JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

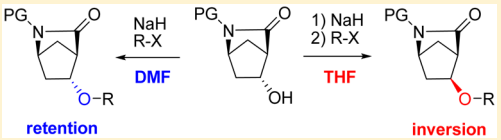
Unexpected Retroaldol-Aldol Reaction during *O*-Alkylation of Hydroxylated Vince Lactam Derivatives

Christoffer Bengtsson, Alexander Wetzel, Joakim Bergman, and Jonas Bråvalt*

Department of Medicinal Chemistry, CVMD iMed, AstraZeneca R&D Mölndal, Pepparedsleden 1, SE-431 83 Mölndal, Sweden

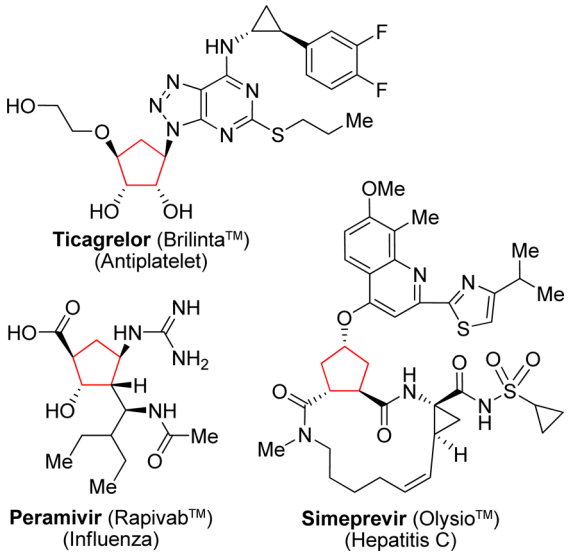
Supporting Information

ABSTRACT: The unexpected retroaldol–aldol reaction during *O*-alkylation of a *β*-hydroxy lactam was found to be highly dependent on the temperature and shows a remarkable solvent effect. In DMF, *O*-alkylation is faster than retroaldol–aldol rearrangement giving exclusively products with *retention* of configuration. In THF, *O*-alkylation is slower than rearrangement, giving selectively products with *inversion* of stereochemistry. In DMSO, a retroaldol reaction followed by fast intramolecular proton transfer occurs to give the ring-opened aldehyde.



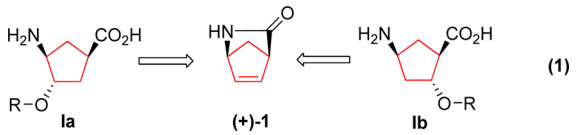
The substituted cyclopentane core represents a ubiquitous structural motif in a wide array of bioactive natural products.[1] In addition, cyclopentanes have also emerged as attractive fragments within drug discovery projects and should now be regarded as privileged scaffolds,[1b] as these core structures are found in an increasing number of approved drugs and drug candidates (Scheme 1).[2]

Scheme 1. Examples of Recently Approved Cyclopentane Containing Drugs



As part of a medicinal chemistry program, we needed access to novel *O*-alkylated cyclopentanol *γ*-amino acid derivatives of type **Ia** and **Ib** (eq 1). We envisioned that these could be obtained from commercially available Vince Lactam[3] (+)-**1** via a hydroboration/*O*-alkylation/lactam-opening reaction sequence.

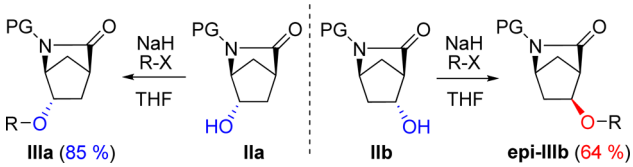
However, our synthetic efforts toward this goal were initially hampered by an unexpected stereochemical outcome during



(1)

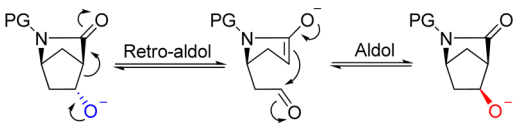
the *O*-alkylation step (Scheme 2). While **IIa** was alkylated uneventfully under standard conditions (NaH in THF) to give

Scheme 2. Initial Observation of an Unexpected Stereochemical Outcome during *O*-Alkylation



IIIa, we found that the corresponding regioisomer **IIb** did not afford the expected product **IIIb** (structure not shown) under identical conditions. Instead, and much to our surprise, we isolated **epi-IIIb** as a single diastereomer.[4]

We hypothesized that the unexpected inversion of stereochemistry was due to a rapid retroaldol–aldol reaction of the alcoholate anion preceding the alkylation event (eq 2). Such



(2)

rearrangement can only operate in *β*-hydroxy carbonyl systems (i.e., **IIb**) and could thus explain the differentiated stereochemical outcome observed for hydroxyl regioisomers **IIa** and **IIb**.

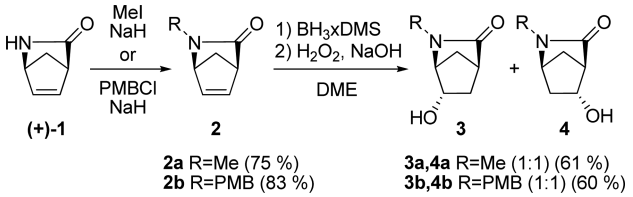
Received: October 16, 2015
Published: December 24, 2015

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708–714

Examples of retroaldol−aldol reactions in the literature include both cyclic and acyclic β-hydroxy carbonyl compounds, usually promoted by strong bases, although other reagents have been reported as well.[5] However, we are not aware of any study describing factors and/or conditions (i.e., temperature, solvents) that would either suppress or promote a retro-aldol−aldol rearrangement. With the exception of a single example,[5a] retroaldol−aldol rearrangement during attempted *O*-alkylation has, to the best of our knowledge, not been described. We argued that finding conditions for selective alkylations with retention of stereochemistry may be challenging, since factors that would suppress the rate of retroaldol−aldol rearrangement (e.g., low temperature) would likely also suppress *O*-alkylation. Promoting the alkylation (e.g., polar aprotic solvents) would likely also speed up the retroaldol reaction. Herein we report the remarkable and unexpected solvent effects that eventually led us to find conditions for either selective alkylations with retention *or* inversion, as well as conditions for the isolation of the putative aldehyde intermediate.

The requisite starting materials for our studies were prepared from commercially available Vince lactam[3] (+)-**1** by *N*-alkylation with MeI or PMBCl to give **2a** and **2b**[6] in 75% and 83% yield, respectively (Scheme 3). A subsequent

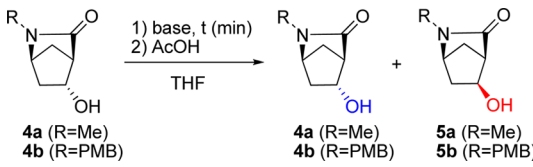
Scheme 3. *N*-Alkylation and Hydroboration of (+)-1 (Vince Lactam)



hydroboration/oxidation[7] reaction gave regioisomeric mixtures (1:1) of the hydroxylated analogues **3a**/**4a** and **3b**/**4b**, respectively, which were separated by chromatography.

To gain a fundamental understanding of the factors influencing the retroaldol−aldol reaction, our investigations commenced with the study of the rearrangement in the absence of alkylating agents. Compound **4a** was treated with different bases for the indicated times (*t*, min) in THF,[8] followed by quench with acetic acid, and analysis of the crude mixtures by ^{1}H NMR (Table 1). The temperature had a marked effect on the rearrangement. At −20 °C, starting material was recovered unchanged after 90 min, whereas, at room temperature, ^{1}H NMR analysis showed complete destruction of **4a** and formation of a complex mixture, probably arising from undesired intermolecular aldol reactions. However, at 0 °C we observed a clean reaction and conversion of **4a** into diastereomeric alcohol **5a**. After 30 min, a ratio of 10:90 was obtained, which did not change with a prolonged reaction time, although decomposition products started to appear after >60 min. Besides sodium hydride, other strong bases such as sodium *tert*-butoxide gave identical results, whereas TBAF[9] showed only poor conversion (entry 7). When DMF was used as solvent, complete decomposition after 15 min was observed even at 0 °C (entry 8). For PMB-protected derivative **4b**, the rearrangement was slower and reached steady state after 60 min (6:94 ratio) (entries 9−10).

Table 1. Conditions Influencing the Retroaldol−Aldol Reaction[a]

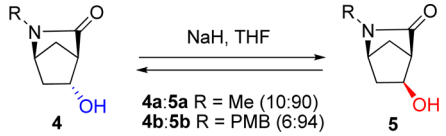


entry	R	base	*T* (°C)	*t* (min)	**4**:**5**[b]
1	Me	NaH	−20	90	100:0
2	Me	NaH	rt	90	–[c]
3	Me	NaH	0	15	40:60
4	Me	NaH	0	30	10:90
5	Me	NaH	0	60	10:90
6	Me	NaO*t*Bu	0	30	10:90
7	Me	TBAF	0	30	80:20
8[d]	Me	NaH	0	15	–[c]
9	PMB	NaH	0	30	20:80
10	PMB	NaH	0	60	6:94
11	PMB	NaHMDS	0	60	6:94
12	PMB	KHMDS	0	60	6:94
13	PMB	LiHMDS	0	60	99:1
14	PMB	LiHMDS	rt	3600	30:70

[a]Reactions performed at 0.1 M concentration of **4**. [b]Ratios determined by ^{1}H NMR of the crude products. [c]Complex mixture/decomposition. [d]Reaction performed in DMF.

We speculated that the propensity to form alcohol **5** over **4** may be due to chelation with the lactam carbonyl in the aldol reaction. Previous studies on intramolecular aldol condensations have shown that the counterion plays a crucial role whether the reaction proceeds via a Zimmerman−Traxler (closed transition state) or an open transition state.[10] Various counterions were investigated by deprotonation of **4b** with their corresponding HMDS bases (entries 11−14). While Na^+ and K^+ gave identical results, reaction with Li^+ was considerably slower and the strongly coordinating $MgBr^+$ proved to be ineffective. This would suggest an open transition state rather than the aldol reaction proceeding via a Zimmerman−Traxler transition state.

In addition, treating *either* compound **4a,b** or **5a,b** with NaH in THF at 0 °C for 1 h, followed by quench with AcOH, gave the same equilibrium ratios as observed in Table 1 (10:90 for R = Me and 6:94 for R = PMB) regardless of starting from **4** or **5** (eq 3). These results indicate that the reaction is an equilibrium driven by thermodynamics in favor of isomer **5**.[11]

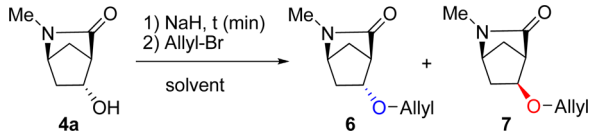


(3)

With this information in hand, we next studied the retroaldol−aldol reaction in competition with alkylation by an alkylating agent (allyl bromide). Treatment of **4a** with NaH in THF with allyl bromide present (*t* = 0 min) gave a 1:1 mixture of **6** and **7** (Table 2, entry 1). With increasing time for deprotonation before addition of allyl bromide, increasing ratios of **7** were isolated. Interestingly, a 30 min deprotonation time resulted in formation of **7** as a single isomer. Since a 10:90 equilibrium mixture of **4a**/**5a** is obtained in the absence of an electrophile, the exclusive formation of **7** can be explained by a

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708−714

Table 2. Retroaldol−Aldol versus Alkylation: Effect of Deprotonation Time (t, min), Concentration, and Solvent[a]



entry	solvent	t (min)	6:7	total yield (%)
1	THF	0	50:50	62
2	THF	15	5:95	58
3	THF	30	0:100	61
4	THF	60	0:100	59
5	THF[b]	0	20:80	66
6	DMF	0	100:0	67

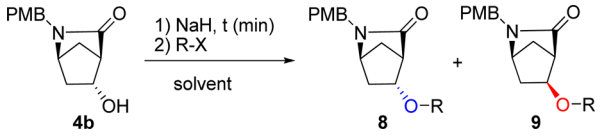
[a]All reactions performed at 0 °C at 0.1 M concentration except where indicated. [b]Reaction performed at 0.02 M concentration.

faster allylation of **5a** compared to **4a** according to the Curtin−Hammet principle.[12] As was already observed from the study in Table 1, PMB-protected derivative **4b** required a longer deprotonation time (60 min) to achieve good selectivity for the allylated derivative with inversion of stereochemistry. While the concentration of the reaction had only a minor effect (entry 1 vs 5), we observed a strong solvent effect. Performing the reaction in DMF (entry 6) gave exclusive formation of **6** with retention of configuration. The fast, direct allylation in DMF requires the electrophile to be present during deprotonation; otherwise, complete decomposition was observed.

Taken together, these studies showed that direct alkylation with retention of configuration can be selectively obtained in DMF with an alkylating agent present during deprotonation. In contrast, performing the deprotonation in THF and allowing the retroaldol−aldol to reach equilibrium before addition of the alkylating agent selectively give products with inversion of configuration. Applying these optimized reaction conditions for direct alkylation of **4b** (DMF, t = 0 min) with a set of alkyl halides gave O-alkylated compounds **8a−f** with retention of configuration (Table 3). The same set of alkyl halides gave under optimized conditions for retroaldol−aldol reaction followed by alkylation (THF, t = 60 min) the corresponding O-alkylated derivatives **9a−f** with almost complete inversion.

To shed more light on the mechanism of the retroaldol−aldol reaction, we attempted to trap or isolate the putative aldehyde intermediate (see eq 2). However, performing the isomerization of **4b** in the presence of reactive species (e.g., MeMgBr or $LiBH_4$) only returned unreacted starting material. Likewise, monitoring the reaction by ^{1}H NMR in d^6-THF showed a mixture of starting material **4b** and the epimerized isomer **5b**, whereas no aldehyde signal was detected. In d^7-DMF we only observed decomposition of **4b** and formation of a complex mixture likely due to retroaldol reaction followed by unselective intermolecular aldol reactions. Surprisingly, when d^6-DMSO was used as solvent we observed rapid and clean formation of enolate **12** as a mixture of E/Z-enolates (2:1 ratio), which was verified by extensive NMR studies[13] (Scheme 4). Intermediate **12** is stable for several hours and showed no decomposition in d^6-DMSO solution at room temperature. After protonation with d-TFA, the ^{1}H NMR spectrum showed clean formation of aldehyde **13**, with full H/D-exchange in the α-position of the aldehyde. Notably, no H/D exchange in the α-position of the amide was observed, indicating a fast intramolecular proton transfer from the initially formed

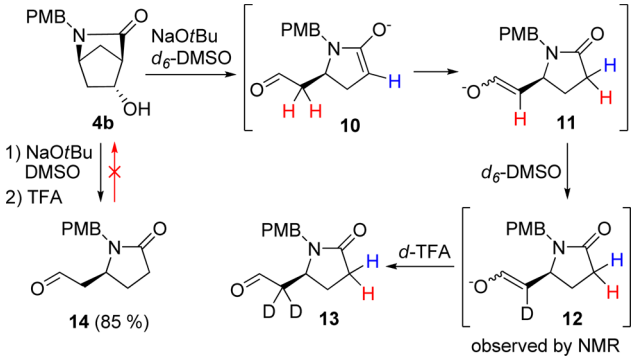
Table 3. Alkylations with Selective Retention or Inversion



ID	R-X	Solvent	8 : 9	Yield (%)
8a		DMF[a]	100:0	85
8b		DMF[a]	100:0	79
8c		DMF[a]	100:0	83
8d	BnBr	DMF[a]	100:0	84
8e		DMF[a]	100:0	30
8f	MeI	DMF[a]	100:0	87
9a		THF[b]	<2:98	62
9b		THF[b]	<2:98	65
9c		THF[b]	<2:98	71
9d	BnBr	THF[b]	<2:98	64
9e		THF[b]	<2:98	61
9f	MeI	THF[b]	<2:98	61

[a]Reaction performed at 0 °C for 2 h with electrophile present (t = 0 min). [b]Compound **4b** treated with NaH for 1 h at 0 °C, then addition of electrophile and stirring continued overnight (0 °C to rt).

Scheme 4. Retroaldol Reaction in DMSO



amide enolate **10** into aldehyde enolate **11**.[14] This is in sharp contrast to reactions performed in THF where the putative aldehyde intermediate **10** instead undergoes an intramolecular aldol reaction (*vide supra*).

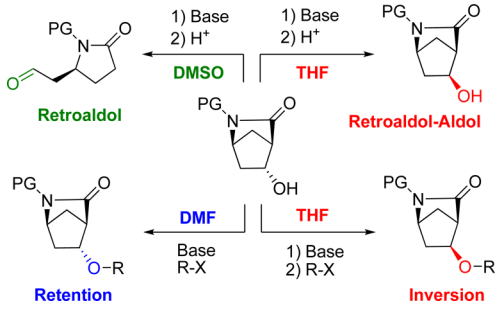
For preparative purposes, treatment of **4b** with either NaH or NaOtBu in DMSO, followed by acidic workup, gave aldehyde **14** in 85% isolated yield (Scheme 4). It is worth noting that the reverse reaction, i.e. treatment of aldehyde **14** with a base under a variety of conditions, resulted in unselective intermolecular aldol reactions; no formation of compound **4b** (or stereoisomer **5b**) was observed.

In summary, the retroaldol−aldol reaction of 5-hydroxy-2-azabicyclo[2.2.1]heptan-3-one was found to be highly dependent on the temperature and exhibits strong and unexpected solvent effects (Scheme 5). Based on these results we have

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708−714

developed conditions for selective *O*-alkylations with *either* retention *or* inversion.

Scheme 5. Summary



EXPERIMENTAL SECTION

General Methods. All dry solvents and reagents were used as received from commercial suppliers. NaH was used as a 60% dispersion in mineral oil. Column chromatography was employed on normal phase silica gel (230–400 mesh, 60 Å, eluents given in brackets). Chiral chromatography separations were performed either by chiral HPLC using heptane/EtOH/TEA as eluent or by chiral SFC using MeOH/CO_2 as eluent. Optical rotation was measured with a polarimeter at 20 °C and 589 nm. IR was recorded on $CHCl_3$ solutions (compound concentration = 10 mg/mL) using a spectrometer equipped with an IR-probe. ^{1}H and ^{13}C NMR spectra were recorded on spectrometers with 400, 500, or 600 MHz at 298 K and calibrated using the residual peak of solvent as an internal standard [$CDCl_3$ ($CHCl_3$ δ_H 7.26 ppm, $CDCl_3$ δ_C 77.16 ppm), d_6-DMSO (d_5-DMSO δ_H 2.5 ppm, d_6-DMSO δ_C 39.5 ppm)]. HRMS data were obtained on an LC-TOF instrument with positive electrospray ionization (ES^+) and Leu-enkephalin as a calibration chemical or by using GC-TOF equipment with field ionization (FI^+) and chloropentafluorobenzene as a calibration chemical.

(1S,4R)-2-Methyl-2-azabicyclo[2.2.1]hept-5-en-3-one (**2a**). To a suspension of NaH (2.09 g, 52.2 mmol) in dry THF (60 mL) was added (1*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) (4.75 g, 43.5 mmol) dissolved in dry THF (30 mL) at 0 °C. The suspension was stirred at 0 °C for 30 min, and then MeI (6.8 mL, 108.8 mmol) was added. The icebath was removed, and the mixture was allowed to attain rt and was stirred for 16 h. The reaction was carefully quenched by addition of saturated NH_4Cl (aq) and diluted with EtOAc. The phases were separated, and the water phase was extracted several times with DCM. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 30:70) to give **2a** as a colorless oil (4.00 g, 75%). $[\alpha]_D^{20}$ +357 (*c* 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77–6.72 (m, 1H), 6.53–6.48 (m, 1H), 4.01–3.97 (m, 1H), 3.19–3.14 (m, 1H), 2.53 (s, 3H), 2.20–2.15 (m, 1H), 2.02–1.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.8, 139.0, 137.9, 65.0, 58.0, 53.4, 31.3. IR λ 1697, 1518 cm^{-1}. HRMS (FI) calcd $[M]^+$ for C_7H_9NO 123.0684; obsd 123.0683.

(1S,4R)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (**2b**).[15] (1*S*,4*R*)-2-Azabicyclo[2.2.1]hept-5-en-3-one (**1**) (11 g, 100.8 mmol) was dissolved in dry DMF (80 mL) and cooled to 0 °C with an icebath. NaH (4.43 g, 110.9 mmol) was added portionwise, and the reaction was stirred at 0 °C for 5 min. 1-(Chloromethyl)-4-methoxybenzene (15 mL, 110.9 mmol) was added over 10 min followed by tetrabutylammonium iodide (3.72 g, 10.1 mmol), the icebath was removed, and the reaction was stirred at rt for 4.5 h. The reaction mixture was diluted with brine and extracted by EtOAc (water was added to get separation of phases), and the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10 to 60:40) to give **2b** as a colorless solid (21.4 g, 93%). $[\alpha]_D^{20}$ +81 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09–7.04 (m, 2H), 6.82–6.78 (m, 2H), 6.49–6.46 (m, 2H), 4.28 (d, 1H, *J* = 15 Hz), 3.99–3.96 (m, 1H), 3.95 (d, 1H, *J* = 15 Hz), 3.74 (s, 3H), 3.34–3.30 (m, 1H), 2.24–2.20 (m, 1H), 2.03–1.99 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.8, 159.0, 139.7, 136.9, 129.7 (2C), 128.3, 113.9 (2C), 62.5, 58.3, 55.2, 53.8, 47.2. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{14}H_{15}NO_2$ 230.1181; obsd 230.1189.

(1S,4R,6S)-6-Hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (3a) and (1S,4R,5R)-5-Hydroxy-2-methyl-2-azabicyclo[2.2.1]-heptan-3-one (**4a**). (1*S*,4*R*)-2-Methyl-2-azabicyclo[2.2.1]hept-5-en-3-one (**2a**) (6.71 g, 54.5 mmol) was dissolved in dry DME (115 mL) and cooled to 0 °C with an icebath. Borane dimethyl sulfide complex (5.68 mL, 59.9 mmol) was added, and the reaction was stirred at 0 °C for 10 min before the icebath was removed. The reaction continued for 2.5 h at rt (monitored by TLC, heptane/EtOAc 30:70, visulized by $KMnO_4$). The reaction was cooled with an icebath, and 3 M NaOH (5.45 mL, 16.4 mmol) and 30% H_2O_2 (11 mL, 136.2 mmol) were added. The icebath was removed, and the reaction was stirred at rt for 1 h. NaCl was added, and the reaction mixture was extracted by EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (EtOAc to EtOAc/MeOH 90:10) to give a 1:1 mixture of regioisomers **3a** and **4a** (4.7 g, 61%). The regioisomers were separated by chiral SFC, Chiralpak AD, 250 mm × 30 mm, 5 μm, 30 °C, 120 bar, 150 mL/min, 12% MeOH in CO_2 to give **3a** and **4a**, respectively, as colorless solids.

(1S,4R,6S)-6-Hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**3a**). $[\alpha]_D^{20}$ +115 (*c* 1.0, MeCN). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.14–4.08 (d, 1H, *J* = 10 Hz), 3.52 (s, 1H), 3.36 (s, 1H), 2.72 (s, 3H), 2.65–2.61 (m, 1H), 2.05–1.99 (m, 1H), 1.90–1.82 (m, 2H), 1.59–1.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.9, 70.4, 66.0, 44.0, 36.6, 36.3, 28.0. IR λ 1697, 1521 cm^{-1}. HRMS (FI) calcd $[M]^+$ for $C_7H_{11}NO_2$ 141.0790; obsd 141.0791

(1S,4R,5R)-5-Hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**4a**). $[\alpha]_D^{20}$ +89 (*c* 1.0, MeCN). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.21–4.17 (d, 1H, *J* = 5 Hz), 3.82 (s, 1H), 3.70–3.66 (m, 1H), 2.80–2.72 (m, 1H), 2.67 (s, 3H), 2.15–2.09 (m, 1H), 2.00–1.90 (m, 2H), 1.6–1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.0, 70.3, 61.2, 54.8, 38.2, 36.8, 27.9. IR λ 1693, 1521 cm^{-1}. HRMS (FI) calcd $[M]^+$ for $C_7H_{11}NO_2$ 141.0790; obsd 141.0794.

(1S,4R,6S)-6-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (3b) and (1S,4R,5R)-5-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (**4b**). (1*S*,4*R*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (**2b**) (17.6 g, 76.8 mmol) was dissolved in dry DME (160 mL) and cooled to 0 °C with an icebath. Borane dimethyl sulfide complex (8.0 mL, 84.4 mmol) was added, the icebath was removed, and the stirring continued for 2 h at rt. The reaction was cooled with an icebath, and 3 M NaOH (7.7 mL, 23.0 mmol) and 30% H_2O_2 (21.7 mL, 268.7 mmol) were added. The icebath was removed, and the reaction was stirred at rt for 1 h. NaCl was added, and the reaction mixture was diluted by EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 50:50 to 0:100 then EtOAc/MeOH 95:5) to give a 1:1 mixture of regioisomers **3b** and **4b** (11.2 g, 60%). The regioisomers were separated by chiral HPLC, Reprosil NR, 250 mm × 50 mm, 8 μm, 42 °C, 120 mL/min, heptane/EtOH/TEA 80:20:0.1 to give **3b** and **4b**, respectively, as colorless solids.

(1S,4R,6S)-6-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**3b**).[6] $[\alpha]_D^{20}$ +18 (*c* 1.0, MeCN). ^{1}H NMR (d_6-DMSO, 600 MHz) δ 7.18–7.14 (m, 2H), 6.92–6.88 (m, 2H), 4.29 (d, 1H, *J* = 12 Hz), 4.00 (d, 1H, *J* = 12 Hz), 3.78–3.75 (m, 1H), 3.74 (s, 3H), 3.41–3.38 (m, 1H), 2.55–2.51 (m, 1H), 1.81–1.76 (m, 1H), 1.74–1.67 (m, 2H), 1.42–1.37 (m, 1H). ^{13}C NMR (d_6-DMSO, 150 MHz) δ 176.8, 158.5, 129.7, 129.0 (2C), 114.0 (2C), 69.6, 62.9, 55.0, 43.3, 43.2, 36.1, 35.3. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{14}H_{17}NO_3$ 248.1286; obsd 248.1286.

(1S,4R,5R)-5-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**4b**). $[\alpha]_D^{20}$ +7 (*c* 1.0, MeCN). ^{1}H NMR (d_6-DMSO, 600 MHz) δ 7.17–7.13 (m, 2H), 6.91–6.87 (m, 2H), 5.11 (d, 1H, *J* = 6 Hz), 4.30 (d, 1H, *J* = 12 Hz), 3.94–3.90 (m, 1H), 3.87 (d, 1H, *J* = 12 Hz), 3.73 (s, 3H), 3.66–3.63 (m, 1H), 2.54 (s, 1H), 1.89–1.83 (m,

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708–714

1H), 1.80−1.71 (m, 2H), 1.34−1.28 (m, 1H). ^{13}C NMR (d_6-DMSO, 150 MHz) δ 175.0, 158.5, 129.4, 129.0 (2C), 113.9 (2C), 69.0, 57.9, 55.0, 54.0, 43.2, 38.6, 36.3. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{14}H_{17}NO_3$ 248.1286; obsd 248.1280.

General Procedure A for Table 1. To a suspension of base (0.35 mmol) in dry THF (1.0 mL) was added alcohol **4** (0.18 mmol) dissolved in THF/DMF 2:1 (0.6 mL) at the designated temperature. The reaction was stirred at this temperature for a certain time (see Table 1) and then quenched with AcOH (5 drops). The solvent was removed under reduced pressure, the residue was dissolved in $CDCl_3$, and the ratio **4**:**5** was determined by ^{1}H NMR.

*(1S,4R,5S)-5-Hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**5a**).* Compound **5a** was synthesized from **4a** according to general procedure A. The crude material was purified by column chromatography on silica gel (DCM, DCM/MeOH 25:1) to give **5a** as a colorless oil (18.5 mg, 0.13 mmol, 73%). $[\alpha]_D^{20}$ +33 (*c* 17.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.64 (m, 1H), 3.94 (bs, 1H), 3.62 (m, 1H), 2.94 (m, 1H), 2.79 (s, 3H), 2.08 (m, 1H), 1.87 (m, 1H), 1.45 (m, 2H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 71.0, 61.0, 52.6, 39.4, 35.9, 27.6. HRMS (ES) calcd $[M + H]^+$ for $C_7H_{11}NO_2$ 142.0868; obsd 142.0870.

*(1S,4R,5S)-5-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**5b**).* Compound **5b** was synthesized from **4b** according to general procedure A. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 50:50 to 0:100 then EtOAc/MeOH 95:5) to give **5b** as a colorless solid (0.37 g, 82%). $[\alpha]_D^{20}$ +15 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22−7.16 (m, 2H), 6.87−6.82 (m, 2H), 4.71 (d, 1H, *J* = 15 Hz), 4.71−4.66 (m, 1H), 3.97 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.61−3.57 (m, 1H), 3.08−3.03 (m, 1H), 2.10−2.02 (m, 1H), 1.89−1.82 (m, 1H), 1.47−1.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 159.1, 129.6 (2C), 129.1, 114.1 (2C), 71.1, 58.1, 55.4, 53.0, 43.9, 39.9, 36.5. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{14}H_{17}NO_3$ 248.1286; obsd 248.1287.

*(1S,4R,5R)-5-(Allyloxy)-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**6**).* Allyl bromide (92 μL, 1.06 mmol) and NaH (28 mg, 0.71 mmol) were mixed in dry DMF (0.8 mL) and cooled to 0 °C with an icebath. (1*S*,4*R*,5*R*)-5-Hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**3**) (50 mg, 0.35 mmol) dissolved in dry DMF (0.8 mL) was added, and the reaction was stirred for 2 h at 0 °C. The reaction mixture was quenched with brine and extracted by EtOAc, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 30:70) to give compound **6** as a colorless oil (43 mg, 67%). $[\alpha]_D^{20}$ +43 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.92−5.79 (m, 1H), 5.24 (d, 1H, *J* = 16 Hz), 5.14 (d, 1H, *J* = 8 Hz), 4.06−3.88 (m, 2H), 3.83 (d, 1H, *J* = 4 Hz), 3.65 (s, 1H), 2.90 (s, 1H), 2.65 (s, 3H), 2.12−2.03 (m, 1H), 1.94−1.82 (m, 2H), 1.64−1.57 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 133.5, 116.2, 76.6, 69.6, 59.6, 49.8, 35.9, 35.8, 26.8. IR λ 1697, 1521 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{10}H_{15}NO_2$ 182.1181; obsd 182.1174.

*(1S,4R,5S)-5-(Allyloxy)-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**7**).* A slurry of NaH (28 mg, 0.71 mmol) in dry THF (2 mL) was cooled to 0 °C with an icebath, and (1*S*,4*R*,5*R*)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-3-one (**3**) (50 mg, 0.35 mmol) dissolved in THF/DMF 2:1 (1.2 mL) was added. The reaction was stirred at 0 °C for 30 min. Allyl bromide (61 μL, 0.71 mmol) was added, and the reaction was stirred for 15 h (0 °C to rt). The reaction mixture was diluted with brine and extracted by EtOAc, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 70:30 to 20:80) to give compound **7** as a colorless oil (39 mg, 61%). $[\alpha]_D^{20}$ −22 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94−5.84 (m, 1H), 5.30−5.23 (m, 1H), 5.18−5.13 (m, 1H), 4.32−4.26 (m, 1H), 4.19−4.12 (m, 1H), 3.97−3.90 (m, 1H), 3.65−3.61 (m, 1H), 3.07−3.03 (m, 1H), 2.80 (s, 3H), 2.12−2.04 (m, 1H), 1.96−1.89 (m, 1H), 1.54−1.48 (m, 1H), 1.44−1.39 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 134.7, 117.5, 77.6, 70.4, 60.4, 49.5, 39.0, 34.7, 27.5. IR λ 1697, 1521 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{10}H_{15}NO_2$ 182.1181; obsd 182.1174.

*General procedure B: Alkylation of (1S,4R,5R)-5-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (4b) with Selective Retention (**8a−f**).* A slurry of NaH (24 mg, 0.61 mmol) and electrophile (see Table 3) (0.61 mmol) in dry DMF (2.5 mL) was cooled to 0 °C with an icebath, and (1*S*,4*R*,5*R*)-5-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (**4b**) (75 mg, 0.30 mmol) dissolved in dry DMF (0.5 mL) was added. The reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with brine and extracted by EtOAc, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography.

*(1S,4R,5R)-5-(Allyloxy)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**8a**).* Compound **8a** was synthesized according to general procedure B. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **8a** as a colorless oil (74 mg, 85%). $[\alpha]_D^{20}$ +4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16−7.11 (m, 2H), 6.87−6.81 (m, 2H), 5.92−5.81 (m, 1H), 5.29−5.22 (m, 1H), 5.18−5.13 (m, 1H), 4.52 (d, 1H, *J* = 15 Hz), 4.05−3.90 (m, 2H), 3.90−3.86 (m, 1H), 3.84 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.65−3.62 (m, 1H), 3.00−2.97 (m, 1H), 1.98−1.91 (m, 1H), 1.91−1.82 (m, 2H), 1.58−1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 159.2, 134.5, 129.4 (2C), 128.9, 117.2, 114.2 (2C), 77.7, 70.6, 58.0, 55.4, 51.1, 44.3, 37.5 (2C). IR λ 1695, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{17}H_{21}NO_3$ 288.1599; obsd 288.1610.

*(1S,4R,5R)-2-(4-Methoxybenzyl)-5-((2-methylallyl)oxy)-2-azabicyclo[2.2.1]heptan-3-one (**8b**).* Compound **8b** was synthesized according to general procedure B. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **8b** as a colorless oil (72 mg, 79%). $[\alpha]_D^{20}$ +1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.11 (m, 2H), 6.88−6.82 (m, 2H), 4.96−4.93 (m, 1H), 4.88−4.85 (m, 1H), 4.54 (d, 1H, *J* = 15 Hz), 3.94−3.82 (m, 3H), 3.84 (d, 1H, *J* = 15 Hz), 3.79 (s, 3H), 3.66−3.62 (m, 1H), 3.00−2.97 (m, 1H), 1.98−1.91 (m, 1H), 1.91−1.81 (m, 2H), 1.73−1.68 (m, 3H), 1.59−1.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 159.2, 142.0, 129.4 (2C), 129.0, 114.2 (2C), 112.3, 77.6, 73.6, 58.0, 55.4, 51.2, 44.3, 37.6, 37.4, 19.6. IR λ 1696, 1515 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{18}H_{23}NO_3$ 302.1756; obsd 302.1752.

*(1S,4R,5R)-2-(4-Methoxybenzyl)-5-((3-methylbut-2-en-1-yl)oxy)-2-azabicyclo[2.2.1]-heptan-3-one (**8c**).* Compound **8c** was synthesized according to general procedure B. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **8c** as a colorless oil (79 mg, 83%). $[\alpha]_D^{20}$ −3 (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.11 (m, 2H), 6.87−6.81 (m, 2H), 5.33−5.26 (m, 1H), 4.53 (d, 1H, *J* = 15 Hz), 4.04−3.84 (m, 3H), 3.84 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.65−3.61 (m, 1H), 3.03−2.99 (m, 1H), 1.97−1.90 (m, 1H), 1.90−1.81 (m, 2H), 1.74−1.70 (m, 3H), 1.67−1.63 (m, 3H), 1.56−1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 159.2, 137.6, 129.4 (2C), 129.0, 120.7, 114.2 (2C), 77.5, 66.2, 58.0, 55.4, 51.0, 44.3, 37.5 (split, 2C), 25.9, 18.1. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{19}H_{25}NO_3$ 316.1913; obsd 316.1924.

*(1S,4R,5R)-5-(Benzyloxy)-2-(4-methoxybenzyl)-2-azabicyclo-[2.2.1]heptan-3-one (**8d**).* Compound **8d** was synthesized according to general procedure B. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **8d** as a colorless oil (86 mg, 84%). $[\alpha]_D^{20}$ −1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.25 (m, 5H), 7.18−7.13 (m, 2H), 6.89−6.83 (m, 2H), 4.56 (d, 1H, *J* = 15 Hz), 4.55 (d, 1H, *J* = 15 Hz), 4.48 (d, 1H, *J* = 15 Hz), 3.98 (dd, 1H, *J* = 2.5, 7 Hz), 3.85 (d, 1H, *J* = 15 Hz), 3.80 (s, 3H), 3.68−3.64 (m, 1H), 3.09−3.05 (m, 1H), 2.01−1.94 (m, 1H), 1.91−1.89 (m, 3H), 1.65−1.58 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 159.2, 138.0, 129.4 (2C), 128.9, 128.5 (2C), 127.8, 127.7 (2C), 114.2 (2C), 77.8, 71.7, 58.0, 55.4, 51.1, 44.3, 37.6, 37.5. IR λ 1689, 1514 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{21}H_{23}NO_3$ 338.1756; obsd 338.1759.

*Ethyl 2-(((1S,4R,5R)-2-(4-Methoxybenzyl)-3-oxo-2-azabicyclo-[2.2.1]heptan-5-yl)oxy)-acetate (**8e**).* Compound **8e** was synthesized according to general procedure B. The crude material was purified by

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708−714

column chromatography on silica gel (heptane/EtOAc 70:30 to 30:70) to give **8e** as a colorless oil (30 mg, 30%). $[\alpha]_D^{20}$ +7 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.11 (m, 2H), 6.88−6.82 (m, 2H), 4.52 (d, 1H, *J* = 15 Hz), 4.19 (q, 2H, *J* = 5 Hz), 4.13−4.04 (m, 2H), 3.95−3.91 (m, 1H), 3.85 (d, 1H, *J* = 15 Hz), 3.79 (s, 3H), 3.67−3.64 (m, 1H), 3.01−2.98 (m, 1H), 2.04−1.97 (m, 1H), 1.92−1.88 (m, 2H), 1.68−1.62 (m, 1H), 1.27 (t, 3H, *J* = 5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.1, 170.2, 159.3, 129.4 (2C), 128.8, 114.2 (2C), 79.3, 67.2, 61.2, 58.0, 55.4, 51.0, 44.4, 37.6, 37.5, 14.3. IR λ 1756, 1693, 1521 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{18}H_{23}NO_5$ 334.1654; obsd 334.1667.

*(1S,4R,5R)-5-Methoxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**8f**).* Compound **8f** was synthesized according to general procedure B. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 70:30 to 35:65) to give **8f** as a colorless oil (69 mg, 87%). $[\alpha]_D^{20}$ +8 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.11 (m, 2H), 6.87−6.82 (m, 2H), 4.52 (d, 1H, *J* = 15 Hz), 3.86 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.75−3.71 (m, 1H), 3.65−3.61 (m, 1H), 3.32 (s, 3H), 3.03−2.99 (m, 1H), 1.97−1.89 (m, 1H), 1.89−1.75 (m, 2H), 1.52−1.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 159.2, 129.4 (2C), 128.9, 114.2 (2C), 79.7, 58.0, 57.3, 55.4, 50.5, 44.3, 37.4, 37.3. IR λ 1693, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{15}H_{19}NO_3$ 262.1443; obsd 262.1433.

*General Procedure C: Alkylation of (1S,4R,5R)-5-Hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (**4b**) with Selective Inversion (**9a−f**).* A slurry of NaH (24 mg, 0.61 mmol) in dry THF (2 mL) was cooled to 0 °C with an icebath, and (1*S*,4*R*,5*R*)-5-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (**4b**) (75 mg, 0.30 mmol) dissolved in dry THF/DMF 2:1 (1 mL) was added. The reaction was stirred at 0 °C for 1 h. The electrophile (see Table 3) (0.61 mmol) was added, and the reaction was stirred for 15 h (0 °C to rt). The reaction mixture was diluted with brine and extracted by EtOAc, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography.

*(1S,4R,5S)-5-(Allyloxy)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**9a**).* Compound **9a** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **9a** as a colorless oil (54 mg, 62%). $[\alpha]_D^{20}$ −32 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.22−7.16 (m, 2H), 6.87−6.81 (m, 2H), 5.97−5.86 (m, 1H), 5.32−5.25 (m, 1H), 5.20−5.14 (m, 1H), 4.63 (d, 1H, *J* = 15 Hz), 4.32−4.26 (m, 1H), 4.20−4.13 (m, 1H), 4.05 (d, 1H, *J* = 15 Hz), 3.97−3.91 (m, 1H), 3.78 (s, 3H), 3.61−3.57 (m, 1H), 3.14−3.10 (m, 1H), 2.01−1.94 (m, 1H), 1.91−1.84 (m, 1H), 1.43−1.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 159.1, 134.7, 129.6 (2C), 129.3, 117.3, 114.0 (2C), 77.6, 70.3, 57.6, 55.4, 49.9, 43.9, 39.5, 35.2. IR λ 1697, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{17}H_{21}NO_3$ 288.1599; obsd 288.1608.

*(1S,4R,5S)-2-(4-Methoxybenzyl)-5-((2-methylallyl)oxy)-2-azabicyclo[2.2.1]heptan-3-one (**9b**).* Compound **9b** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **9b** as a colorless oil (59 mg, 65%). $[\alpha]_D^{20}$ −30 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.22−7.17 (m, 2H), 6.86−6.81 (m, 2H), 4.98−4.95 (m, 1H), 4.89−4.85 (m, 1H), 4.61 (d, 1H, *J* = 15 Hz), 4.28−4.22 (m, 1H), 4.06 (d, 1H, *J* = 15 Hz), 4.05 (d, 1H, *J* = 10 Hz), 3.84 (d, 1H, *J* = 10 Hz), 3.78 (s, 3H), 3.61−3.57 (m, 1H), 3.13−3.10 (m, 1H), 2.00−1.93 (m, 1H), 1.91−1.84 (m, 1H), 1.75−1.72 (m, 3H), 1.43−1.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 159.1, 142.1, 129.6 (2C), 129.4, 114.0 (2C), 112.4, 77.4, 73.1, 57.7, 55.4, 49.9, 43.9, 39.5, 35.1, 19.7. IR λ 1700, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{18}H_{23}NO_3$ 302.1756; obsd 302.1757.

*(1S,4R,5S)-2-(4-Methoxybenzyl)-5-((3-methylbut-2-en-1-yl)oxy)-2-azabicyclo[2.2.1]-heptan-3-one (**9c**).* Compound **9c** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **9c** as a colorless oil (68 mg, 71%). $[\alpha]_D^{20}$ −37 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21−7.16 (m, 2H), 6.87−6.81 (m, 2H), 5.37−5.31 (m, 1H), 4.69 (d, 1H, *J* = 15 Hz), 4.31−4.25 (m, 1H), 4.22−4.15 (m, 1H), 3.96 (d, 1H, *J* = 15 Hz), 3.95−3.89 (m, 1H), 3.78 (s, 3H), 3.59−3.56 (m, 1H), 3.15−3.12 (m, 1H), 2.03−1.95 (m, 1H), 1.90−1.84 (m, 1H), 1.75−1.71 (m, 3H), 1.71−1.67 (m, 3H), 1.47−1.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 159.1, 137.2, 129.5 (2C), 129.4, 121.0, 114.0 (2C), 77.6, 65.8, 57.5, 55.4, 49.9, 43.8, 39.5, 35.3, 25.9, 18.2. IR λ 1700, 1514 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{19}H_{25}NO_3$ 316.1913; obsd 316.1926.

*(1S,4R,5S)-5-(Benzyloxy)-2-(4-methoxybenzyl)-2-azabicyclo-[2.2.1]heptan-3-one (**9d**).* Compound **9d** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **9d** as a colorless oil (65 mg, 64%). $[\alpha]_D^{20}$ −48 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.25 (m, 5H), 7.23−7.18 (m, 2H), 6.85−6.80 (m, 2H), 4.75 (d, 1H, *J* = 10 Hz), 4.65 (d, 1H, *J* = 15 Hz), 4.44 (d, 1H, *J* = 10 Hz), 4.35−4.29 (m, 1H), 4.08 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.63−3.59 (m, 1H), 3.24−3.20 (m, 1H), 2.01−1.94 (m, 1H), 1.94−1.88 (m, 1H), 1.48−1.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 159.1, 138.0, 129.6 (2C), 129.4, 128.5 (2C), 128.2 (2C), 127.7, 114.0 (2C), 77.5, 71.2, 57.7, 55.4, 49.9, 44.0, 39.5, 35.2. IR λ 1700, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{21}H_{23}NO_3$ 338.1756; obsd 338.1752.

*Ethyl 2-(((1S,4R,5S)-2-(4-Methoxybenzyl)-3-oxo-2-azabicyclo-[2.2.1]heptan-5-yl)oxy)-acetate (**9e**).* Compound **9e** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 70:30 to 35:65) to give **9e** as a colorless oil (62 mg, 61%). $[\alpha]_D^{20}$ −46 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21−7.16 (m, 1H), 6.87−6.81 (m, 2H), 4.63 (d, 1H, *J* = 15 Hz), 4.49−4.44 (m, 1H), 4.25 (d, 1H, *J* = 15 Hz), 4.19 (q, 2H, *J* = 5 Hz), 4.09 (d, 1H, *J* = 15 Hz), 4.02 (d, 1H, *J* = 15 Hz), 3.78 (s, 3H), 3.62−3.58 (m, 1H), 3.15−3.11 (m, 1H), 2.08−2.00 (m, 1H), 1.92−1.85 (m, 1H), 1.55−1.48 (m, 1H), 1.42−1.38 (m, 1H), 1.27 (t, 3H, *J* = 5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 170.2, 159.1, 129.6 (2C), 129.1, 114.1 (2C), 78.6, 66.3, 60.9, 57.6, 55.4, 49.6, 43.9, 39.5, 35.3, 14.3. IR λ 1753, 1700, 1518 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{18}H_{23}NO_5$ 334.1654; obsd 334.1654.

*(1S,4R,5S)-5-Methoxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (**9f**).* Compound **9f** was synthesized according to general procedure C. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20 to 50:50) to give **9f** as a colorless oil (48 mg, 61%). $[\alpha]_D^{20}$ −19 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21−7.16 (m, 2H), 6.87−6.81 (m, 2H), 4.68 (d, 1H, *J* = 15 Hz), 4.17−4.12 (m, 1H), 3.97 (d, 1H, *J* = 15 Hz), 3.79 (s, 3H), 3.61−3.57 (m, 1H), 3.38 (s, 3H), 3.18−3.14 (m, 1H), 2.02−1.94 (m, 1H), 1.91−1.85 (m, 1H), 1.43−1.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 159.1, 129.6 (2C), 129.3, 114.1 (2C), 80.2, 57.5, 57.3, 55.4, 49.7, 43.8, 39.4, 34.9. IR λ 1697, 1514 cm^{-1}. HRMS (ES) calcd $[M + H]^+$ for $C_{15}H_{19}NO_3$ 262.1443; obsd 262.1452.

*(S)-2-(1-(4-Methoxybenxyl)-5-oxopyrrolidin-2-yl)acetaldehyde (**14**).*[16] A solution of (1*S*,4*R*,5*R*)-5-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (**4b**) (18.0 mg, 0.073 mmol) in dry DMSO (0.5 mL) was treated with NaO*t*Bu (20.0 mg, 0.208 mmol) at room temperature. After 20 min, trifluoroacetic acid (0.1 mL) was added and the solution was stirred for further 15 min. The mixture was diluted with water (5.0 mL), and the crude product was extracted with DCM (2 × 5.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (TBME/MeOH 12:1) gave **14** as a colorless oil (14.8 mg, 82%). $[\alpha]_D^{20}$ +2 (*c* 1.0, CH_3CN). ^1H NMR ($CDCl_3$, 500 MHz) δ 9.80 (t, 1H, *J* = 1.3 Hz), 7.27 (m, 2H), 6.98 (m, 2H), 4.88 (d, 1H, *J* = 15.1 Hz), 4.18 (d, 1H, *J* = 15.1 Hz), 4.07 (m, 1H), 3.92 (s, 3H), 2.89 (m, 1H), 2.65 (m, 2H), 2.55 (m, 1H), 2.39 (m, 1H), 1.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.3, 174.9, 159.1, 129.1, 128.3, 114.1, 55.2, 52.3, 47.5, 44.0, 29.8, 24.9. HRMS (FI) calcd $[M]^+$ for $C_{14}H_{17}NO_3$ 247.1208; obsd 247.1227.

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708−714

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02404.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds; NMR studies of intermediate **12** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jonas.branalt@astrazeneca.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Tomas Leek and Lena von Sydow for HRMS measurements, Gunnar Grönberg for NMR-studies, and Magnus Polla for useful chemistry discussions.

■ REFERENCES

(1) (a) Heasley, B. *Eur. J. Org. Chem.* **2009**, *2009*, 1477. (b) Heasley, B. *Curr. Org. Chem.* **2014**, *18*, 641.

(2) For Simeprevir; see: Simeprevir; Rosenquist, Å.; Samuelsson, B.; Johansson, P.-O.; Cummings, M. D.; Lenz, O.; Raboisson, P.; Simmen, K.; Vendeville, S.; de Kock, H.; Nilsson, M.; Horvath, A.; Kalmeijer, R.; de la Rosa, G.; Beumont-Mauviel, M. *J. Med. Chem.* **2014**, *57*, 1673.

(3) Singh, R.; Vince, R. *Chem. Rev.* **2012**, *112*, 4642.

(4) Relative stereochemistry was confirmed by NOE-correlation experiments.

(5) See for example: (a) Duddeck, H.; Feuerhelm, H. T.; Snatzke, G. *Tetrahedron Lett.* **1979**, *20*, 829. (b) Hamelin, O.; Deprés, J.-P.; Greene, A. E. *J. Am. Chem. Soc.* **1996**, *118*, 9992. (c) Jung, M. E.; Chang, J. J. *Org. Lett.* **2012**, *14*, 4898 and references cited therein.

(6) Lu, H.; Silverman, R. B. *J. Med. Chem.* **2006**, *49*, 7404.

(7) To the best of our knowledge, this is the first example of hydroboration/oxidation of Vince lactam or *N*-protected derivatives thereof; see also ref 3.

(8) Due to poor solubilities of **4a** and **4b** in THF at 0.1 M concentration, a small amount of DMF (ca. 10%) was added to give homogeneous solutions and reproducible results, while having only a minor effect on reactivity/selectivity.

(9) For successful use of TBAF in THF for retroaldol−aldol reactions, see for example ref 5b.

(10) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.

(11) A relative energy difference of 1.1 kcal/mol in favor of **5a** (versus **4a**) was calculated using the MM2 force field, which may indicate a similar relative energy difference for the corresponding intermediate metal alcoholates.

(12) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(13) See Supporting Information.

(14) Addition of electrophiles (e.g., methyl iodide) to enolate **12** resulted in mixtures of products methylated at the aldehyde α-position (including *O*-alkylation), while no methylation in the α-position of the amide was observed.

(15) Palmer, C. F.; McCague, R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1201.

(16) Feutran, S. A.; McAlonan, H.; Stevenson, P. J.; Walker, A. D. *Tetrahedron Lett.* **2009**, *50*, 3669.

DOI: 10.1021/acs.joc.5b02404
J. Org. Chem. 2016, 81, 708−714