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Synthesis of Highly Substituted Azepanones from 2*H*-Azirines by a Stepwise Annulation/Ring-Opening Sequence

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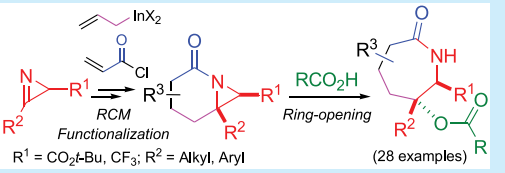
Supporting Information

ABSTRACT: Bicyclic aziridines possessing a 1-azabicyclo[4.1.0]heptan-2-one core were prepared from 2*H*-azirines by a stepwise annulation sequence involving a diastereoselective allylindanation, an *N*-acylation, and a ring-closing metathesis to construct the six-membered ring. After hydrogenation or functionalization of the olefin, regioselective ring opening of the resulting azabicyclic compounds with carboxylic acids (or sulfur nucleophiles) afforded highly substituted azepanones possessing an ester moiety or a trifluoromethyl group and a tetrasubstituted carbon at the α and β positions of the nitrogen atom, respectively.



Substituted nitrogen heterocycles belong to the group of the most important scaffolds in medicinal chemistry.[1] Whereas piperidines and pyrrolidines lie in the top ten of the most frequently encountered heterocycles in marketed drugs,[2] azepanes and their derivatives are also attracting an increasing interest in new lead compound discovery.[3] The fungal metabolite protein kinase inhibitor balanol is undoubtedly the most cited example of a natural product incorporating an azepane ring.[4] Additional examples of bioactive synthetic azepane derivatives include the opioid analgesic meptazinol,[5] the 11β-hydroxy-steroid type 1 dehydrogenase inhibitor **1**,[6] and azepanone **2**,[7] which is a neurokinin-1 receptor antagonist (Figure 1).

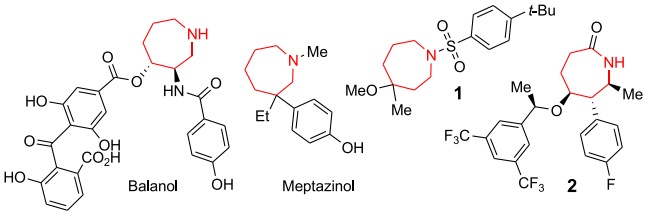
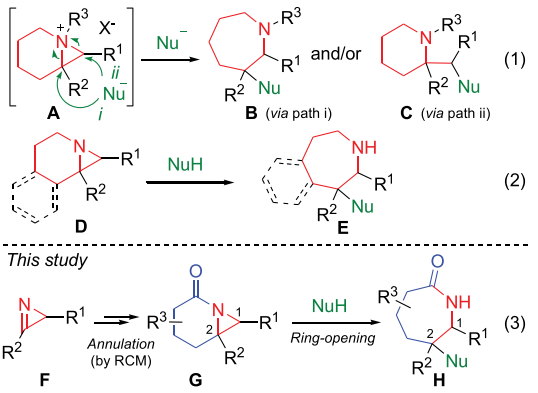


Figure 1. Bioactive azepanes and azepanones.

In this context, the development of synthetic strategies for azepane derivatives with unique substitution patterns is of prime interest. Among the different routes toward these seven-membered heterocycles, the nucleophilic ring opening of 1-azoniabicyclo[4.1.0]heptanes **A** (usually generated by intramolecular nucleophilic substitution) offers an interesting entry to azepanes **B** substituted at the β position of the nitrogen atom.[8,9] The regioselectivity of the ring opening, which can concurrently lead to piperidines **C**, depends on the substituents, the nucleophiles, and the reaction conditions (Scheme 1, eq 1).[8,9] By contrast, the ring opening of bicyclic aziridines **D** has been considerably less investigated to access

Scheme 1. Ring Opening of Bicyclic Aziridiniums and Aziridines toward Azepanes



azepanes **E**, besides examples dealing with substrates in which the shared C−N bond lies at the benzylic position of an electron-rich (fused) aromatic group (Scheme 1, eq 2).[10,11] Herein, we report our studies of the ring opening of azabicyclic compounds **G** incorporating an *N*-acyl aziridine, readily assembled from 2*H*-azirines **F** by a stepwise annulation sequence featuring a ring-closing metathesis to construct the fused six-membered ring, as a route to azepane derivatives **H** (Scheme 1, eq 3).

Although the nucleophilic ring opening of bicyclic sulfonamides, sulfamates, or oxazolidinones incorporating an

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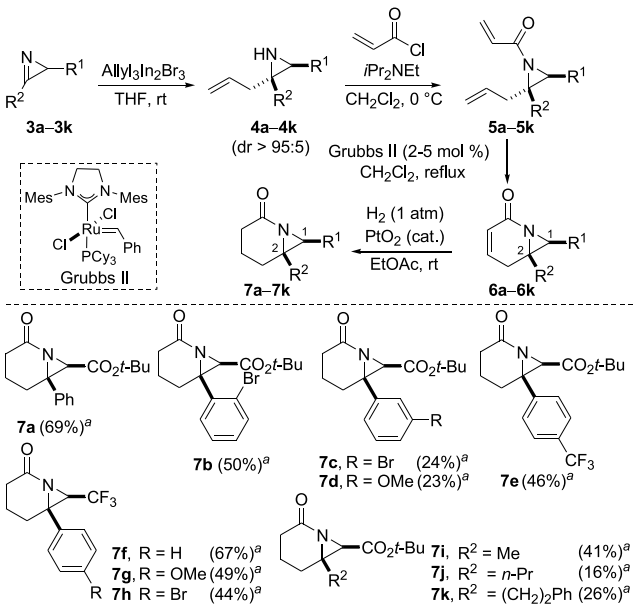
aziridine has been well investigated,[12] the synthesis and reactivity of azabicyclic compounds **G**, substituted at both C1 and C2, have not been explored.[13] From these latter substrates, formation of the desired azepanones **H** requires that the nucleophilic attack occur at the most substituted carbon atom (C2) so the choice of the substituents (R^1 and R^2) appears to be crucial for controlling the regioselectivity. Because the nucleophilic ring opening of aziridines in the presence of a Lewis or a Brønsted acid promoter is known to be disfavored at the adjacent position of an ester and a trifluoromethyl group,[14] those two latter substituents were selected at C1 in compounds **G**. The requisite substrates were prepared from 2*H*-azirines **3a**–**3k**,[15,16] which were first involved in a diastereoselective allylation (with allylindium sesquibromide, THF, rt) leading to aziridines **4a**–**4k**, respectively (>95:5 dr).[17] Acylation of the nitrogen atom with acryloyl chloride and subsequent ring-closing metathesis of dienes **5a**–**5k** in the presence of Grubbs second-generation catalyst (CH_2Cl_2, reflux) enabled the construction of the six-membered ring and afforded azabicyclic compounds **6a**–**6k**, respectively.[18] Our investigations of the ring opening of the three-membered ring were first carried out on bicyclic aziridines **7a**–**7k** obtained by hydrogenation of unsaturated compounds **6a**–**6k**, respectively, catalyzed by PtO_2 (EtOAc, rt). Diversely substituted 1-azabicyclo[4.1.0]heptan-2-ones armed with a *tert*-butyl ester at C1 and possessing either an aryl (**7a**–**7e**) or an alkyl substituent (**7j**–**7k**) at C2 or with a trifluoromethyl substituent at C1 and an aryl substituent at C2 (**7f**–**7h**) were thus obtained in moderate to good overall yields (16–69%, four steps from the corresponding azirines **3a**–**3k**) as single diastereomers (>95:5 dr) (Scheme 2).

The ring opening of azabicyclic compounds **7a**–**7i** was first attempted with acetic acid as the nucleophile in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid promoter (CH_2Cl_2, 0 °C).[14g] Under these mild conditions, the ring opening of **7a** proceeded regioselectively and led to a 90:10 diastereomeric mixture of azepanone **8a** and its epimer at the tetrasubstituted carbon atom in 85% yield. The relative configuration of the major diastereomer **8a**, which was unambiguously established by X-ray diffraction analysis,[19] showed that this latter compound arises from ring opening of **7a** by AcOH with inversion of configuration at C2. The phenyl group at C2 that is able to stabilize an adjacent carbocation may explain the formation of the minor epimer of **8a** at C2.[20] The ring opening is very sensitive to steric hindrance, and azepanone **8b** could not be obtained from **7b** possessing an *o*-bromophenyl group at C2. No reaction occurred at rt, and substrate **7b** underwent decomposition under harsher conditions. Substitution of the aryl group at the *meta* or *para* position was tolerated as illustrated with the isolation of azepanones **8c**–**8e** (53–68%). Substrates **7f**–**7h** also reacted well and delivered trifluoromethylated azepanones **8f** (85%), **8g** (66%), and **8h** (70%), respectively.[21] It is worth noting that less diastereocontrol (85:15 dr) was observed in the case of **8g** possessing a *p*-methoxyphenyl group, which is best able to stabilize a carbocation at C2, compared to the other products **8c**–**8h**. Although substrate **7i** possessing a methyl group at C2 smoothly reacted under these conditions, the expected azepanone **8i** was isolated in modest yield (60%) because the tertiary alkyl fluoride **9i** (31%) was formed as a byproduct. Ring opening of activated aziridines or epoxides by fluoride has already been reported in the presence of $BF_3{\cdot}OEt_2$.[22] This side reaction may become competitive in the case of **7i**, which presumably reacts with AcOH at a rate slower than that of the analogous aziridine **7a** possessing a phenyl group, which can stabilize a positive charge at C2 in the transition state.[23] The relative configuration of **8c**–**8i** was assigned by analogy with azepanone **8a** (ring opening proceeding with inversion of configuration at C2) (Scheme 3).

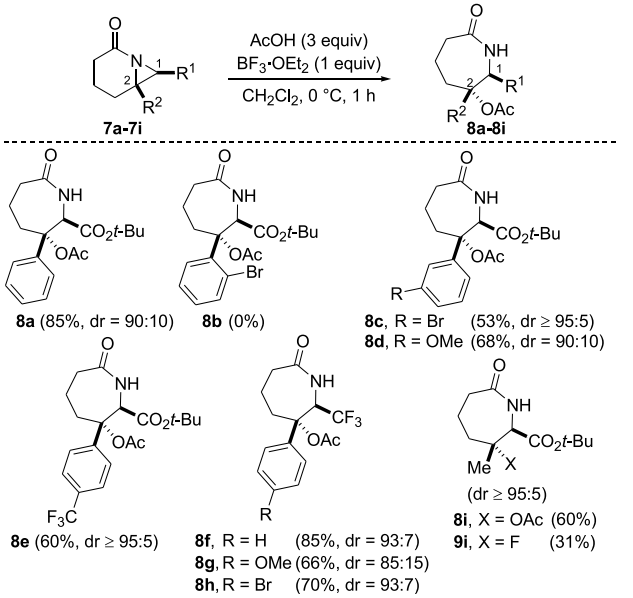
Solvolysis in acetic acid (65 °C, 2 h) was then investigated as an alternative method.[14d] Under these conditions, substrate **7a** led to a 70:30 mixture of azepanone **8a** and unsaturated lactam **10**, arising from the ring opening of the aziridine by an elimination reaction, which could not be separated by flash chromatography.[24] By contrast, solvolytic conditions turned

Scheme 2. Preparation of Azabicyclic Compounds 7a–7k[a]



[a]Overall yields from the corresponding azirines (four steps).

Scheme 3. Ring Opening of Azabicyclic Compounds 7a–7i with AcOH Promoted by $BF_3{\cdot}OEt_2$



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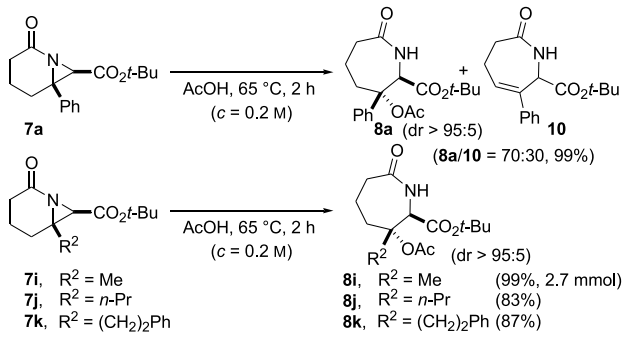
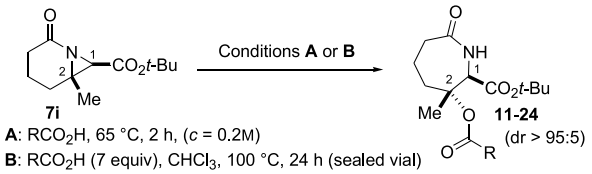
out to be appropriate for achieving the ring opening of aziridines **7i**–**7k** possessing an alkyl group at C2, which afforded azepanones **8i** (99%) (2.7 mmol scale), **8j** (83%), and **8k** (87%), respectively, in high yields and as single diastereomers (Scheme 4).

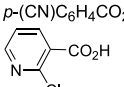
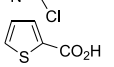
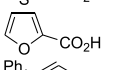
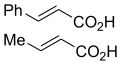
Scheme 4. Solvolysis of 7a and 7i–7k in AcOH



Solvolysis of aziridine **7i** was then achieved by heating in propionic acid, 4-pentenoic acid, and methoxyacetic acid (conditions A, Table 1, entries 1–3) to afford azepanones **11**

Table 1. Ring Opening of Aziridine 7i with Carboxylic Acids



entry	RCO_2H	conditions	product	yield
1	$EtCO_2H$	A	11	68%
2	$CH_2{=}CH(CH_2)_2CO_2H$	A	12	71%
3	$MeOCH_2CO_2H$	A	13	81%
4	$BrCH_2CO_2H$	A	14	26%
5	$BrCH_2CO_2H$	B	14	49%
6	$PhCO_2H$	B	15	83%
7	*o*-$IC_6H_4CO_2H$	B	16	74%
8	*p*-$BrC_6H_4CO_2H$	B	17	54%
9	*p*-$(CF_3)C_6H_4CO_2H$	B	18	65%
10	*p*-$(CN)C_6H_4CO_2H$	B	19	77%
11		B	20	38%
12		B	21	83%
13		B	22	71%
14		B	23	75%
15		B	24	85%

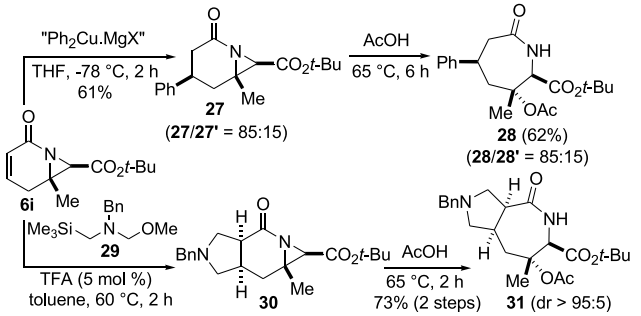
(68%), **12** (71%), and **13** (81%), respectively. With the more acidic bromoacetic acid, significant decomposition of **7i** was observed and the ring-opening product **14** was isolated in low yield (26%) (Table 1, entry 4). An improvement was observed upon using an excess of bromoacetic acid (7 equiv), although heating in chloroform (100 °C, 24 h) was now required to trigger the ring opening of **7i** (conditions B). With this alternative procedure, azepanone **14** was isolated in 49% yield (Table 1, entry 5) and the scope was then extended to a variety of carboxylic acids that could not be used as a solvent. Substituted benzoic acids (Table 1, entries 6–10), heteroaromatic acids (Table 1, entries 11–13), and α,β-unsaturated carboxylic acids (Table 1, entries 14 and 15) were involved as nucleophiles in the ring opening of **7i** to produce the corresponding azepanones **15**–**24** (38–85%) (Table 1).[25]

The reactivity of bicyclic aziridines **7a** and **7i** was also investigated in the presence of sulfur nucleophiles. Ring opening of **7a** with benzyl mercaptan in the presence of $BF_3{\cdot}OEt_2$ proceeded regioselectively and produced thioether **25** in high yield (85%) as a single diastereomer. On the other hand, solvolysis of **7i** in thioacetic acid led to azepanone **26** (71%, >95:5 dr) (Scheme 5).

Scheme 5. Ring Opening of 7a and 7i with Sulfur Nucleophiles

With the goal of accessing azepanones possessing additional stereocenters, the functionalization of the α,β-unsaturated *N*-acyl-aziridine **6i**, the precursor of aziridine **7i**, was investigated. Thus, 1,4-addition of a magnesium phenylcuprate (generated from PhMgCl and CuI) to **6i** afforded a diastereomeric mixture of azabicyclic compounds **27** and **27′** in an 85:15 ratio. The relative configuration of the major diastereomer **26** indicated that the addition of the organocuprate preferentially occurred on the convex face of azabicyclic compound **6i**.[26] Solvolysis of the **27**/**27′** mixture in AcOH afforded a diastereomeric mixture of ring-opened products **28** and **28′** from which the major diastereomer **28** was isolated in 62% yield. Substrate **6i** was also engaged in a 1,3-dipolar cycloaddition with the azomethine ylide generated *in situ* from reagent **29** (cat. TFA, toluene, 60 °C), and the crude cycloadduct **30** was directly solvolyzed in AcOH to afford bicyclic azepanone **31** (73%, two steps from **6i**) (Scheme 6).[26]

Scheme 6. Functionalization of 6i and Subsequent Ring Opening with AcOH



Azepanones can serve as precursors of substituted azepanes. Thus, reduction of azepanone **8i** with $LiAlH_4$ delivered azepane **32** (70%) containing a primary alcohol and a tertiary alcohol. Chemoselective reduction of the amide in **8i** could be carried out using $BH_3{\cdot}THF$ to afford azepane **33** in 61% yield, albeit with some epimerization (90:10 dr) (Scheme 7).

In conclusion, we have reported the synthesis of new scaffolds possessing a 1-azabicyclo[4.1.0]heptan-2-one core

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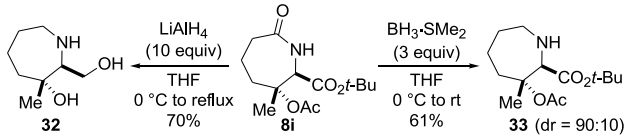
Scheme 7. Access to Azepanes 32 and 33



from 2*H*-azirines through a stepwise annulation process. These latter azabicyclic compounds can be functionalized and undergo regioselective ring opening with carboxylic acids or sulfur nucleophiles to afford azepanones possessing an ester functional group or a trifluoromethyl substituent at the α position of the nitrogen atom as well as a tetrasubstituted carbon atom at the β position. This work complements the current knowledge of regioselective ring-opening reactions involving bicyclic aziridines and further highlights the interest of strained ring-cleavage strategies as a route to seven-membered nitrogen heterocycles. Other applications of these processes are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00999.

Experimental procedures, characterization data, and spectra for all new compounds (PDF)

Accession Codes

CCDC 1900066 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.
(2) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5859.
(3) Zha, G.-F.; Rakesh, K. P.; Manukumar, H. M.; Shantharam, C. S.; Long, S. *Eur. J. Med. Chem.* **2019**, *162*, 465−494.
(4) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452−6453.
(5) Holmes, B.; Ward, A. *Drugs* **1985**, *30*, 285−312.
(6) Neelamkavil, S. F.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J.; Zhang, L.; Terracina, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4563−4565.
(7) Elliott, J. M.; Carlson, E. J.; Chicchi, G. G.; Dirat, O.; Dominguez, M.; Gerhard, U.; Jelley, R.; Jones, A. B.; Kurtz, M. M.; Tsao, K. I.; Wheeldon, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2929−2932.
(8) For a review, see: Dolfen, J.; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Ha, H.-J. *Adv. Synth. Catal.* **2016**, *358*, 3485−3511.
(9) (a) Chong, H.-S.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2080−2086. (b) Vervisch, K.; D'hooghe, M.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 7734−7744. (c) Lee, K. M.; Kim, J. C.; Kang, P.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron* **2012**, *68*, 883−893. (d) Anxionnat, B.; Robert, B.; George, P.; Ricci, G.; Perrin, M.-A.; Gomez-Pardo, D.; Cossy, J. *J. Org. Chem.* **2012**, *77*, 6087−6099. (e) Zhou, J.; Yeung, Y.-Y. *Org. Lett.* **2014**, *16*, 2134−2137. (f) Choi, J.; Yadav, N. N.; Ha, H.-J. *Asian J. Org. Chem.* **2017**, *6*, 1292−1307.
(10) For recent reviews highlighting the synthetic utility of aziridines, see: (a) Macha, L.; D'hooghe, M.; Ha, H.-J. *Synthesis* **2019**, *51*, 1491−1515. (b) Singh, G. S.; Sudheesh, S.; Keroletswe, N. *ARKIVOC* **2019**, *2018*, 50−113.
(11) (a) Blaskó, G.; Elango, V.; Murugesan, N.; Shamma, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1246−1248. (b) Hanaoka, M.; Inoue, M.; Nagami, K.; Shimada, Y.; Yasuda, S. *Heterocycles* **1982**, *19*, 313−318. (c) Hanaoka, M.; Ashimori, A.; Yamagishi, H.; Yasuda, S. *Chem. Pharm. Bull.* **1983**, *31*, 2172−2175. (d) Hanaoka, M.; Kim, S. K.; Inoue, M.; Nagami, K.; Shimada, Y.; Yasuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 1434−1443. (e) Alvernhe, G.; Laurent, A.; Touhami, K.; Bartnik, R.; Mloston, G. *J. Fluorine Chem.* **1985**, *29*, 363−384.
(12) For examples, see: (a) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327−2329. (b) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. (c) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (d) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377−6386. (e) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331−11342. (f) Wehn, P. W.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802−3805. (g) Malik, G.; Estéoule, A.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2011**, *76*, 7438−7448. (h) Rigoli, J. W.; Boralsky, L. A.; Hershberger, J. C.; Marston, D.; Meis, A. R.; Guzei, I. A.; Schomaker, J. M. *J. Org. Chem.* **2012**, *77*, 2446−2455. (i) Goto, A.; Yoshimura, S.; Nakao, Y.; Inai, M.; Asakawa, T.; Egi, M.; Hamashima, Y.; Kondo, M.; Kan, T. *Org. Lett.* **2017**, *19*, 3358−3361.
(13) One previous example of a substrate of type **G**, unsubstituted at C1, has been reported. Subsequent nucleophilic additions occur either at C1 or on the carbonyl group: Wu, X.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2003**, *59*, 1483−1491.
(14) Ring opening of aziridines under these conditions occurs at the carbon best able to stabilize a positive charge. For examples, see: (a) Berse, C.; Bessette, P. *Can. J. Chem.* **1971**, *49*, 2610−2611. (b) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 121−126. (c) Quinze, K.; Laurent, A.; Mison, P. *J. Fluorine Chem.* **1989**, *44*, 233−265. (d) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59−68. (e) Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* **1996**, *37*, 6893−6896. (f) Davoli, P.; Forni, A.; Franciosi, C.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2361−2371. (g) Papa, C.; Tomasini, C. *Eur. J. Org. Chem.* **2000**, *2000*, 1569−1576. (h) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Synlett* **2001**, *2001*, 0679−0681. (i) Chai, Z.; Bouillon, J.-P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471−9473. (j) Moens, M.; De Kimpe, N.; D'hooghe, M. *J. Org. Chem.* **2014**, *79*, 5558−5568. (k) Angyal, A.; Demjén, A.; Wéber, E.; Kovács, A. K.; Wölfling, J.; Puskás, L. G.; Kanizsai, I. *J. Org. Chem.* **2018**, *83*, 3570−3581.
(15) For reviews, see: (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: New York, 1996; Vol. *1A*, pp 1−60. (b) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E. M.; de Los

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Santos, J. M. *Eur. J. Org. Chem.* **2001**, *2001*, 2401−2414. (c) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363−3401.
(16) Azirines possessing an ester moiety were prepared from the corresponding β-keto esters. For the preparation of trifluoromethyl azirines, see: He, Y.-T.; Wang, Q.; Zhao, J.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. *Chem. Commun.* **2015**, *51*, 13209−13212.
(17) Hirashita, T.; Toumatsu, S.; Imagawa, Y.; Araki, S.; Setsune, J.-i. *Tetrahedron Lett.* **2006**, *47*, 1613−1616.
(18) Related RCM reactions with *N*-allyl-aziridines were unsuccessful: Davoli, P.; Spaggiari, A.; Ciamaroni, E.; Forni, A.; Torre, G.; Prati, F. *Heterocycles* **2004**, *63*, 2495−2514.
(19) CCDC 1900066 (**8a**) contains the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(20) We checked that compound **8a** does not epimerize under the reaction conditions.
(21) For a recent approach toward 2-trifluoromethylazepanes, see: Masson, G.; Rioton, S.; Gomez-Pardo, D.; Cossy, J. *Org. Lett.* **2018**, *20*, 5019−5022 and references therein .
(22) (a) Hu, X. E. *Tetrahedron Lett.* **2002**, *43*, 5315−5318. (b) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 2218−2220.
(23) Attempts to favor the formation of tertiary fluoride **9i** by addition of excess $BF_3{\cdot}OEt_2$ or water were unsuccessful.
(24) The **8a**:**10** ratio did not change over the course of the reaction or if the mixture was again subjected to the reaction conditions, which suggests that **10** is not formed from **8a** by elimination of AcOH.
(25) Attempts to deacetylate **8i** under alkaline conditions to the tertiary alcohol (that could have been further esterified) were unsuccessful. β-Elimination of the acetate occurred as the main side reaction.
(26) The related configuration of **27** and **31** was ascertained by NMR (NOESY). See the Supporting Information.

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