JOC The Journal of Organic Chemistry

Article

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Competitive Ring Expansion of Azetidines into Pyrrolidines and/or Azepanes

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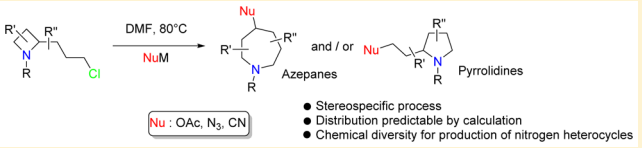
Supporting Information

ABSTRACT: Azetidines fitted with a 3-hydroxypropyl side chain at the 2-position undergo intramolecular *N*-alkylation after activation of the primary alcohol, and the produced 1-azonia-bicyclo[3.2.0]heptane is opened by different nucleophiles (cyanide, azide, or acetate anions) to produce mixtures of ring expanded pyrrolidines and azepanes, or a unique type of compound. Distribution of produced five- or seven-membered rings depends on the substitution pattern on the azetidine ring and on its side chain, together with the nature of the nucleophile used in the expansion process. Observed regioselectivities for nucleophilic opening are rationalized by quantum mechanical DFT calculations and are in good agreement with experimental results.



INTRODUCTION

Because of their important ring strain, azetidines have emerged as privileged scaffolds for ring expansion and ring opening processes,[1] but when *N*-alkyl azetidines are involved in such reactions, opening of the four-membered ring by a nucleophile requires activation of the amino moiety by a Lewis or Brønsted acid. Alternatively, preformed azetidinium ions, as easy to handle forms of "activated" azetidines,[2] react smoothly with a wide array of nucleophiles to afford the corresponding ring opened product with predictable regioselectivity and through a clean S_N2 mechanism.[3] The intramolecular versions of such a reaction have been studied only quite recently, essentially due to the lack of efficient synthetic routes to the required azetidinic substrates. Thus, 4−5 ring expansions readily occur to give 3-substituted pyrrolidines in a stereospecific manner,[4] which is also the case for 4−6 ring expansions, leading to piperidines, which were lately described by D'hooghe et al.[5] This article reports our investigation on such processes involving 4−7 ring expansions, and leading to either azepanes[6] and/or pyrrolidines through a competitive process. The search for parameters in order to favor one process over the other is put in light herein through the examination of the scope of this reaction, and is guided by theoretical calculations (Scheme 1).

RESULTS AND DISCUSSION

The azetidines required to conduct this ring expansion study were prepared from 2-hydroxymethyl azetidines **1**−**3**[7] through a two-step sequence involving (i) a one-pot Swern/Wittig olefination, yielding unsaturated esters **4**−**6** with high (*E*)-selectivity, followed by (ii) a reduction with $LiAlH_4$, affording directly azetidines **7**, **8**, **10** fitted with the required propanol side chain through reduction of both the ester and the alkene.[8] In the case of ester **5**, this reduction afforded an unseparable mixture of **8** and allylic alcohol **9**, and compound **8** was separated from **9** via its acetate. Alternatively, conjugate addition of thiophenol on ester **4** gave the corresponding diastereoisomeric adducts **11a** and **11b** with modest diastereoselectivity, which could be separated and were converted to alcohols **12a** and **12b** in good yields. Despite our efforts, we were unable to determine at this stage the relative configurations of these compounds, and it was tentatively indirectly assigned later, based on their different behavior in the ring expansion process. All of these compounds were selected in order to examine the influence of the substitution pattern on the projected ring expansion on (i) the nitrogen substituent with **8**, (ii) the azetidine ring with **10**, and (iii) the pending side chain with **12a,b** (Scheme 2). These hydroxylated azetidines were next engaged in the ring expansion process.

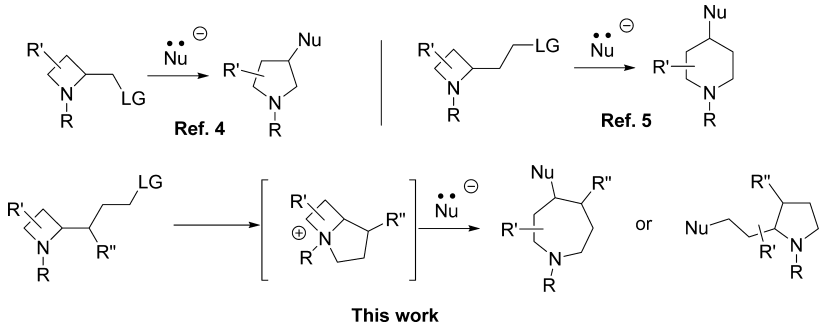
The ring expansion process was first conducted with **7**. To this end, this alcohol was transformed into a primary chloride by reaction with thionyl chloride in CH_2Cl_2, and the produced compound was found sufficiently stable to be isolated through alkaline workup with Na_2CO_3. It was immediately reacted with 10 equiv of the required nucleophile (sodium acetate, potassium cyanide, or sodium azide) in DMF at 80 °C, to afford variable ratios of pyrrolidines **13**−**15** and azepanes **16**−**18** as unseparable compounds (Scheme 3):

This first set of experiments demonstrates the feasibility of this ring expansion, which, contrary to its lower homologues

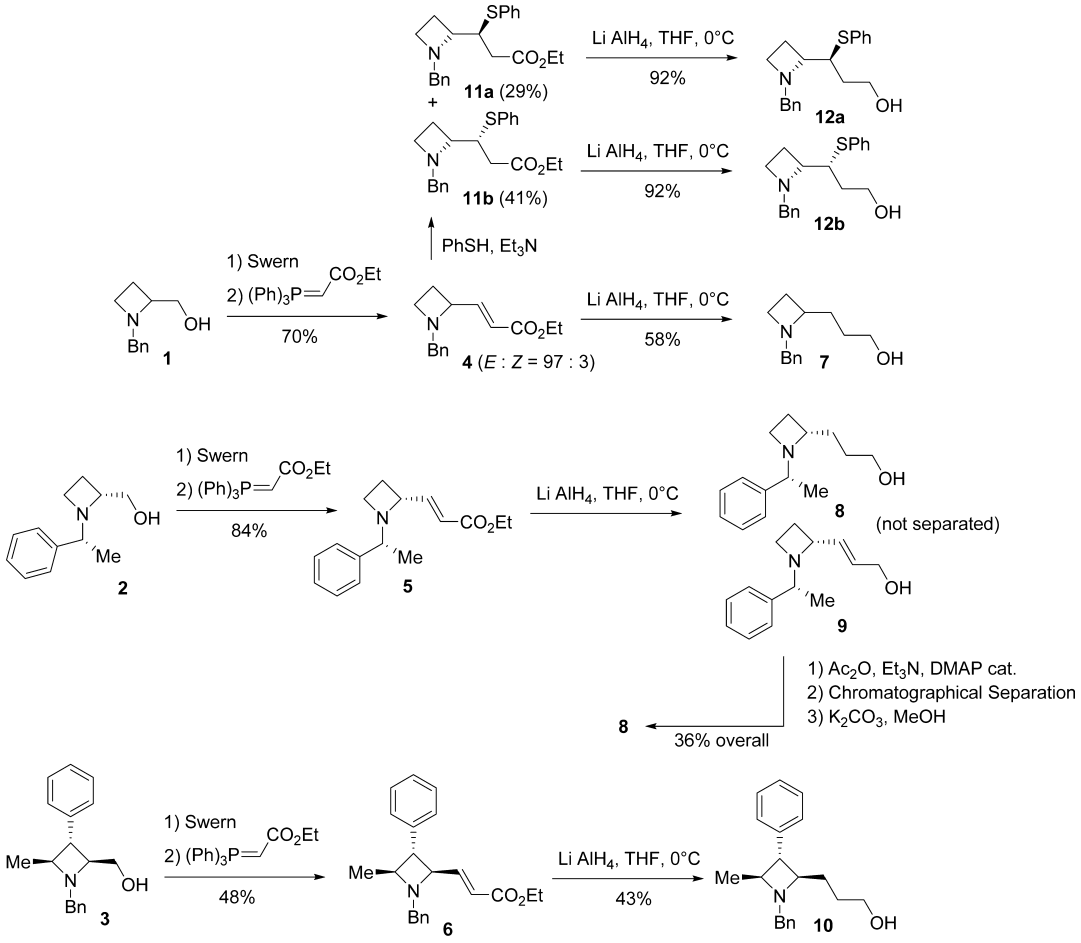
Received: June 1, 2016
Published: July 11, 2016

DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685

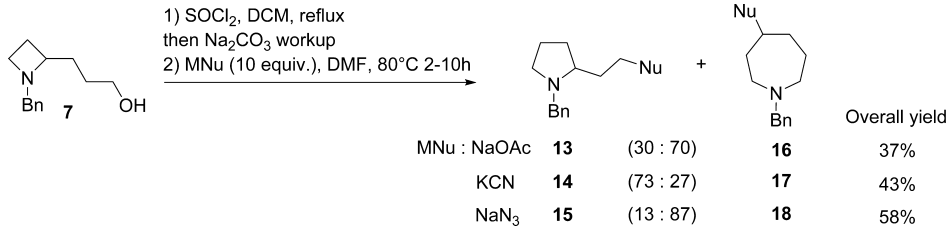
Scheme 1. Intramolecular Ring Expansions of Azetidines Leading to Five- to Seven-Membered Rings



Scheme 2. Structures and Yields of Prepared Azetidines 7, 8, 10, 12a, and 12b, Substrates for Ring Expansion Study



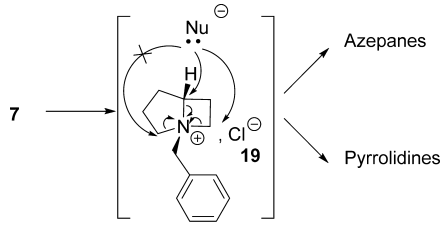
Scheme 3. Ring Expansion Process of 7 Affords Variable Amounts of Pyrrolidines and Azepanes Depending on the Nature of the Nucleophile



mentioned in Scheme 1, is not a totally regioselective process, but leads to competitive nucleophilic substitution at the bridgehead carbon and at the methylene of the four-membered ring in the intermediate 1-azonia-bicyclo[3.2.0]heptane **19**[9] (Scheme 4). This distribution results from a kinetic control, considering the exothermicity of this reaction (vide supra for

DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685

Scheme 4. Intermediate Bicyclic Ammonium Is Opened at the Bridgehead Carbon and at the Methylene Carbon of the Four-Membered Ring

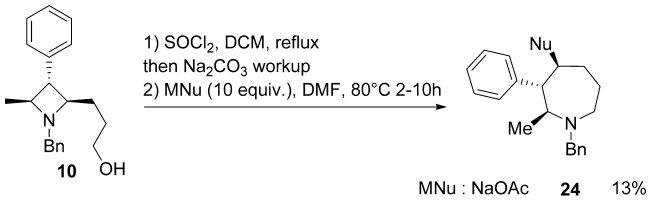


calculations). We have also checked in the case of **13**:**16** mixture, that the ratio is not modified by prolonged heating in DMF. It should be noted that the other possible product, resulting from nucleophilic substitution at the methylene of the five-membered ring that would lead to an azetidine, could not be detected in the crude reaction mixture. Worthy of note also is that no chlorinated ring expanded products were detected. Though the produced nitrogen heterocycles could not be separated by chromatography, their quantification by ^{1}H NMR in these mixtures is facilitated by the fact that diastereotopic N-CH_2Ph protons appear almost as a singlet in azepanes and as split AB systems in pyrrolidines.[6c]

Next was studied the influence of the substitution at the benzylic position of the azetidine with (*R*)-phenylethylamine-derived azetidine **8**. This compound was treated following the same conditions and afforded the ring expanded products with different distributions compared with the previous case. In fact, acetate and azide anions led uniquely to azepanes **20** and **23** as judged by examination of the crude mixture by NMR, while cyanide ion roughly behaved similarly compared with the previous case, yielding a mixture of pyrrolidine **21** and azepane **22**, that could be conveniently separated by flash chromatography (Scheme 5). The production of unique diastereoisomers here denotes the stereospecificity of this ring expansion process. The higher ratio of azepane production in the cases of acetate and azide anions is in accordance with the intervention of an intermediate bicyclic ammonium ion, because the added methyl group at the benzylic position encumbers the space needed for the S_N2 process at the methylene carbon that would lead to pyrrolidines.

When ephedrine-derived azetidine **10** was tested in this reaction, the ring expansion process became totally regioselective, and only azepanes **24**−**26** could be detected and isolated, albeit in modest yields, in the case of cyanide and acetate anions. This increased selectivity appears to be quite logical since S_N2 mechanisms are known to be disfavored with a higher degree of substitution on the reacting carbon atom and would thus disfavor in this case the nucleophilic attack on the methyl substituted carbon in the intermediate bicyclic ammonium that would lead to the pyrrolidine (Scheme 6).

Scheme 6. Methyl Substitution at the Carbon Atom Totally Inhibits the Competitive Attack by the Nucleophile Leading to Pyrrolidines and Thus Favors Azepane Production



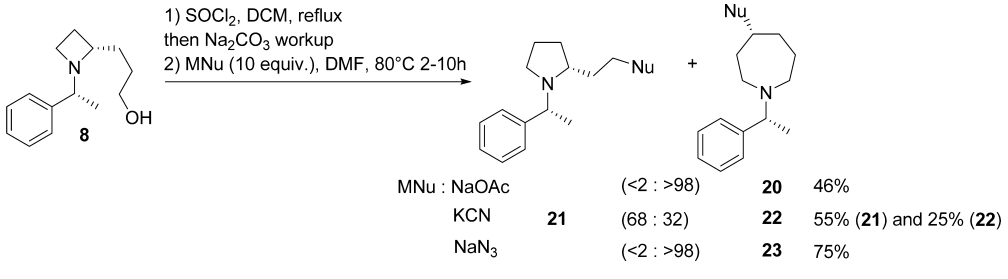
MNu :			
NaOAc	**24**	13%	
KCN	**25**	26%	
NaN_3	**26**	60%	

Finally, diastereoisomers **12a**,**b** were engaged in the ring expansion reaction, using NaOAc and NaN_3 as nucleophiles, and these diastereoisomers displayed a striking difference of reactivity. Stereoisomer **12b** led to the formation of a 1/1 ratio of pyrrolidines **27**, **29** and azepanes **28**, **30**, whereas **12a** led exclusively to pyrrolidines **31**, **32** (Scheme 7). This clear-cut difference in reactivity gives indirect evidence to assign the relative configurations in **12a**,**b**. Indeed, in the rigid bicyclic ammonium ion **33** derived from **12a**, the ideal trajectory of the incoming nucleophile leading to the azepane, and respecting that the S_N2 mechanism is hampered by the thiophenyl group and therefore, only pyrrolidines are produced. This is not the case in bicyclic ammonium ion **34** derived from epimer **12b**, in which 50% of the S_N2 reaction occurs at the bridgehead carbon to produce azepanes (Figure 1). Compounds **12a** and **12b** were thus assigned as *anti* and *syn*, respectively.

PCM/PBE0/6-311+G(d,p) calculations (Table 1) were conducted in DMF solution in order to simulate the nucleophilic opening of intermediate **19** with our selected nucleophiles (acetate, cyanide, and azide anions) and to determine the relative energies of transition states (TSs) for each process (1−3) (Figure 2, Figures S1−S3 in the Supporting Information). The most energetically stable ionic pair (IP-3) was taken as reference.

The calculations showed that, in DMF solution, the minimal energy paths leading to four-, five -, and seven-membered cyclic products are one-step exothermic reactions. Products **5C** correspond to pyrrolidines **13**−**15**, products **7C** correspond to azepanes **16**−**18**, and additional calculations were done for four-membered products **4C**, which correspond to azetidine **7**. Ionic pairs **IP-1**, **IP-2**, **IP-3** correspond to systems **19** (vide supra). Obtained data are in good agreement with experimental results and predict the distribution of pyrrolidines and azepanes depending on the nature of the incoming nucleophile. Thus, in

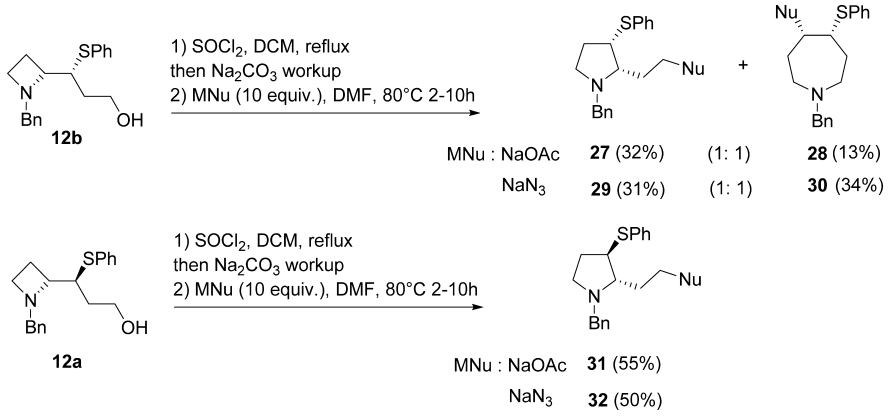
Scheme 5. Substitution at the Benzylic Position Favors Production of Azepanes When Acetate and Azide Anions Are Involved



MNu :				
NaOAc		(<2 : >98)	**20**	46%
KCN	**21**	(68 : 32)	**22**	55% (**21**) and 25% (**22**)
NaN_3		(<2 : >98)	**23**	75%

DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685

Scheme 7. Epimeric Azetidines 12a,b Display Drastically Different Reactivity



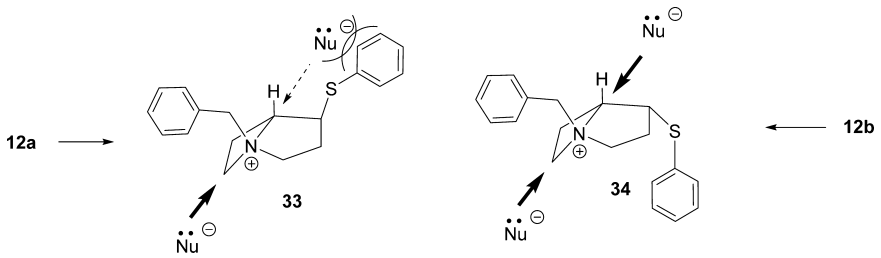


Figure 1. Bicyclic ammonium **33** exclusively leads to pyrrolidines, whereas epimer **34** leads to mixtures of pyrrolidines and azepanes.

Table 1. Total Energies Including Zero-Point Energy Correction E_0 + ZPE (a.u.) and Relative Energies ΔE (kcal/mol) of the Structures Involved in the Isomerization Processes (Depicted in Figure 2 and Calculated at the PCM/PBE0/6-311+G(d,p) Level of Theory in DMF Solution). The Most Stable Ionic Pair (IP-3) Was Taken as Reference

	(a) X = −OCOCH$_3$		(b) X = −N$_3$		(c) X = −CN	
	E_0 + ZPE	ΔE	E_0 + ZPE	ΔE	E_0 + ZPE	ΔE
IP-3	−788.381217	0	−724.168169	0	−652.850214	0
TS-3	−788.336819	27.9	−724.121355	29.4	−652.803966	29.0
4-C	−788.380353	0.5	−724.166954	0.8	−652.885521	−22.2
IP-2	−788.380846	0.2	−724.165623	1.6	−652.850462	−0.2
TS-2	−788.352946	17.7	−724.137831	19.0	−652.82287	17.2
5-C	−788.405492	−15.2	−724.192698	−15.4	−652.910942	−38.1
IP-1	−788.379405	1.1	−724.167705	0.3	−652.850294	−0.1
TS-1	−788.355076	16.4	−724.140182	17.6	−652.82219	17.6
7-C	−788.398584	−10.9	−724.184943	−10.5	−652.90029	−31.4

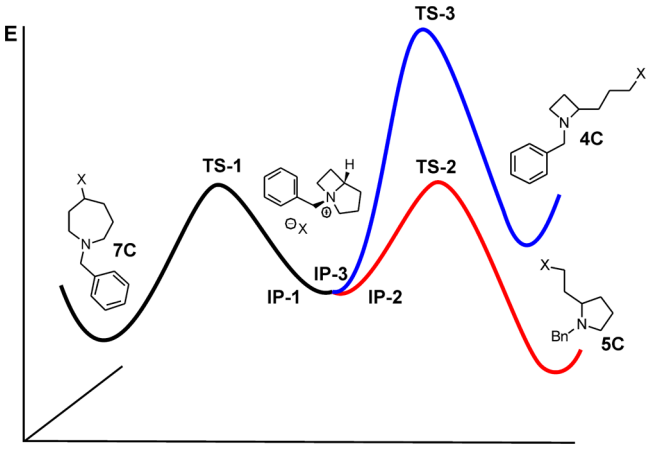


Figure 2. Energy profiles in DMF solution (PCM/PBE0/6-311+G-(d,p) calculations). The most energetically stable ionic pair (**IP-3**) was taken as reference.

the case of the acetate anion, transition state **TS-1** leading to azepane **16** lies about 1.3 kcal·mol^{-1} under the one leading to the pyrrolidine **13**, (**TS-2**), which represents a value of 6.3 for rate constants ratio at 80 °C (2.3 for experimental data) and a distribution of 14:86 in favor of the azepane (30:70 for experimental data). In the case of the cyanide anion, the transition state for production of azepane **17** lies about 0.4 kcal·mol^{-1} above the one leading to pyrrolidines **14**, which represents a value of 1.8 for rate constants ratio at 80 °C (2.7 for experimental data) and a distribution of 64:36 favoring now the pyrrolidine (73:27 for experimental data). Finally, in the case of the azide anion, calculations accurately predict the preferred formation of the azepane over the pyrrolidine (12:88), which perfectly fits with experimental data (13:87). It should be noted that these theoretical data were obtained in simulated DMF solution, and calculations run in simulated DMSO instead of DMF gave roughly similar results (see the SI).

DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685

CONCLUSIONS

In conclusion, we have studied in depth the ring expansion of azetidines into azepanes and/or pyrrolidines through a 1-azonia-bicyclo[3.2.0]heptane intermediate and we have delineated the main parameters to favor production of azepanes or pyrrolidines in this nonselective ring expansion process. Considering the easy access to 2-functionalized azetidines in enantiomerically pure form, this new ring expansion is of interest for the production of new pyrrolidines and azepanes which are of high relevance in medicinal chemistry.[10]

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a spectrometer at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are reported in hertz and rounded up to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septuplet (sep), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ_H = 7.26 ppm for the signal of the residual $CHCl_3$ in $CDCl_3$ and δ_C = 77.0 ppm for the central signal of $CDCl_3$). Assignments for signals from ^{1}H and ^{13}C in the NMR spectra were validated by two-dimensional correlated spectroscopy (2D COSY) and heteronuclear multiple bond correlation (HMBC). High-resolution mass spectra (HR-MS) were obtained on a Q-TOF mass spectrometer. IR data were collected with an ATR-FT-IR spectrometer. All reactions were carried out under argon. Column chromatography was performed on silica gel (230−400 mesh) with use of various mixtures of CH_2Cl_2 (DCM), petroleum ether (35−60 °C fraction) (PE), EtOAc, and methanol. TLC was performed on Kieselgel 60 F254 plates. Melting points are uncorrected. THF was distilled under argon from sodium using benzophenone as indicator. Dichloromethane was distilled from calcium hydride. Isomeric ratios were determined by NMR analysis of crude reaction mixtures before purification.

General Procedure for Swern Oxidation/Wittig Reaction. To a solution of dimethyl sulfoxide (2 equiv) in dichloromethane (1 mL/mmol) cooled at −78 °C was added oxalyl chloride (1.5 equiv). The solution was stirred at −78 °C for 15 min before adding dropwise a solution of azetidine **1**−**3** (1 equiv) in dichloromethane (1 mL/mmol). After stirring at −78 °C for 30 min, triethylamine (4 equiv) was added to the reaction mixture. After 10 min, a solution of [(ethoxycarbonyl)methylene]triphenylphosphorane (2 equiv) in dichloromethane (1.5 mL/mmol) cooled at −78 °C was added dropwise to the reaction mixture. The mixture was allowed to warm to room temperature and stirred for 1 h. Water was added to the reaction mixture. The aqueous layer was separated and extracted twice with dichloromethane. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Ethyl 3-(1-Benzylazetidin-2-yl)prop-2*E*-enoate (*E*)-4. Eluent for flash chromatography: EtOAc/PE 10/90. Yield: 1.88 g, 68%. Yellow oil. R_f: 0.44 (EP/EtOAc 75/25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.23 (m, 5H, Ph), 6.94 (dd, J = 5.7 and 15.6 Hz, 1H, H_β), 5.96 (d, J = 15.6 Hz, 1H, H_α), 4.19 (q, J = 6.9 Hz, 2H, OCH_2), 3.81 (m, 2H, 2-H and NC*H*HPh), 3.41 (d, J = 12.9 Hz, 1H, NCH*H*Ph), 3.33−3.27 (m, 1H, 4-H), 2.94−2.86 (m, 1H, 4′-H), 2.25−2.15 (m, 1H, 3-H), 2.12−2.00 (m, 1H, 3′-H), 1.29 (t, J = 6.9 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (CO), 148.7 (C_β), 137.6 (C_q), 128.8, 128.3, 127.1 (CH_{Ar}), 120.7 (C_α), 65.4 (C_2), 62.0 (NCH_2Ph), 60.3 (OCH_2), 51.3 (C_4), 24.8 (C_3), 14.3 (Me) ppm. IR: ν_{max} = 2982, 2959, 2826, 1714, 1654, 1453, 1366, 1294, 1261, 1159, 1038, 979, 734, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{15}H_{20}NO_2$ $[MH]^+$: 246.1494; found: 246.1491.

Ethyl 3-(1-Benzylazetidin-2-yl)prop-2*Z*-enoate (*Z*)-4. Eluent for flash chromatography: EtOAc/PE 10/90. Yield: 58 mg, 2%. Yellow oil. R_f: 0.26 (EP/EtOAc 75/25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29−7.22 (m, 5H, Ph), 6.26 (dd, J = 7.2 and 11.7 Hz, 1H, H_β), 5.57 (d, J = 11.7 Hz, 1H, H_α), 4.75−4.67 (m, 1H, 2-H), 4.16 (q, J = 7.2 Hz, 2H, OCH_2), 3.65 (d, part of AB syst., J = 12.6 Hz 1H, NC*H*HPh), 3.58 (d, part of AB syst., J = 12.6 Hz 1H, NCH*H*Ph), 3.38−3.25 (m, 1H, 4-H), 2.97−2.89 (m, 1H, 4′-H), 2.41−2.32 (m, 1H, 3-H), 2.08−1.96 (m, 1H, 3′-H), 1.29 (t, J = 7.2 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9 (CO), 152.3 (C_β), 137.8 (C_q), 129.0, 128.4, 127.1 (CH_{Ar}), 118.6 (C_α), 63.5 (C_2), 62.9 (NCH_2Ph), 60.0 (OCH_2), 51.9 (C_4), 24.8 (C_3), 14.3 (Me) ppm. IR: ν_{max} = 2978, 2957, 2931, 2824, 2824, 1715, 1637, 1453, 1412, 1363, 1184,1028, 819, 731, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{15}H_{20}NO_2$ $[MH]^+$: 246.1494; found: 246.1491.

Ethyl [1(1*R*),2*R*]-3-[1-(1-Phenyl-ethyl)-azetidin-2-yl]prop-2*E*-enoate 5. Eluent for flash chromatography: EtOAc/PE 5/95. Yield: 6.13 g, 84%. Yellow oil. R_f: 0.50 (PE/EtOAc 95/5), $[\alpha]_D^{20}$: + 104 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.12 (m, 6H, Ph and H_β), 6.17 (d, J = 15.6 Hz, 1H, H_α), 4.24 (bs, 2H, OCH_2), 3.81 (bs, 1H, 2-H), 3.41 (bs, 1H, C*H*CH_3), 3.16−3.01 (m, 1H, 4-H), 2.74−2.70 (m, 1H, 4′-H), 2.17−2.14 (m, 1H, 3-H), 2.00−1.92 (m, 1H, 3′-H), 1.33 (bs, 3H, CH_2CH_3), 1.17 (bs, 3H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (CO), 151.1 (C_β), 143.4 (C_q), 128.3, 127.3, 127.0 (CH_{Ar}), 120.6 (C_α), 68.3 ($NCHCH_3$), 64.8 (C_2), 60.3 (OCH_2), 50.0 (C_4), 23.8 (C_3), 21.9 ($NCHCH_3$), 14.3 (CH_2CH_3) ppm. IR: ν_{max} = 2970, 2934, 2832, 1715, 1655, 1450, 1369, 1261, 1162, 1029, 981, 759 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{16}H_{22}NO_2$ $[MH]^+$: 260.1651; found: 260.1651.

Ethyl [2*R*,3*S*,4*S*]-3-[1-(1-Phenyl-ethyl)-3-phenyl-4-methyl-azetidin-2-yl]prop-2*E*-enoate 6. Eluent for flash chromatography: EtOAc/PE 10/90. Yield: 1.68 g, 48%. Yellow oil. R_f: 0.18 (DCM/MeOH 95/5). $[\alpha]_D^{20}$: + 26 (c 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.17 (m, 10H, Ph), 7.00 (dd, J = 6.0 and 15.6 Hz, 1H, H_β), 5.98 (d, J = 15.6 Hz, 1H, H_α), 4.18 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.81 (d, part of AB syst., J = 15.6 Hz, 1H, NC*H*HPh), 3.71−3.62 (m, 2H, NCH*H*Ph and 2-H), 3.29−3.24 (m, 1H, 4-H), 2.98 (m, 1H, 3-H), 1.29 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.08 (d, J = 6.0 Hz, 3H, $NCHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (CO), 148.1 (C_β), 139.7, 137.6 (C_q), 129.5, 128.5, 128.2, 127.2, 126.8 (CH_{Ar}), 121.6 (C_α), 69.2 (C_2), 66.2 (C_4), 61.1 (NCH_2), 60.3 (OCH_2), 51.9 (C_3), 21.1 ($CHCH_3$), 14.2 ($NCHCH_3$) ppm. IR: ν_{max} = 3092, 3060, 3028, 2976, 2921, 2858, 2831, 2800, 1715, 1652, 1495, 1453, 1394, 1264, 1160, 1029, 980, 746, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{22}H_{26}NO_2$ $[MH]^+$: 336.1964; found: 336.1968.

Synthesis of Products 11a and 11b. To a solution of compound **4** (600 mg, 2.45 mmol) in dichloromethane (2 mL) at 0 °C was added triethylamine (0.66 mL, 4.9 mmol) and thiophenol (0.5 mL, 4.9 mmol). The mixture was allowed to warm to room temperature, stirred for 16 h, and diluted with dichloromethane (50 mL). The layer was successively washed with aqueous 2 M NaOH solution (20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

3-(*R)-(1-Benzylazetidin-2-yl)-3-(*S**)-phenylsulfanyl-propionic Acid Ethyl Ester 11a.** Eluent for flash chromatography: EtOAc/PE 10/90. Yield: 0.252 g, 29%. Yellow oil. R_f: 0.42 (EP/EtOAc 90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, J = 6.9 Hz, 2H, Ph), 7.33−7.21 (m, 8H, Ph), 4.08 (q, J = 7.2 Hz, 2H, OCH_2), 3.92 (d, part of AB syst., J = 12.9 Hz, 1H, NC*H*HPh), 3.65−3.58 (m, 1H, C*H*SPh), 3.51−3.46 (m, 1H, 2-H), 3.42 (d, part of AB syst., J = 12.9 Hz, 1H, NCH*H*Ph), 3.26−3.20 (m, 1H, 4-H), 2.99 (dd, 1H, J = 15.9 Hz and J = 6 Hz, C*H*HCO_2Et), 2.77−2.69 (m, 1H, 4′-H), 2.44 (dd, 1H, J = 15.9 Hz and J = 8.1 Hz, CH*H*CO_2Et), 2.01−1.92 (m, 2H, 3-H and 3′-H), 1.22 (t, 3H, J = 7.2 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (CO), 138.1, 134.6 (C_q), 131.8, 128.9, 128.6, 128.2, 126.9 (CH_{Ar}), 67.5 (C_2), 62.2 (NCH_2Ph), 60.5 (OCH_2), 50.2 (C_4), 47.4 (CHSPh), 35.7 (CH_2CO), 20.1 (C_3), 14.1 (CH_3) ppm. IR: ν_{max} = 3061, 2978, 2931, 2829, 2789, 1730, 1582, 1475, 1452, 1438, 1371, 1151, 737, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{26}NO_2S$ $[MH]^+$: 356.1684; found: 356.1680.

3-(*R)-(1-Benzylazetidin-2-yl)-3-(*R**)-phenylsulfanyl-propionic Acid Ethyl Ester 11b.** Eluent for flash chromatography:

DOI: 10.1021/acs.joc.6b01325
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EtOAc/PE 10/90. Yield: 0.356 g, 41%. Yellow oil. R_f: 0.35 (EP/EtOAc 90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.8 Hz, 2H, Ph), 7.44−7.24 (m, 8H, Ph), 4.18−4.09 (m, 2H, OCH_2), 3.90 (d, part of AB syst., J = 12.9 Hz, 1H, NC*H*HPh), 3.57−3.51 (m, 1H, C*H*SPh), 3.43 (d, part of AB syst., J = 12.9 Hz, 1H, NCH*H*Ph), 3.39−3.36 (m, 1H, 2-H), 3.28−3.23 (m, 1H, 4-H), 2.82−2.70 (m, 2H, C*H*HCO$_2$Et and 4′-H), 2.47 (dd, 1H, J = 15.6 Hz and J = 8.4 Hz, CH*H*CO$_2$Et), 2.18−2.11 (m, 1H, 3-H), 2.02−1.93 (m, 3′-H), 1.26 (t, 3H, J = 7.2 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171 (CO), 138.1, 134.0 (C_q), 133.1, 128.8, 128.6, 129.3, 127.4, 127.0 (CH_{Ar}), 67.9 (C_2), 63.3 (OCH_2), 60.6 (NCH_2Ph), 50.8 (*C*HSPh), 50.4 (C_4), 36.8 (CH_2CO), 22.3 (C_3), 14.2 (CH_3) ppm. IR: ν_{max} = 3061, 3025, 2978, 2956, 2830, 2789, 1731, 1655, 1582, 1475, 1452, 1438, 1268, 1152, 1026, 737, 694 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{26}NO_2S$ $[MH]^+$: 356.1684; found: 356.1681.

General Procedure for the Preparation of Azetidines with a 3-Hydroxypropyl Side Chain at the 2-Position. To a suspension of $LiAlH_4$ (6.5 equiv) in THF (1.5 mL/mmol) at 0 °C was added a solution of azetidine (1 equiv) in THF (5 mL/mmol). The mixture was refluxed for 2 h. After cooling the mixture to 0 °C, it was successively diluted with water (1 mL/g of $LiAlH_4$), 2 M NaOH aqueous solution (1 mL/g of $LiAlH_4$), and water (3 mL/g of $LiAlH_4$). The resulting solid was filtered and washed with Et_2O and concentrated under reduced pressure. The crude product was purified by flash chromatography. In the case of **5**, its reduction afforded a crude mixture of **8** and **9**, which was acetylated in DCM (6 mL/mmol) in the presence of triethylamine (3 equiv) and acetic anhydride (2 equiv). After 3 h, the solvents were removed. The crude product was purified by flash chromatography (2% MeOH in EP/EtOAc 50/50). Deprotection of pure acetylated compound **Ac-8** (or **Ac-9**) was conducted in methanol (8 mL/mmol) in the presence of K_2CO_3 (1.6 equiv) within 3 h to afford **8** (or **9**) after usual workup.

3-(1-Benzylazetidin-2-yl)-propan-1-ol 7. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.243 g, 58%. Colorless oil. R_f: 0.36 (DCM/MeOH 50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29−7.18 (m, 5H, Ph), 3.74 (d, part of AB syst., J = 12.6 Hz, 1H, NC*H*HPh), 3.61−3.55 (m, 2H, C*H*HOH and NCH*H*Ph), 3.50−3.47 (m, 1H, 2-H), 3.37−3.26 (m, 2H, C*H*HOH and 4-H), 2.95−2.87 (m, 1H, 4′-H), 2.16−2.03 (m, 1H, 3-H), 1.93−1.83 (m, 1H, 3′-H), 1.69−1.56 (m, 2H, C*H*HCH$_2$OH and C*H*HCH$_2$CH$_2$OH), 1.51−1.36 (m, 2H, CH*H*CH$_2$OH and CH*H*CH$_2$CH$_2$OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9 (C_q), 129.3, 128.5, 127.7 (CH_{Ar}), 66.2 (C_2), 62.6 (CH_2OH), 61.7 (NCH_2Ph), 50.6 (C_4), 31.7 ($CH_2CH_2CH_2OH$), 27.5 (CH_2CH_2OH), 20.8 (C_3) ppm. IR: ν_{max} = 3333, 2931, 2844, 1495, 1453, 1358, 1162, 1058, 962, 732, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{13}H_{20}NO$ $[MH]^+$: 206.1545; found: 206.1551.

[1(1*R*),2*S*]-3-[1-(1-Phenyl-ethyl)-azetidin-2-yl]-propan-1-ol 8. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.304 g, 36%. Colorless oil. R_f: 0.50 (DCM/MeOH 50/50). $[\alpha]_D^{20}$: + 57 (c 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30−7.23 (m, 5H, Ph), 3.81−3.78 (m, 1H, C*H*HOH), 3.63−3.47 (m, 3H, CH*H*OH, 2-H and C*H*CH$_3$), 3.07−3.01 (m, 1H, 4-H), 2.77−2.69 (m, 1H, 4′-H), 2.11−2.02 (m, 1H, 3-H), 1.92−1.79 (m, 4H, C*H*$_2$CH$_2$CH$_2$OH, CH$_2$C*H*HOH and 3′-H), 1.70−1.66 (m, 1H, CH$_2$CH*H*OH), 1.33 (d, J = 4.8 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.4 (C_q), 128.5, 128.3, 127.3 (CH_{Ar}), 68.5 ($NCHCH_3$), 65.3 (C_2), 62.7 (CH_2OH), 49.1 (C_4), 34.3 ($CH_2CH_2CH_2OH$), 27.6 (CH_2CH_2OH), 21.6 (Me), 19.0 (C_3) ppm. IR: ν_{max} = 3333, 2970, 2931, 2859, 2831, 1493, 1451, 1280, 1228, 1168, 1074, 1051, 1028, 1001, 978, 759, 699 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{14}H_{22}NO$ $[MH]^+$: 220.1701; found: 220.1699.

[1(1*R*),2*R*]-3-[1-(1-Phenyl-ethyl)-azetidin-2-yl]-prop-2*E*-en-1-ol 9. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.142 g, 17%. Colorless oil. R_f: 0.70 (DCM/MeOH 50/50). $[\alpha]_D^{20}$: + 75 (c 0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.22 (m, 5H, Ph), 6.01 (dd, J = 6.9 and 15.6 Hz, 1H, H_β), 5.90−5.81 (m, 1H, H_α), 4.18 (d, J = 5.1 Hz, 2H, CH_2OH), 3.73−3.66 (m, 1H, 2-H), 3.43 (q, J = 6.3 Hz, 1H, C*H*CH$_3$), 3.05−2.99 (m, 1H, 4-H), 2.72−2.64 (m, 1H, 4′-H), 2.23 (bs, 1H, OH), 2.09−1.93 (m, 2H, 3-H and 3′-H), 1.23 (d, J = 6.3 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3 (C_β), 135.5 (C_q), 129.7 (C_α), 128.3, 127.4, 127.0 (CH_{Ar}), 68.4 ($NCHCH_3$), 66.6 (C_2), 63.1 (CH_2OH), 49.8 (C_4), 23.9 (C_3), 21.6 (Me) ppm. IR: ν_{max} = 3332, 3029, 2968, 2925, 2830, 1493, 1450, 1371, 1279, 1215, 1171, 1140, 1097, 1051, 973, 758, 699 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{14}H_{20}NO$ $[MH]^+$: 218.1545; found: 218.1542.

(2*R*,3*S*,4*S*)-3-(1-Benzyl-4-methyl-3-phenylazetidin-2-yl)-propan-1-ol 10. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.119 g, 43%. Colorless oil. R_f: 0.15 (DCM/MeOH 95/5). $[\alpha]_D^{20}$: − 13 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42−7.18 (m, 10H, Ph), 3.82−3.66 (m, 3H, C*H*HOH and NCH_2), 3.38−3.16 (m, 4H, CH*H*OH, 2-H, 3-H, and 4-H), 1.92−1.73 (m, 2H, C*H*HCH$_2$OH and C*H*HCH$_2$CH$_2$OH), 1.63−1.53 (m, 1H, CH*H*CH$_2$OH), 1.49−1.37 (m, 1H, CH*H*CH$_2$CH$_2$OH), 1.12 (d, J = 5.7 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.2, 136.7 (C_q), 129.8, 128.6, 128.5, 127.6, 127.3, 126.7 (CH_{Ar}), 69.7 (C_2), 66.3 (C_4), 62.8 (NCH_2), 61.6 (OCH_2), 46.9 (C_3), 31.1 ($CH_2CH_2CH_2OH$), 27.9 (CH_2CH_2OH), 19.6 (Me) ppm. IR: ν_{max} = 3366, 3087, 3065, 3028, 2919, 2849, 2791, 1602, 1495, 1453, 1367, 1331, 1107, 1062, 1029, 1014, 738, 696 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{20}H_{26}NO$ $[MH]^+$: 296.2014; found: 296.2009.

3-(*R)-(1-Benzylazetidin-2-yl)-3-(*S**)-phenylsulfanyl-propan-1-ol 12a.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.238 g, 92%. Yellow oil. R_f: 0.32 (DCM/MeOH 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.21 (m, 10H, Ph), 3.76−3.67 (m, 2H, C*H*HOH and NC*H*HPh), 3.54−3.48 (m, 2H, NCH*H*Ph and 2-H), 3.39−3.26 (m, 2H, CH*H*OH and 4-H), 2.95−2.87 (m, 1H, 4′-H), 2.80−2.76 (m, 1H, C*H*SPh), 2.29−2.13 (m, 1H, 3-H), 2.08−1.96 (m, 2H, 3′-H and C*H*HCH$_2$OH) 1.79−1.74 (m, 1H, CH*H*CH$_2$OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 134.0 (C_q), 132.0, 129.5, 128.9, 128.5, 127.7, 127.2 (CH_{Ar}), 67.1 (C_2), 62.5 (NCH_2Ph), 61.4 (CH_2OH), 50.2 (C_4), 49.7 (CHSPh), 33.9 (CH_2CH_2OH), 17.7 (C_3) ppm. IR: ν_{max} = 3329, 3059, 3025, 2931, 2842, 1582, 1479, 1452, 1438, 1361, 1164, 1025, 736, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{19}H_{24}NOS$ $[MH]^+$: 314.1579; found: 314.1586.

3-(*R)-(1-Benzylazetidin-2-yl)-3-(*R**)-phenylsulfanyl-propan-1-ol 12b.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/5/95. Yield: 0.265 g, 92%. Yellow oil. R_f: 0.24 (DCM/MeOH 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, J = 6.9 Hz, 2H, Ph), 7.44−7.24 (m, 8H, Ph), 4.32 (d, part of AB syst., J = 12.6 Hz, 1H, NC*H*HPh), 4.07−4.00 (m, 1H, C*H*HOH), 3.76−3.62 (m, 2H, CH*H*OH and OH), 3.60−3.49 (m, 2H, 2-H and C*H*SPh), 3.46 (d, part of AB syst., J = 12.6 Hz, 1H, NCH*H*Ph), 3.21−3.14 (m, 1H, 4-H), 2.18−1.99 (m, 3H, 3-H and CH_2CH$_2$OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.8, 134.5 (C_q), 132.2, 129.1, 128.9, 128.4, 127.3, 127.2 (CH_{Ar}), 67.7 (C_2), 63.5 (NCH_2Ph), 58.4 (CH_2OH), 52.6 (CHSPh), 49.4 (C_4), 32.9 (CH_2CH_2OH), 21.8 (C_3) ppm. IR: ν_{max} = 3317, 3059, 3021, 2926, 2844, 1582, 1494, 1478, 1452, 1437, 1348, 1231, 1156, 1024, 738, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{19}H_{24}NOS$ $[MH]^+$: 314.1579; found: 314.1581.

General Procedure for the Ring Expansion of the Azetidines with a 3-Hydroxypropyl Side Chain at the 2-Position into Pyrrolidines and/or Azepanes. To a solution of azetidine (1 equiv) in DCM (1 mL/0.1 mmol) was added thionyl chloride (2 equiv). The reaction mixture was stirred for 2 h at reflux, cooled to ambient temperature, before eliminating solvents under reduced pressure. The residue was dissolved in a 1/2 water acetonitrile mixture (2 mL/0.1 mmol) containing sodium carbonate (4 equiv). After 5 min, solvents were eliminated under reduced pressure. The dry residue was dissolved in DMF (1 mL/0.1 mmol) before adding the nucleophile (10 equiv). After stirring for 2 h at 80 °C, the reaction mixture was cooled to ambient temperature before eliminating DMF under reduced pressure. The residue was taken up in ethyl acetate. The organic phase was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography.

DOI: 10.1021/acs.joc.6b01325
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Acetic Acid 2-(1-Benzylpyrrolidin-2-yl)-ethyl Ester 13 and Acetic Acid 1-Benzylazepan-4-yl Ester 16. Before purification by flash chromatography, a 30/70 mixture of pyrrolidine **13** and azepane **16** was obtained. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 46 mg, 37%. Yellow oil. R_f: 0.52 (DCM/MeOH 50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.25 (m, 5H^{py} and 5H^{az}, Ph), 5.07−5.00 (m, 1H^{az}, 4-H^{az}), 4.21−4.15 (m, 2H^{py}, OCH_2^{py}), 4.04 (d, part of AB syst., J = 12.9 Hz, 1H^{py}, NCH*H*Ph^{py}), 3.64 (s, 2H^{az}, NCH_2Ph^{az}), 3.24 (d, part of AB syst., J = 12.9 Hz, 1H^{py}, NCH*H*Ph^{py}), 2.97−2.90 (m, 1H^{py}, 5-H^{py}), 2.75−2.64 (m, 1H^{py} and 2H^{az}, 5′-H^{py}, 2-H^{az} and 7-H^{az}), 2.60−2.52 (d, 1H^{py} and 1H^{az}, 7′-H^{az} and 2-H^{py}), 2.20−2.11 (m, 1H^{py}, 5-H^{py}), 2.06 (s, 3H^{py}, $COCH_3^{py}$), 2.04 (s, 3H^{az}, $COCH_3^{az}$), 2.01−1.95 (m, 2H^{py} and 2H^{az}, 3-H^{az}, 5-H^{az}, 3-H^{py} and C*H*HCH$_2$O^{py}), 1.85−1.58 (m, 5H^{py} and 4H^{az}, 3′-H^{az}, 5′-H^{az}, 6-H^{az}, 6′-H^{az}, 3-H^{py}, CH*H*CH$_2$O^{py}, 3-H^{py}, 4-H^{py} and 4′-H^{py}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (C_q^{py}), 170.5 (C_q^{az}), 139.3 (C_q^{py}), 139.1 (C_q^{az}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 120.2 (C_{Ar}), 126.9 (C_{Ar}), 74.0 (C_4^{az}), 62.8 (NCH_2Ph^{az}), 62.4 (CH_2OAc^{py}), 61.3 (C_2^{py}), 58.5 (NCH_2Ph^{py}), 55.8 (C_2^{az}), 53.9 (C_5^{py}), 49.9 (C_7^{az}), 34.0 (C_3^{az}), 32.9 ($CH_2CH_2OAc^{py}$), 32.4 (C_5^{az}), 30.3 (C_3^{py}), 23.3 (C_6^{az}), 22.1 (C_4^{py}), 21.5 (CH_3^{az}), 21.0 (CH_3^{py}) ppm. IR: ν_{max} = 2938, 2813, 2782, 1731, 1494, 1452, 1364, 1241, 1155, 1023, 940, 729, 698 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{15}H_{22}NO_2$ [MH]$^+$: 248.1651; found: 248.1649.

3-(1-Benzylpyrrolidin-2-yl)-propionitrile 14 and 1-Benzyl-azepane-4-carbonitrile 17. Before purification by flash chromatography, a 73/27 mixture of pyrrolidine **14** and azepane **17** was obtained. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 46 mg, 43%. Yellow oil. R_f: 0.31 (DCM/MeOH 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.24 (m, 5H^{py} and 5H^{az}, Ph), 3.94 (d, part of AB syst., J = 13.2 Hz, 1H^{py}, NC*H*HPh^{py}), 3.65 (s, 2H^{az}, NCH_2Ph^{az}), 3.30 (d, part of AB syst., J = 13.2 Hz, 1H^{py}, NCH*H*Ph^{py}), 2.97−2.89 (m, 1H^{py} and 1Haz, 5-H^{py} and 4-H^{az}), 2.74−2.60 (m, 1H^{py} and 4H^{az}, 2-H^{py}, 2-H^{az} and 7-H^{az}), 2.53−2.29 (m, 2H^{py}, CH_2CN), 2.25−2.16 (m, 1H^{py}, 5′-H^{py}), 2.05−1.89 (m, 2H^{py} and 4H^{az}, 5-H^{az}, 5′-H^{az}, 3-H^{az}, 3′-H^{az}, 3-H^{py} and C*H*HCH$_2$CN^{py}), 1.84−1.66 (m, 3H^{py} and 2H^{az}, 6-H^{az}, 6′-H^{az}, CH*H*CH$_2$CN^{py}, 4-H^{py} and 4′-H^{py}), 1.58−1.47 (m, 1H^{py}, 3′-H^{py}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5 (C_q^{az}), 139.3 (C_q^{py}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (C_{Ar}), 127.0 (C_{Ar}), 123.2 (CN^{az}), 120.3 (CN^{py}), 62.9 (NCH_2Ph^{az}), 62.3 (C_2^{py}), 58.8 (NCH_2Ph^{py}), 54.8 (C_7^{az}), 54.3 (C_5^{py}), 51.9 (C_2^{az}), 32.0 (C_3^{az}), 30.1 (C_5^{az}), 29.6 (C_3^{py}), 29.5 ($CH_2CH_2CN^{py}$), 28.8 (C_4^{az}), 26.4 (C_6^{az}), 22.2 (C_4^{py}), 13.1 (CH_2CN^{py}) ppm. IR: ν_{max} = 2931, 2876, 2793, 2244, 1494, 1452, 1367, 1209, 1124, 1073, 1027, 736, 698 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{14}H_{19}N_2$ [MH]$^+$: 215.1548; found: 215.1546.

2-(2-Azido-ethyl)-1-benzylpyrrolidine 15 and 4-Azido-1-benzylazepane 18. Before purification by flash chromatography, a 13/87 mixture of pyrrolidine **15** and azepane **18** was obtained. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 67 mg, 58%. Yellow oil. R_f: 0.62 (DCM/MeOH 90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.26 (m, 5H^{py} and 5H^{az}, Ph), 4.02 (d, part of AB syst., J = 12.9 Hz, 1H^{py}, NC*H*HPh^{py}), 3.73−3.68 (m, 1H^{az}, 4-H^{az}), 3.65 (s, 2H^{az}, NCH_2Ph^{az}), 3.50−3.31 (m, 2H^{py}, CH_2N_3), 3.27 (d, part of AB syst., J = 12.9 Hz, 1H^{py}, NCH*H*Ph^{py}), 2.99−2.85 (m, 1H^{py}, 5-H^{py}), 2.76−2.54 (m, 1H^{py} and 4H^{az}, 2-H^{py}, 2-H^{az}, 2′-H^{az}, 7-H^{az} and 7′-H^{az}), 2.22−2.12 (m, 1H^{py}, 5′-H^{py}), 2.07−1.97 (m, 2H^{py} and 2H^{az}, 5-H^{az}, 3-H^{az}, 3-H^{py} and C*H*HCH$_2$N$_3^{py}$), 1.87−1.73 (m, 3H^{py} and 3H^{az}, 6-H^{az}, 3′-H^{az}, 5′-H^{az}, CH*H*CH$_2$N$_3^{py}$, 4-H^{py} and 4′-H^{py}), 1.68−1.58 (m, 1H^{py} and 1H^{az}, 6′-H^{az} and 3′-H^{py}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5 (C_q^{az}), 137.4 (C_q^{py}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.2 (C_{Ar}), 127.0 (C_{Ar}), 126.9 (C_{Ar}), 62.9 (NCH_2Ph^{az}), 61.6 (C_2^{py}), 61.4 (C_4^{az}), 58.8 (NCH_2Ph^{py}), 55.5 (C_7^{az}), 54.2 (C_5^{py}), 50.3 (C_2^{az}), 48.8 (CH_2N_3), 34.1 (C_3^{az}), 33.1 ($CH_2CH_2N_3$), 32.3 (C_5^{az}), 30.3 (C_3^{py}), 24.2 (C_6^{az}), 22.2 (C_4^{py}) ppm. IR: ν_{max} = 3060, 3029, 2937, 2811, 2777, 2088, 1494, 1452, 1352, 1250, 1153, 1104, 1027, 966, 730, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{13}H_{19}N_4$ [MH]$^+$: 231.1610; found: 231.1604.

Acetic Acid (1(*1R*),*4R*)-1-(1-Phenyl-ethyl)-azepan-4-yl Ester 20. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/3/97. Yield: 54 mg, 46%. Yellow oil. R_f: 0.40 (DCM/MeOH 90/10). $[\alpha]_D^{20}$: − 8 (c 1.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.23 (m, 5H, Ph), 5.01−4.97 (m, 1H, C*H*OAc), 3.75 (q, J = 6.6 Hz, 1H, C*H*CH$_3$), 2.68−2.56 (m, 4H, 2 × NCH_2), 2.03 (s, 3H, $COCH_3$), 2.00−1.87 (m, 2H, 3-H and 5-H), 1.84−1.67 (m, 2H, 3′-H, 5′-H and 6-H), 1.62−1.49 (m, 1H, 6′-H), 1.36 (d, J = 6.6 Hz, 3H, CHCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (CO), 144.4 (C_q), 128.1, 127.5, 126.7 (C_{Ar}), 74.3 (*C*HOAc), 63.5 (*C*HCH$_3$), 51.9 (C_7), 46.6 (C_2), 34.7 (C_3), 32.2 (C_5), 23.9 (C_6), 21.5 ($COCH_3$), 18.0 (CH*C*H$_3$) ppm. IR: ν_{max} = 3029, 2935, 2813, 2768, 1730, 192, 1450, 1364, 1241, 1164, 1019, 700 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{16}H_{24}NO_2$ [MH]$^+$: 262.1807; found: 262.1811.

[1(1*R*),2*R*]-3-[1-(1-Phenyl-ethyl)-pyrrolidin-2-yl]-propionitrile 21. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/3/97. Yield: 53 mg, 55%. Yellow oil. R_f: 0.44 (DCM/MeOH 90/10). $[\alpha]_D^{20}$: − 16 (c 1.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.24 (m, 5H, Ph), 3.69 (q, 1H, J = 6.6 Hz, C*H*CH$_3$), 2.96−2.85 (m, 2H, 2-H and 5-H), 2.57−2.49 (m, 1H, 5′-H), 2.33−2.10 (m, 2H, CH_2CN), 1.98−1.86 (m, 1H, 3-H), 1.76−1.67 (m, 2H, 4-H and 4′-H), 1.55−1.45 (m, 2H, 3′-H and C*H*HCH$_2$CN), 1.39 (d, 3H, J = 6.6 Hz, CH_3), 1.37−1.29 (m, 1H, CH*H*CH$_2$CN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0 (C_q), 128.3, 128.1, 127.5, 127.1, 126.7 (C_{Ar}), 120.2 (CN), 61.2 (*C*HCH$_3$), 60.1 (C_2), 50.2 (C_5), 30.5 (*C*H$_2$CH$_2$CN), 30.0 (C_3), 23.5 (C_4), 18.0 (CH_3) 13.3 (CH_2CN) ppm. IR: ν_{max} = 2967, 2930, 2873, 2808, 2243, 1492, 1451, 1374, 1302, 1278, 1155, 1121, 1085, 766, 700 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{15}H_{21}N_2$ [MH]$^+$: 229.1705; found: 229.1703.

(1(1*R*),*4R*)-1-(1-Phenyl-ethyl)-azepane-4-carbonitrile 22. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/3/97. Yield: 24 mg, 25%. Colorless oil. R_f: 0.54 (DCM/MeOH 90/10). $[\alpha]_D^{20}$: − 13 (c 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.22 (m, 5H, Ph), 3.80 (q, 1H, J = 6.6 Hz, C*H*CH$_3$), 2.92−2.84 (m, 1H, C*H*CN), 2.76−2.63 (m, 4H, 2 × NCH_2), 2.04−1.75 (m, 5H, 3-H, 3′-H, 5-H, 5′-H and 6-H), 1.68−1.56 (m, 1H, 6′-H), 1.37 (d, J = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.1 (C_q), 128.1, 127.5, 126.8 (C_{Ar}), 123.3 (CN), 63.3 (*C*HCH$_3$), 51.2 (C_7), 48.4 (C_2), 32.7 (C_3), 30.1 (C_5), 28.8 (*C*HCN), 27.2 (C_6), 17.0 (CH_3) ppm. IR: ν_{max} = 3060, 3024, 2936, 2817, 2235, 1492, 1450, 1372, 1202, 1162, 1096, 1027, 912, 700 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{15}H_{21}N_2$ [MH]$^+$: 229.1705; found: 229.1702.

(1(1*R*),*4R*)-4-Azido-1-(1-phenyl-ethyl)-azepane 23. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/3/98. Yield: 73 mg, 75%. Yellow oil. R_f: 0.24 (DCM/MeOH 95/5). $[\alpha]_D^{20}$: − 17 (c 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.23 (m, 5H, Ph), 3.77 (q, 1H, J = 6.9 Hz, C*H*CH$_3$), 3.66−3.59 (m, 1H, C*H*N$_3$), 2.76−2.66 (m, 3H, 7-H, 7′-H and 2-H), 2.62−2.53 (m, 1H, 2′-H), 2.02−1.92 (m, 2H, 3-H and 5-H), 1.84−1.66 (m, 3H, 6-H, 5′-H and 3′-H), 1.65−1.49 (m, 1H, 6′-H), 1.38 (d, J = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4 (C_q), 128.1, 127.5, 126.7 (C_{Ar}), 63.6 (*C*HCH$_3$), 61.6 (*C*HN$_3$), 51.7 (C_7), 46.9 (C_2), 34.9 (C_3), 32.1 (C_5), 24.9 (C_6), 17.9 (CH_3) ppm. IR: ν_{max} = 2975, 2934, 2817, 2773, 2086, 1491, 1450, 1368, 1250, 1163, 1106, 1027, 968, 765, 699 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{14}H_{21}N_4$ [MH]$^+$: 245.1766; found: 245.1765.

Acetic Acid (2*S*,3*S*,4*S*)-1-Benzyl-2-methyl-3-phenyl-azepan-4-yl Ester 24. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 15 mg, 13%. Yellow oil. R_f: 0.75 (DCM/MeOH 95/5). $[\alpha]_D^{20}$: + 35 (c 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45−7.13 (m, 8H, Ph), 7.08 (d, J = 5.7 Hz, 2H, Ph), 5.72−5.66 (m, 1H, C*H*OAc), 3.82 (d, part of AB syst., J = 13.5 Hz, 1H, NC*H*HPh), 3.72 (d, part of AB syst., J = 13.5 Hz, 1H, NCH*H*Ph), 3.19−3.14 (m, 1H, NC*H*CH$_3$), 2.84−2.75 (m, 2H, C*H*Ph and NC*H*HCH$_2$), 2.59−2.52 (1H, m, NCH*H*CH$_2$), 2.17−2.12 (m, 1H, C*H*HCHOAc), 1.72−1.63 (3H, m, CH*H*CHOAc and CH_2CH_2CHOAc), 1.54 (s, 3H, Me), 0.95 (d, J = 6.6 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 140.4 (C_q), 128.7, 128.4, 128.2, 128.1, 126.9, 126.1 (C_{Ar}), 74.8 (CHOAc), 61.0 (NCHCH$_3$), 59.2 (CHPh), 58.7 (NCH$_2$Ph), 46.5 (NCH$_2$), 34.8

DOI: 10.1021/acs.joc.6b01325
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(CH_2CHOAc), 25.1 (NCH_2CH_2), 20.8 ($COCH_3$), 13.0 ($NCHCH_3$) ppm. IR: ν_{max} = 3027, 2966, 2931, 2853, 2813, 1728, 1494, 1452, 1370, 1241, 1163, 1129, 1023, 960, 754, 733, 699 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{22}H_{28}NO_2$ $[MH]^+$: 338.2120; found: 338.2124.

(2*S*,3*S*,4*S*)-1-Benzyl-2-methyl-3-phenyl-azepane-4-carbonitrile 25. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/1/99. Yield: 31 mg, 26%. Yellow oil. R_f: 0.77 (DCM/MeOH 99/1). $[\alpha]_D^{20}$: + 154 (c 2.34, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.23 (m, 8H, Ph), 7.12 (d, J = 6.9 Hz, 2H, Ph), 3.80−3.68 (m, 3H, NCH_2Ph and $CHCN$), 3.15−3.05 (m, 1H, $NCHCH_3$), 2.88−2.79 (m, 1H, $NCHHCH_2$), 2.70 (t, J = 9.0 Hz, 1H, $CHPh$), 2.61−2.55 (1H, m, $NCHHCH_2$), 2.41−2.31 (m, 1H, $CHHCHCN$), 1.92−1.83 (1H, m, $CHHCHCN$), 1.80−1.70 (m, 1H, $CHHCH_2CHCN$), 1.66−1.54 (m, 1H, $CHHCH_2CHCN$), 0.97 (d, J = 6.3 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 140.1 (C_q), 128.8, 128.7, 128.3, 128.1, 127.3, 127.1 (C_{Ar}), 122.9 (CN), 61.8 ($NCHCH_3$), 59.1 (NCH_2Ph), 56.5 ($CHPh$), 46.7 (NCH_2), 34.1 ($CHCN$), 33.0 (CH_2CHCN), 27.1 (NCH_2CH_2), 12.0 (Me) ppm. IR: ν_{max} = 3027, 2932, 2235, 1601, 1493, 1452, 1372, 1265, 1193, 1130, 1079, 1025, 733, 698 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{25}N_2$ $[MH]^+$: 305.2018; found: 305.2012.

(2*S*,3*S*,4*S*)-4-Azido-1-benzyl-2-methyl-3-phenyl-azepane 26. Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/1/99. Yield: 80 mg, 60%. Yellow oil. R_f: 0.82 (DCM/MeOH 99/1). $[\alpha]_D^{20}$: + 119 (c 2.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44−7.22 (m, 8H, Ph), 7.14 (d, J = 6.9 Hz, 2H, Ph), 4.26−4.18 (m, 1H, CHN_3), 3.81 (d, J = 13.5 Hz, 1H, $NCHHPh$), 3.73 (d, J = 13.5 Hz, 1H, $NCHHPh$), 3.24−3.14 (m, 1H, $NCHCH_3$), 2.90−2.82 (m, 1H, $NCHHCH_2$), 2.70 (t, J = 9.3 Hz, 1H, $CHPh$), 2.65−2.57 (1H, m, $NCHHCH_2$), 2.40−2.31 (m, 1H, $CHHCHCN_3$), 1.88−1.76 (2H, m, $CHHCHCN_3$ and $CHHCH_2CHN_3$), 1.72−1.65 (m, 1H, $CHHCH_2CHN_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 140.4 (C_q), 128.7, 128.5, 128.3, 127.0, 126.6 (C_{Ar}), 64.4 (CHN_3), 61.7 ($NCHCH_3$), 59.0 ($CHPh$), 58.7 (NCH_2Ph), 47.0 (NCH_2), 34.2 (CH_2CHN_3), 25.8 (NCH_2CH_2), 12.9 (Me) ppm. IR: ν_{max} = 3026, 2931, 2089, 1600, 1493, 1451, 1260, 1163, 1133, 1026, 956, 732, 698 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{20}H_{25}N_4$ $[MH]^+$: 321.2079; found: 321.2077.

Acetic Acid (2*S,3*S**)-2-(1-Benzyl-3-phenylsulfanyl-pyrrolidin-2-yl)-ethyl Ester 27.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 25 mg, 32%. Yellow oil. R_f: 0.23 (DCM/MeOH 98/2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.23 (m, 10H, Ph), 4.31−4.16 (m, 2H, CH_2OAc), 4.03 (d, part of AB syst., J = 13.2 Hz, 1H, $NCHHPh$), 3.58−3.52 (m, 1H, CHN), 3.36 (d, part of AB syst., J = 13.2 Hz, 1H, $NCHHPh$), 2.95−2.90 (m, 1H, $NCHH$), 2.61 (bs, 1H, $CHSPh$), 2.51−2.42 (m, 1H, $NCHH$), 2.30−2.17 (m, 1H, NCH_2CHH), 2.09−1.89 (m, 2H, OCH_2CH_2), 2.01 (s, 3H, OAc), 1.87−1.80 (m, 1H, NCH_2CHH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (CO), 136.6, 135.9 (C_q), 130.4, 129.0, 128.8, 128.3, 127.1, 126.6 (CH_{Ar}), 67.2 ($CHSPh$), 61.6 (OCH_2), 58.9 (NCH_2Ph), 52.1 (NCH_2), 49.8 (NCH), 31.95 (NCH_2CH_2), 31.91 (OCH_2CH_2), 21.0 (Me) ppm. IR: ν_{max} = 3069, 3024, 2966, 2933, 2795, 1736, 1584, 11480, 1438, 1365, 1232, 1026, 910, 736 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{26}NO_2S$ $[MH]^+$: 356.1684; found: 356.1681.

Acetic Acid (4*S,5*R**)-1-Benzyl-5-phenylsulfanyl-azepan-4-yl Ester 28.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 15 mg, 13%. Yellow oil. R_f: 0.16 (DCM/MeOH 98/2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45−7.43 (m, 2H, Ph), 7.37−7.24 (m, 8H, Ph), 5.11−5.09 (m, 1H, $CHOAc$), 3.66 (bs, 2H, NCH_2Ph), 3.54−3.48 (m, 1H, $CHSPh$), 2.93−2.62 (m, 4H, 2 × NCH_2), 2.23−1.86 (m, 4H, CH_2), 1.96 (s, 3H, OAc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (CO), 132.2, 129.8, 129.2, 129.1, 128.7, 127.5 (CH_{Ar}), 75.7 ($CHOAc$), 62.0 (NCH_2Ph), 51.6 (NCH_2CH_2CHOAc), 51.0 ($CHSPh$), 48.8 (NCH_2CH_2CHOAc), 29.0 (CH_2CHOAc and CH_2CHSPh), 21.1 (Me) ppm. IR: ν_{max} = 3060, 3029, 2939, 2817, 2777, 1732, 2582, 1438, 1234, 1025, 730 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{26}NO_2S$ $[MH]^+$: 356.1684; found: 356.1680.

(2*S,3*S**)-2-(2-Azido-ethyl)-1-benzyl-3-phenylsulfanyl-pyrrolidine 29.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 33 mg, 31%. Yellow oil. R_f: 0.76 (DCM/MeOH 98/2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.25 (m, 10H, Ph), 4.00 (d, part of AB syst., J = 13.2 Hz, 1H, $NCHHPh$), 3.52−3.35 (m, 4H, $NCHHPh$, CH_2N_3 and $CHSPh$), 2.96−2.91 (m, 1H, $NCHH$), 2.64−2.59 (m, 1H, NCH), 2.52−2.43 (m, 1H, $NCHH$), 2.29−2.16 (m, 1H, NCH_2CHH), 2.02−1.90 (1H, $CHHCH_2N_3$), 1.87−1.80 (m, 2H, NCH_2CHH and $CHHCH_2N_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 135.7 (C_q), 130.6, 129.0, 128.7, 128.3, 127.1, 126.7 (CH_{Ar}), 67.5 (NCH), 59.1 (NCH_2Ph), 52.3 (NCH_2), 49.9 ($CHSPh$), 48.0 (CH_2N_3), 32.3 ($CH_2CH_2N_3$), 31.9 (NCH_2CH_2) ppm. IR: ν_{max} = 3060, 3027, 2931, 2687, 2796, 2092, 1584, 1494, 1480, 1452, 1438, 1261, 1025, 909, 736 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{19}H_{23}N_4S$ $[MH]^+$: 339.1643; found: 339.1639.

(3*S,4*R**)-4-Azido-1-benzyl-5-phenylsulfanyl-azepane 30.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/2/98. Yield: 37 mg, 34%. Yellow oil. R_f: 0.50 (DCM/MeOH 98/2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48−7.45 (m, 2H, Ph), 7.37−7.25 (m, 8H, Ph), 3.77−3.71 (m, 1H, CHN_3), 3.66−3.55 (m, 2H, NCH_2Ph), 3.40−3.34 (m, 1H, $CHSPh$), 2.88−2.80 (1H, m, $NCHHCH_2CHN_3$), 2.77−2.60 (m, 2H, NCH_2CH_2CHSPh), 2.56−2.48 (m, 1H, $NCHHCH_2CHN_3$), 2.19−2.11 (m, 2H, $CHHCHCN_3$ and $CHHCHSPh$), 2.01−1.86 (m, 2H, $CHHCHN_3$ and $CHHCHSPh$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 134.6 (C_q), 132.3, 129.1, 128.8, 128.3, 127.4, 127.1 (C_{Ar}), 65.6 (CHN_3), 62.7 (NCH_2Ph), 53.0 ($CHSPh$), 52.8 (NCH_2CH_2CHSPh), 50.0 ($NCH_2CH_2CHN_3$), 32.0 (CH_2CHSPh), 31.6 (CH_2CHN_3) ppm. IR: ν_{max} = 3065, 3029, 2939, 2813, 2777, 2090, 1693, 1473, 1451, 1438, 1252, 1150, 908, 730 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{19}H_{23}N_4S$ $[MH]^+$: 339.1643; found: 339.1639.

Acetic Acid (2*S,3*R**)-2-(1-Benzyl-3-phenylsulfanyl-pyrrolidin-2-yl)-ethyl Ester 31.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/1/99. Yield: 63 mg, 55%. Colorless oil. R_f: 0.45 (DCM/MeOH 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42−7.21 (m, 10H, Ph), 4.33−4.19 (m, 2H, CH_2OAc), 4.01 (d, part of AB syst., J = 13.2 Hz, 1H, $NCHHPh$), 3.84−3.77 (m, 1H, CHN), 3.46 (d, part of AB syst., J = 13.2 Hz, 1H, $NCHHPh$), 3.12−3.00 (m, 2H, $NCHH$ and $CHSPh$), 2.42−2.33 (m, 1H, $NCHH$), 2.30−2.17 (m, 1H, NCH_2CHH), 2.15−2.05 (m, 2H, OCH_2CHH), 2.02 (s, 3H, OAc), 2.00−1.87 (m, 2H, NCH_2CHH and OCH_2CHH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (CO), 139.0, 136.5 (C_q), 130.0, 128.9, 128.7, 128.2, 127.0, 126.2 (CH_{Ar}), 63.4 ($CHSPh$), 62.4 (OCH_2), 58.9 (NCH_2Ph), 51.5 (NCH_2), 49.2 (NCH), 31.9 (NCH_2CH_2), 29.6 (OCH_2CH_2), 21.0 (Me) ppm. IR: ν_{max} = 3061, 3025, 2962, 2933, 2792, 1733, 1583, 1479, 1452, 1438, 1234, 1026, 734, 697 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{21}H_{26}NO_2S$ $[MH]^+$: 356.1684; found: 356.1691.

(2*S,3*R**)-2-(2-Azido-ethyl)-1-benzyl-3-phenylsulfanyl-pyrrolidine 32.** Eluent for flash chromatography: 16 M aq. NH_3/MeOH/DCM 0.1/1/99. Yield: 54 mg, 50%. Colorless oil. R_f: 0.72 (DCM/MeOH 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42−7.20 (m, 10H, Ph), 4.01 (d, part of AB syst., J = 13.5 Hz, 1H, $NCHHPh$), 3.84−3.77 (m, 1H, $CHSPh$), 3.51−3.36 (m, 3H, $NCHHPh$ and CH_2N_3), 3.12−3.03 (m, 2H, NCH and $NCHH$), 2.42−2.34 (m, 1H, $NCHH$), 2.30−2.20 (m, 1H, NCH_2CHH), 2.10−1.98 (1H, $CHHCH_2N_3$), 1.96−1.83 (m, 2H, NCH_2CHH and $CHHCH_2N_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.0, 136.4 (C_q), 129.8, 129.0, 128.8, 128.3, 127.1, 126.3 (CH_{Ar}), 63.6 (NCH), 59.3 (NCH_2Ph), 51.7 (NCH_2), 49.0 ($CHSPh$ and CH_2N_3), 30.0 (NCH_2CH_2), 32.0 ($CH_2CH_2N_3$) ppm. IR: ν_{max} = 3061, 3025, 2926, 2864, 2792, 2089, 1583, 1479, 1452, 1437, 1349, 1258, 1112, 1089, 1070, 1025, 735, 690 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd. for $C_{19}H_{23}N_4S$ $[MH]^+$: 339.1643; found: 339.1637.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01325.

DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685

Computational details (PDF)
Copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The University of Versailles St-Quentin-en-Yvelines and the CNRS are acknowledged for financial support. Quantum chemical calculations were made with the financial support of the Russian Science Foundation (project No. 14-13-00103).

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DOI: 10.1021/acs.joc.6b01325
J. Org. Chem. 2016, 81, 6677−6685