)-N-[(4-methoxyphenyl)methyl]-acetamide (**2b**).* After completion of the Wharton reaction under basic conditions (14 h), triethylamine (3 equiv) and acetic anhydride (5 equiv) were added at 0 °C. The reaction mixture was stirred at room temperature for an additional 2 h. After treatment as described in the general procedure, 67 mg (60% yield) of the pure product was obtained as a colorless oil upon purification by preparative TLC, eluting with hexane/ethyl acetate (1:1).

Major rotamer: $^1$H NMR $\delta$: 7.11 (2H, d, $^2J$ = 8.7; Ar($o$)); 6.88 (2H, d, $^2J$ = 8.7; Ar($m$)); 5.88–5.84 (1H, m, H-3); 5.48–5.42 (1H, m, H-2); 5.36–5.31 (1H, m, H-1); 4.47 (1H, d, $^2J$ = 17.6; $CH_2$–Ar); 4.39 (1H, d, $^2J$ = 17.6; $CH_2$–Ar); 3.80 (3H, s, –OMe); 1.99 (3H, s, $CH_3$ Ac); 1.97–1.91 (2H, m, H-4); 1.83–1.56 (3H, m, H-5, H-6); 1.44–1.37 (1H, m, H-6). $^{13}$C NMR $\delta$: 172.0 (Ac (C═O)); 158.6 (Ar($p$) (C–OMe)); 131.9 (C-3); 130.6 (Ar $C_q$); 128.0 (C-2); 126.8 (Ar($o$)); 114.1 (Ar($m$)); 55.3 (–OMe); 51.3 ($CH_2$–Ar); 47.5 (C-1); 27.7 (C-6); 24.6 (C-4); 22.5 ($CH_3$ Ac); 21.4 (C-5). IR (NaCl): 1639 (C═O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$ 260.1651; found 260.1645. $R_f$ = 0.49 (hexane/ethyl acetate 1:1).

*(±)-N-(Cyclohex-2-en-1-yl)-N-(prop-2-en-1-yl)acetamide (**2c**).* By means of the procedure used for **2b**, 65 mg (84% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (1:1).

Major rotamer: $^1$H NMR $\delta$: 5.92–5.76 (2H, m, H-3, H-2′); 5.43 (1H, br d, $J_{2,3}$ = 10.1; H-2); 5.29–5.06 (3H, m, H-1, H-3′); 3.95 (2H, m, H-1′); 2.07 (3H, $CH_3$ Ac); 2.06–1.97 (2H, m, H-4); 1.91–1.60 (3H, m, H-5, H-6); 1.42 (1H, tdd, $J$ = 12.4; $J$ = 9.7; $J$ = 2.9; H-6). $^{13}$C NMR $\delta$: 171.4 (Ac (C═O)); 135.5 (C-2′); 131.7 (C-3); 128.1 (C-2); 116.0 (C-3′); 50.9 (C-1); 46.8 (C-1′); 27.6 (C-6); 24.6 (C-4); 22.1 ($CH_3$ Ac); 21.4 (C-5). IR (NaCl): 1643; 1631 (C═O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{18}NO$ 180.1383; found 180.1384. $R_f$ = 0.48 (hexane/ethyl acetate 1:1).

*(±)-N-Butyl-N-(cyclohex-2-en-1-yl)acetamide (**2d**).* By means of the procedure used for **2b**, 80 mg (94% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (1:1).

Two rotamers: $^1$H NMR $\delta$: 5.92–5.84 (1H, m, H-3); 5.51 (0.5H, br d, $J_{2,3}$ = 10.1; H-2); 5.44 (0.5H, br d, $J_{2,3}$ = 10.2; H-2); 5.18–5.12 (0.5H, m, H-1); 4.31–4.26 (0.5H, m, H-1); 3.21–3.04 (2H, m, H-1′); 2.11 (3H, $CH_3$ Ac); 2.06–2.00 (2H, m, H-4); 1.91–1.75 (2H, m, H-5, H-6); 1.72–1.44 (4H, m, H-5, H-6, H-2′); 1.31 (1H, sext, $^3J$ = 7.7; H-3′); 1.29 (1H, sext, $^3J$ = 7.7; H-3′); 0.94 (1.5H, t, $^3J$ = 7.3; H-4′); 0.90 (1.5H, t, $^3J$ = 7.3; H-4′). $^{13}$C NMR $\delta$: 170.7, 170.2 (Ac (C═O)); 131.3, 130.9 (C-3); 128.8, 128.4 (C-2); 55.8, 51.0 (C-1); 44.9, 43.1 (C-1′); 33.5, 31.6 (C-2′); 28.7, 27.6 (C-6); 24.6, 24.4 (C-4); 22.2, 21.9 ($CH_3$ Ac); 21.7, 21.6 (C-5); 20.6, 20.4 (C-3′); 13.9, 13.7 (C-4′). IR (NaCl): 1639 (C═O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{22}NO$ 196.1696; found 196.1688. $R_f$ = 0.31 (hexane/ethyl acetate 2:1).

*(±)-N-Octylcyclohex-2-en-1-amine (**2e**).* By means of the general procedure under acidic conditions, 90 mg (93% yield) of the pure product was obtained as a yellow oil after purification by flash column



DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067–3074

chromatography, eluting with dichloromethane/methanol (95:5), $R_f$ = 0.24 (dichloromethane/methanol 9:1).

*(±)-N-(Cyclohex-2-en-1-yl)-4-methoxyaniline (**2f**).* By means of the general procedure under basic conditions, 47 mg (54% yield) of the pure product was obtained as a yellow oil following purification by preparative TLC, eluting with hexane/ethyl acetate (8:2), $R_f$ = 0.72 (hexane/ethyl acetate 8:2).

*(±)-N-(Cyclohex-2-en-1-yl)-4-methylbenzene-1-sulfonamide (**2g**).* By means of the general procedure under acidic conditions, 57 mg (49% yield) of the pure product was obtained as a white solid after purification by preparative TLC, eluting with hexane/ethyl acetate (6:4), $R_f$ = 0.72 (hexane/ethyl acetate 6:4).

*(±)-N-(Cyclohex-2-en-1-yl)acetamide (**2h**).* By means of the general procedure under acidic conditions, 26 mg (40% yield) of the pure product was obtained as a white solid after purification by preparative TLC, eluting with hexane/ethyl acetate (1:2), $R_f$ = 0.35 (hexane/ethyl acetate 1:2).

*(+)-(1R)-N-[(1R)-1-Phenylethyl]cyclohex-2-en-1-amine (**2i**).* By means of the general procedure under acidic conditions, 54 mg (58% yield) of the pure product was obtained as a pale-yellow oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:2).

$^1$H NMR $\delta$: 7.35 (2H, d, $^2J$ = 7.6; Ar($o$)); 7.32 (2H, t, $^2J$ = 7.6; Ar($m$)); 7.23 (1H, t, $^2J$ = 7.7; Ar($p$)); 5.82 (1H, d, $J_{2,3}$ = 10.4; H-2); 5.73 (1H, d, $J_{3,2}$ = 10.3; H-3); 4.02 (1H, q, $^3J$ = 6.6; CH−Ar); 3.02−2.98 (1H, m, H-1); 2.27 (1H, br s, NH); 2.03−1.87 (2H, m, H-4); 1.79−1.64 (2H, m, H-5, H-6); 1.51−1.38 (2H, m, H-4, H-5); 1.35 (3H, d, $^3J$ = 6.6; Me). $^{13}$C NMR $\delta$: 145.8 (Ar $C_q$); 129.4 (C-2); 128.7 (C-3); 128.4 (Ar($m$)); 126.9 (Ar($p$)); 126.7 (Ar($o$)); 55.0 (CH−Ar); 50.2 (C-1); 30.5 (C-6); 25.3 (C-4); 24.7 (Me); 20.5 (C-5). $[\alpha]_D^{20}$ = +160 ($c$ = 0.8; $CH_2Cl_2$). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{20}N$ 202.1596; found 202.1590. $R_f$ = 0.38 (ethyl acetate).

*(+)-(1S)-N-[(1R)-1-Phenylethyl]cyclopent-2-en-1-amine (**2j**).* By means of the general procedure under basic conditions, 36 mg (44% yield) of the pure product was obtained as a pale-yellow oil after purification by flash column chromatography, eluting with hexane/ethyl acetate (1:2).

$^1$H NMR $\delta$: 7.35 (2H, d, $^2J$ = 6.5; Ar($o$)); 7.32 (2H, t, $^2J$ = 7.4; Ar($m$)); 7.23 (1H, t, $^2J$ = 6.8; Ar($p$)); 5.78 (1H, dq, $J_{2,3}$ = 5.6; $J_{2,1}$ = $J_{2,4}$ = 2.0; H-2); 5.61 (1H, dq, $J_{3,2}$ = 5.6; $J_{3,1}$ = $J_{3,4}$ = 1.9; H-3); 3.89 (1H, q, $^3J$ = 6.6; CH−Ar); 3.68−3.63 (1H, m, H-1); 2.46−2.36 (1H, m, H-4); 2.25−2.09 (2H, m, H-4, H-5); 1.63−1.52 (2H, m, H-5, NH); 1.36 (3H, d, $^3J$ = 6.6; Me). $^{13}$C NMR $\delta$: 145.7 (Ar $C_q$); 133.6 (C-3); 132.3 (C-2); 128.4 (Ar($m$)); 126.93 (Ar($p$)); 126.86 (Ar($o$)); 62.0 (C-1); 56.2 (CH−Ar); 31.1, 31.0 (C-4, C-5); 24.7 (Me). $[\alpha]_D^{20}$ = +50 ($c$ = 0.5; $CH_2Cl_2$). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}N$ 188.1439; found 188.1434. $R_f$ = 0.37 (ethyl acetate).

*(±)-N-(Cyclopent-2-en-1-yl)-4-methylbenzene-1-sulfonamide (**2k**).* By means of the general procedure under acidic conditions, 71 mg (65% yield) of the pure product was obtained as a white solid after purification by preparative TLC, eluting with hexane/ethyl acetate (2:1), $R_f$ = 0.66 (hexane/ethyl acetate 2:1).

*(±)-N-{(1R,6S)-6-[(tert-Butyldimethylsilyl)oxy]cyclohex-2-en-1-yl}-N-[(4-fluorophenyl)methyl]acetamide (**2l**).* By means of the same procedure as used for **2b**, 75 mg (46% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (7:3).

$^1$H NMR $\delta$: 7.14 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.5; $J_{Ar(o),F}$ = 5.4; Ar($o$)); 7.02 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.5; Ar($m$)); 5.80−5.75 (1H, m, H-3); 5.26−5.22 (2H, m, H-2, H-1); 4.68 (1H, d, $^2J$ = 18.3, $CH_2$−Ar); 4.49 (1H, d, $^2J$ = 18.3, $CH_2$−Ar); 4.39−4.35 (1H, m, H-6); 2.33−2.25 (1H, m, H-4); 1.94 (3H, s, Ac ($CH_3$)); 1.88 (1H, dm, $^2J$ = 18.3; H-4); 1.77−1.74 (2H, m, H-5); 0.93 (9H, s, $^t$Bu TBDMS); 0.07 (3H, s, Me TBDMS); 0.04 (3H, s, Me TBDMS). $^{13}$C NMR $\delta$: 172.1 (Ac (C═O)); 161.7 (d, $^1J_{C,F}$ = 245; Ar($p$) (C−F)); 135.3 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 131.6 (C-3); 126.9 (d, $^3J_{C,F}$ = 8; Ar($o$)); 123.3 (C-2); 115.6 (d, $^2J_{C,F}$ = 21; Ar($m$)); 66.8 (C-6); 55.2 (C-1); 50.4 ($CH_2$−Ar); 28.8 (C-5); 25.9 (3 × Me $^t$Bu); 22.4 (Ac ($CH_3$)); 20.1 (C-1); 17.9 ($C_q$ $^t$Bu); −4.8 (Me TBDMS); −4.9 (Me TBDMS). Anal. Calcd for $C_{21}H_{32}FNO_2Si$: C 66.80; N 3.71; H 8.54. Found: C 66.68; N 3.65; H 8.22. $R_f$ = 0.56 (hexane/ethyl acetate 7:3).

*(±)-(1S,2R)-2-{[(4-Fluorophenyl)methyl]amino}cyclohex-3-en-1-ol (**2m**).* By means of the general procedure under acidic conditions, 62 mg (61% yield) of the pure product was obtained as a pale-yellow solid after purification by flash column chromatography, eluting with ethyl acetate.

$^1$H NMR $\delta$: 7.34 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.6; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 5.84 (1H, dtd, $J_{4,3}$ = 10.0; $J$ = 3.7; $J$ = 1.7; H-4); 5.62 (1H, ddt, $J_{3,4}$ = 10.0; $J$ = 3.6; $J$ = 2.0; H-3); 4.14 (2H, br s, NH, OH); 3.93 (1H, d, $^2J$ = 13.0; $CH_2$−Ar); 3.88 (1H, d, $^2J$ = 13.1; $CH_2$−Ar); 3.88−3.85 (1H, m, H-1); 3.22−3.19 (1H, m, H-2); 2.21−2.11 (1H, m, H-5); 2.04−1.95 (1H, m, H-5); 1.69 (2H, q, $J_{6,1}$ = $J_{6,5}$ = 6.2; H-6). $^{13}$C NMR $\delta$: 162.1 (d, $^1J_{C,F}$ = 245; Ar($p$) (C−F)); 135.6 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 130.1 (C-4); 129.8 (d, $^3J_{C,F}$ = 8; Ar($o$)); 126.4 (C-3); 115.4 (d, $^2J_{C,F}$ = 21; Ar($m$)); 65.5 (C-1); 55.2 (C-2); 51.2 ($CH_2$−Ar); 27.0 (C-6); 22.7 (C-5). IR (NaCl): 3400 (OH, NH st.). Mp = 72.5−73 °C. HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{17}FNO$ 222.1294; found 222.1289. $R_f$ = 0.33 (ethyl acetate).

*(−)-N-[(1R,6S)-6-Hydroxycyclohex-2-en-1-yl]-N-(prop-2-en-1-yl)-acetamide (**2n**).* By means of the same procedure as used for **2b**, 71 mg (84% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (1:2).

$^1$H NMR $\delta$: 5.99−5.95 (1H, m, H-3); 5.83 (1H, ddt, $J_{2',3'}$ = 16.2; $J_{2',3'}$ = 10.7; $J_{2',1'}$ = 5.1; H-2′); 5.54 (1H, br d, $J_{2,3}$ = 9.4; H-2); 5.23 (1H, br d, $J_{3',2'}$ = 11.1; H-3′); 5.19 (1H, br d, $J_{3',2'}$ = 18.0; H-3′); 4.98 (1H, br s, H-1); 4.16−4.10 (1H, m, H-6); 4.03 (2H, s, H-1′); 2.56 (1H, br s, OH); 2.37−2.01 (2H, m, H-4); 2.14 (3H, s, Ac ($CH_3$)); 1.83−1.77 (1H, m, H-5); 1.72−1.63 (1H, m, H-5). $^{13}$C NMR $\delta$: 174.6 (Ac (C═O)); 134.9 (C-2′); 132.3 (C-3); 123.7 (C-2); 116.2 (C-3′); 69.7 (C-6); 54.9 (C-1); 49.8 (C-1′); 26.5 (C-5); 22.7 (C-4); 22.3 (Ac ($CH_3$)). IR (NaCl): 1624 (C═O st.). HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{18}NO_2$ 196.1332; found 196.1325. $[\alpha]_D^{20}$ = −52 ($c$ = 0.2; $CH_2Cl_2$). $R_f$ = 0.38 (hexane/ethyl acetate 1:2).

*(±)-N-{(1S,6S)-6-[(tert-Butyldimethylsilyl)oxy]cyclohex-2-en-1-yl}-4-methylbenzene-1-sulfonamide (**2o**).* By means of the general procedure under acidic conditions, 117 mg (67% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (8:2).

$^1$H NMR $\delta$: 7.73 (2H, d, $^2J$ = 8.2; Ar($o$) Ts); 7.27 (2H, d, $^2J$ = 8.1; Ar($m$) Ts); 5.77−5.72 (1H, m, H-3); 5.29 (1H, dm, $J_{2,3}$ = 9.9; H-2); 4.52 (1H, d, $J_{NH,1}$ = 6.5; NH); 3.83−3.80 (1H, m, H-6); 3.48−3.44 (1H, m, H-1); 2.43 (3H, s, Me Ts); 2.14 (1H, dm, $^2J$ = 18.1; H-4); 1.93 (1H, dm, $^2J$ = 18.2; H-4); 1.74−1.57 (2H, m, H-5); 0.84 (9H, s, $^t$Bu TBDMS); 0.05 (3H, s, $CH_3$ TBDMS); 0.04 (3H, s, $CH_3$ TBDMS). $^{13}$C NMR $\delta$: 143.4 (Ar C−$SO_2$ Ts); 137.7 (Ar($p$) Ts); 131.2 (C-3); 129.7 (Ar($m$) Ts); 127.1 (Ar($o$) Ts); 124.0 (C-2); 70.2 (C-6); 54.8 (C-1); 26.8 (C-5); 25.7 (3 × Me $^t$Bu); 21.7 (C-4); 21.5 (Me Ts); 18.0 ($C_q$ $^t$Bu); −4.7 (Me TBDMS); −4.8 (Me TBDMS). Anal. Calcd for $C_{19}H_{31}NO_3SSi$: C 59.80; N 3.67; H 8.19; S 8.40. Found: C 59.80; N 3.58; H 8.26; S 8.21. $R_f$ = 0.53 (hexane/ethyl acetate 8:2).

*(±)-N-{(1R,5S)-5-[(tert-Butyldimethylsilyl)oxy]cyclopent-2-en-1-yl}-N-[(4-fluorophenyl)methyl]acetamide (**2p**).* By means of the procedure used for **2b**, 45 mg (29% yield) of the pure product was obtained as a colorless oil after purification by preparative TLC, eluting with hexane/ethyl acetate (7:3).

$^1$H NMR $\delta$: 7.16 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.6; $J_{Ar(o),F}$ = 5.4; Ar($o$)); 7.04 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.6; Ar($m$)); 5.83−5.79 (1H, m, H-3); 5.55−5.52 (1H, m, H-1); 5.45−5.42 (1H, m, H-2); 4.64 (1H, td, $J_{5,1}$ = $J_{5,4}$ = 6.4; $J_{5,4}$ = 2.3; H-5); 4.53 (1H, d, $^2J$ = 17.5; $CH_2$−Ar); 4.38 (1H, d, $^2J$ = 18.1; $CH_2$−Ar); 2.62 (1H, dm, $^2J$ = 17.3; H-4); 2.28 (1H, dm, $^2J$ = 17.2; H-4); 1.99 (3H, s, Ac ($CH_3$)); 0.91 (9H, s, $^t$Bu TBDMS); 0.08 (3H, s, Me TBDMS); 0.05 (3H, s, Me TBDMS). $^{13}$C NMR $\delta$: 171.9 (Ac (C═O)); 161.8 (d, $^1J_{C,F}$ = 245; Ar($p$) (C−F)); 135.0 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 132.4 (C-3); 127.9 (C-2); 127.1 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.6 (d, $^2J_{C,F}$ = 21; Ar($m$)); 71.2 (C-5); 62.9 (C-1); 49.9 ($CH_2$−Ar); 41.8 (C-4); 25.8 (3 × Me $^t$Bu); 22.2 (Ac ($CH_3$)); 17.9 ($C_q$ $^t$Bu); −4.9 (Me TBDMS); −5.1 (Me TBDMS). Anal. Calcd for $C_{20}H_{30}FNO_2Si$:



DOI: 10.1021/jo5029387
J. Org. Chem. 2015, 80, 3067−3074

C 66.08; N 3.85; H 8.32. Found: C 66.30; N 3.80; H 8.49. $R_f$ = 0.50 (hexane/ethyl acetate 7:3).

*(±)-(1S,2R)-2-{[(4-Fluorophenyl)methyl]amino}cyclopent-3-en-1-ol (**2q**).* By means of the general procedure under acidic conditions, 39 mg (41% yield) of the pure product was obtained as a yellow solid after purification by flash column chromatography, eluting with chloroform/methanol (95:5).

$^1$H NMR $\delta$: 7.32−7.26 (2H, m, Ar($o$)); 7.02 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.3; Ar( $m$)); 5.84−5.81 (1H, m, H-3); 5.62−5.59 (1H, m, H-4); 4.22−4.18 (1H, m, H-1); 3.82 (2H, s, $CH_2$−Ar); 3.70−3.67 (1H, m, H-2); 2.81 (2H, br s, NH, OH); 2.55 (1H, dd, $^2J$ = 17.3; $J$ = 3.9; H-5); 2.34 (1H, d, $^2J$ = 17.2; H-5). $^{13}$C NMR $\delta$: 162.1 (d, $^1J_{C,F}$ = 245; Ar($p$) (C−F)); 135.5 (d, $^4J_{C,F}$ = 3; Ar $C_q$); 132.0 (C-3); 130.5 (C-4); 129.7 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.4 (d, $^2J_{C,F}$ = 21; Ar($m$)); 68.6 (C-1); 65.5 (C-2); 52.2 ($CH_2$−Ar); 40.9 (C-5). IR (NaCl): 3300 (OH, NH st.). Mp = 41.5−42 °C. HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd for $C_{12}H_{15}FNO$ 208.1138; found 208.1132. $R_f$ = 0.44 (chloroform/methanol 9:1).

*(±)-(1S,2R)-2-{[(4-Fluorophenyl)methyl]amino}cyclohept-3-en-1-ol (**2r**).* By means of the general procedure under acidic conditions, 83 mg (77% yield) of the pure product was obtained as a pale-yellow oil after purification by flash column chromatography, eluting with chloroform/methanol (95:5).

$^1$H NMR $\delta$: 7.30 (2H, dd, $J_{Ar(o),Ar(m)}$ = 8.6; $J_{Ar(o),F}$ = 5.5; Ar($o$)); 7.01 (2H, t, $J_{Ar(m),Ar(o)}$ = $J_{Ar(m),F}$ = 8.7; Ar($m$)); 5.96 (1H, dddd, $J_{4,3}$ = 11.3; $J_{4,5}$ = 7.3; $J_{4,5}$ = 5.7; $J_{4,2}$ = 1.7; H-4); 5.50 (1H, br dd, $J_{3,4}$ = 10.9; $J_{3,2}$ = 4.4; H-3); 3.91−3.88 (1H, m, H-1); 3.85 (1H, d, $^2J$ = 13.1; $CH_2$−Ar); 3.77 (1H, d, $^2J$ = 13.1; $CH_2$−Ar); 3.47−3.45 (1H, m, H-2); 2.30−2.15 (2H, br s, OH, NH); 2.18 (1H, dtd, $^2J$ = 15.3; $J_{5,4}$ = $J_{5,6}$ = 7.6; $J_{5,6}$ = 2.9; H-5); 2.11−2.06 (1H, m, H-5); 2.02 (1H, dtd, $^2J$ = 14.1; $J$ = 7.0; $J$ = 3.0; H-7); 1.77 (1H, ddt, $^2J$ = 14.1; $J$ = 10.5; $J$ = 3.3; H-7); 1.61 (1H, dtt, $^2J$ = 13.6; $J$ = 10.3; $J$ = 3.1; H-6); 1.49 (1H, ddt, $^2J$ = 14.1; $J$ = 7.1; $J$ = 3.5; H-6). $^{13}$C NMR $\delta$: 162.0 (d, $^1J_{C,F}$ = 245; Ar($p$) (C−F)); 135.7 (Ar $C_q$); 133.5 (C-4); 131.1 (C-3); 129.8 (d, $^3J_{C,F}$ = 8; Ar($o$)); 115.3 (d, $^2J_{C,F}$ = 21; Ar($m$)); 69.5 (C-1); 61.2 (C-2); 50.9 ($CH_2$−Ar); 35.4 (C-5); 28.6 (C-7); 21.0 (C-6). HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd for $C_{14}H_{19}FNO$ 236.1445; found 236.1441. $R_f$ = 0.64 (chloroform/methanol 9:1).

*(+)-(3aS,4R,7aR)-N-[(4-Methoxyphenyl)methyl]-2,2-dimethyl-3a,4,7,7a-tetrahydro-2H-1,3-benzodioxol-4-amine (**2s**).* By means of the general procedure under acidic conditions, 83 mg (68% yield) of the pure product was obtained as a yellow oil after purification by flash column chromatography, eluting with chloroform/methanol (95:5).

$^1$H NMR $\delta$: 7.26 (2H, d, $^2J$ = 8.6 Hz; Ar($o$)); 6.86 (2H, d, $^2J$ = 8.6; Ar($m$)); 5.82−5.74 (2H, m, H-5, H-6); 4.32 (1H, td, $J_{7a,3a}$ = $J_{7a,7}$ = 6.8; $J_{7a,7}$ = 5.3; H-7a); 4.00 (1H, t, $J_{3a,7a}$ = $J_{3a,4}$ = 6.5; H-3a); 3.88 (1H, d, $^2J$ = 13.1; $CH_2$−Ar); 3.81 (1H, d, $^2J$ = 13.2; $CH_2$−Ar); 3.79 (3H, s, −OMe); 3.25−3.23 (1H, m, H-4); 2.62 (1H, ddd, $^2J$ = 16.0; $J_{7,7a}$ = 6.7; $J_{7,6}$ = 5.0; H-7); 2.21−2.13 (1H, m, H-7); 1.86 (1H, s, NH); 1.41 (3H, s, Me); 1.35 (3H, s, Me). $^{13}$C NMR $\delta$: 158.7 (Ar($p$) (C−OMe)); 132.4 (Ar $C_q$); 129.9 (C-6); 129.4 (Ar($o$)); 125.7 (C-5); 113.8 (Ar($m$)); 108.2 (C-2); 79.2 (C-3a); 72.6 (C-7a); 57.0 (C-4); 55.3 (−OMe); 51.0 ($CH_2$−Ar); 28.7 (C-7); 27.5 (Me); 25.2 (Me). $[\alpha]_D^{20}$ = +45 ($c$ = 0.5; $CH_2Cl_2$). HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd for $C_{17}H_{24}NO_3$ 290.1756; found 290.1751. $R_f$ = 0.71 (chloroform/methanol 9:1).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra of all products, X-ray structures and crystallographic information files for compounds (1*R*,6*R*)-**1i** and (1*R*,5*R*)-**1j**, and a table summarizing the results of other Wharton reactions with compounds **1a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: maycock@itqb.unl.pt.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

S.S. and P.R. thank the Fundação para a Ciência e Tecnologia for Grants SFRH/BD/84309/2012 and SFRH/BD/27423/2006. This work was supported by FCT through Grant PEst-OE/EQB/LA0004/2011 and Projects PTDC/QUI-QUI/104056/2008 and POCI/QUI/62794/2004. The NMR spectrometers are part of The National NMR Facility, supported by Fundação para a Ciência e a Tecnologia (RECI/BBB-BQB/0230/2012). We thank the Analytical Services Unit (ASU) at ITQB for providing CHNS elemental analyses.

## ■ REFERENCES

(1) Wharton, P.; Bohlen, D. *J. Org. Chem.* **1961**, *26*, 3615.
(2) Li, J. J.; Corey, E. J. In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; John Wiley & Sons: Hoboken, NJ, 2010; p 85.
(3) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
(4) (a) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242. (b) Chen, G.; Sasaki, M.; Yudin, A. K. *Tetrahedron Lett.* **2006**, *47*, 255.
(5) Jiang, H.; Holub, N.; Jørgensen, K. A. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20630.
(6) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron Lett.* **2002**, *43*, 4329.
(7) Dupuy, C.; Luche, J. L. *Tetrahedron* **1989**, *45*, 3437.
(8) Thirumoorthi, A.; Elango, K. P. *J. Chem. Sci.* **2007**, *119*, 289.
(9) The corresponding free amine of **2c** oxidized rapidly and that of **2d** was very volatile. Therefore, these products were isolated as their acetamides.
(10) Basic and acidic conditions were tried, and the best results are reported in the table.
(11) (a) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367. (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
(12) Vicario, J. L.; Badia, D.; Carillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219.
(13) The free amines were difficult to purify because during chromatography the product partially lost the TBDMS group.
(14) Barros, M. T.; Matias, P. M.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321.
(15) (a) Kurbanoğlu, N. I.; Çelik, M.; Kilic, H.; Alp, C.; Şahin, E.; Balci, M. *Tetrahedron* **2010**, *66*, 3485. (b) Shih, T.-L.; Li, H.-Y.; Ke, M.-S.; Kuo, W.-S. *Synth. Commun.* **2008**, *38*, 4139.
(16) (a) Johnson, D. S.; Li, J. J. In *The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; John Wiley & Sons: Hoboken, NJ, 2006; p 95. (b) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839.
(17) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; Butterworth-Heinemann: Oxford, U.K., 2003.
(18) Sheldrick, G. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.
(19) Farrugia, L. *J. Appl. Crystallogr.* **1999**, *32*, 837.



DOI: 10.1021/jo5029387
*J. Org. Chem.* 2015, 80, 3067−3074