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Novel Diastereoselective Synthesis of Bicyclic β-Lactams through Radical Cyclization and Their Reduction toward 2-(1-Alkoxy-2-hydroxyethyl)piperidines and 2-(1-Alkoxy-2-hydroxyethyl)azepanes

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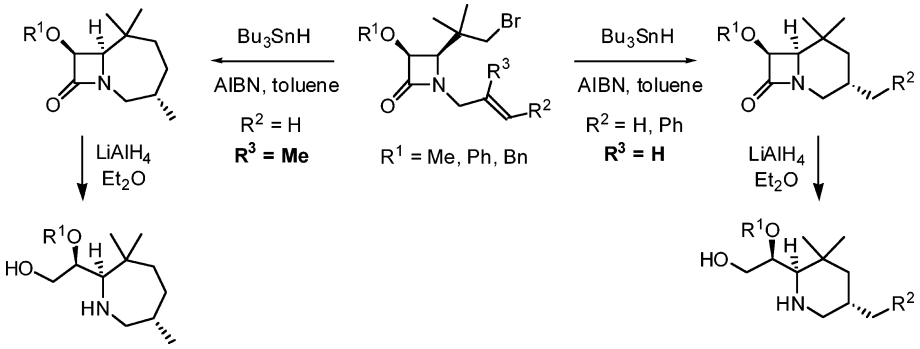

1-Allyl- and 1-(3-phenylallyl)-substituted 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones were transformed into 3-substituted 7-alkoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octane-8-ones through radical cyclization by means of *n*-tributyltin hydride and AIBN in toluene with excellent diastereocontrol (≥99%). The radical cyclization of 4-(2-bromo-1,1-dimethylethyl)-1-(2-methylallyl)azetidin-2-ones afforded 8-alkoxy-3,6,6-trimethyl-1-azabicyclo[5.2.0]nonan-9-ones in good diastereomeric excess (75−78%). The reductive ring opening of 1-azabicyclo[4.2.0]octane-8-ones and 1-azabicyclo[5.2.0]nonan-9-ones with lithium aluminum hydride resulted in novel 2-(1-alkoxy-2-hydroxyethyl)piperidines and -azepanes, which were isolated as single isomers.

Introduction

The extensive use of (β-lactam) antibiotics in the last decades has resulted in the rapid emergence of bacterial resistance and the development of multi-drug-resistant strains.[1] Hence, the search for novel types of bioactive β-lactams has become one of the major challenges in medicinal and pharmaceutical chemistry. The majority of biologically active β-lactams comprises a bicyclic framework bearing the nitrogen atom at the bridgehead. In this way, the lactam functionality has less planarity and resonance stability, favoring nucleophilic attack and consecutive ring opening.[2] Besides their biological relevance, azetidin-2-ones have acquired a prominent place in organic synthesis as building blocks due to their inherent reactivity, which has led to the introduction of the term "β-lactam synthon method" in 1997.[3]

In recent years, more and more efforts have been devoted to the development of new radical cyclization processes, especially in the field of natural product synthesis.[4] Several attractive features of radical chemistry can account for this interest, such

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(1) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395.

(2) Sweet, R. M. In *Cephalosporines and Penicillins, Chemistry and Biology*; Flynn E. H., Ed.; Academic Press: New York, 1972; p 280.

(3) (a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, 377. (c) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631. (d) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.

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as the ability to form new C−C bonds (even at congested sites), functional group tolerance, and high regioselectivity. An important strategy in this respect comprises the formation of C−C bonds through intramolecular *endo*- or *exo*-cyclization of carbon radicals onto alkene moieties.[5] In the literature, several interesting syntheses of bicyclic β-lactams have been reported based on this approach. 1-Azabicyclo[3.2.0]heptan-7-ones and 5-oxa-1-azabicyclo[4.2.0]octan-8-ones have been prepared in good yields by radical annulations of monocyclic β-lactams bearing appropriate appendages by means of tributyltin hydride and azoisobutyronitrile in benzene.[6] An analogous approach with tributyltin hydride and azoisobutyronitrile has been reported for the synthesis of a 3-methylene-1-azabicyclo[5.2.0]non-4-en-9-one.[7] Furthermore, the 6-*endo*-*trig* cyclization of an *N*-allyl-7-bromo-3*a*-methylhexahydroindolinone system has been described under high dilution conditions with tributyltin hydride and a catalytic amount of AIBN toward a tricyclic γ-lactam, whereas also 5-*exo*-*trig* cyclization was observed as a minor reaction pathway if the radical reaction was executed with only tributyltin hydride and no AIBN.[8]

In continuation of our interest in the synthesis of novel bicyclic β-lactams,[9] an efficient and straightforward radical approach toward 1-azabicyclo[4.2.0]octan-8-ones and 1-azabicyclo[5.2.0]nonan-9-ones with excellent diastereocontrol is described in the present paper. The bicyclic azetidin-2-ones obtained in this work were subsequently transformed into functionalized 2-(1-alkoxy-2-hydroxyethyl)piperidine and -azepane derivatives as single diastereomers via a reductive ring opening. Besides the frequent occurrence of azaheterocyclic systems in bioactive compounds, 2-(1-alkoxy-2-hydroxyethyl)piperidines and -azepanes are of general importance in medicinal chemistry due to the presence of a 1,2,3-triheteroatom-substituted submoiety,[10] and analogous compounds have been described as cardiovascular agents.[11] Furthermore, 2-(1,2-dihydroxyethyl)-piperidine has been used as an intermediate in the synthesis of pipecolic acid (a component of several secondary metabolites in plants and fungi[12]), as a precursor of nonribosomal peptides with novel pharmacological activities,[13] and as a key structural component in the synthesis of the NMDA receptor antagonists etoxadrol **1** and dexoxadrol **2** (Figure 1).[14,15]

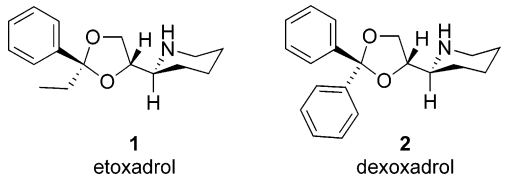


FIGURE 1.

Results and Discussion

N-Allyl-β-bromoimine **4a** was prepared in good yield via imination of 3-bromo-2,2-dimethylpropanal **3** in diethyl ether at room temperature utilizing 1 equiv of allylamine in the presence of $MgSO_4$ (Scheme 1).[16] Accordingly, *N*-(3-phenylallyl)-β-bromoimine **4b** and *N*-(2-methyl-2-propenyl)-β-bromoimine **4c** were prepared in excellent yields via imination of 3-bromo-2,2-dimethylpropanal **3** in the presence of $MgSO_4$ and Et_3N utilizing 1 equiv of the corresponding allylammonium bromide (Scheme 1), which were prepared from the corresponding allylic bromides using a 7 N solution of ammonia in methanol under high pressure.[17] 3-Bromo-2,2-dimethylpropanal **3** was obtained via oxidation of 3-bromo-2,2-dimethyl-1-propanol with pyridinium chlorochromate, mixed with silica, in dichloromethane in 75% yield.[16]

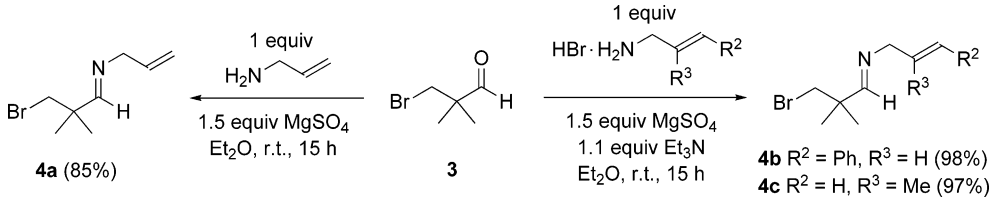
Subsequently, the obtained imines **4** were used as substrates for a Staudinger reaction with different ketenes toward the corresponding β-lactams. Thus, treatment of *N*-allylimine **4a** and *N*-(3-phenylallyl)imine **4b** with 1.3 equiv of methoxy-, phenoxy-, or benzyloxyacetyl chloride in the presence of triethylamine in dichloromethane afforded 1-allyl-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **5a**−**c** and 1-(3-phenylallyl)-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **5d**−**f** in 63−90% yield (Scheme 2, Table 1).[18]

An important issue in the Staudinger synthesis of β-lactams involves the diastereocontrol. The stereochemical outcome of the Staudinger reaction toward azetidin-2-ones **5** was shown to be *cis* based on the coupling constants between the protons at C3 and C4 in ^1H NMR (5.2−5.5 Hz).[19] The *cis*/*trans* stereoselectivity is dependent on the competition between ring closure and isomerization of the imino moiety in the zwitterionic intermediate. Electron-donating ketene substituents and electron-withdrawing imine substituents lead to a preference for *cis*-β-lactam formation,[20] although different experimental factors such as the solvent, the base, the temperature, and the chloride anion could affect the stereochemical outcome.[21]

The synthesis of the targeted bicyclic azetidin-2-ones **6** was accomplished via the unprecedented intramolecular ring closure of 4-(2-bromo-1,1-dimethylethyl)azetidinones **5** through a radicalar reaction triggered by the organotin reagent tributyltin

(4) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793.
(5) Zhang, W. *Tetrahedron* **2001**, *57*, 7237.
(6) (a) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689. (b) Alcaide, B.; Benito, J. L.; Rodriguez-Campos, I. M.; Rodriguez-Lopez, J.; Rodriguez-Vicente, A.; Sierra, M. A.; Garcia-Granda, S.; Gutierrez-Rodriguez, A. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1055. (c) Lee, E.; Kim, S. K.; Kim, J. Y.; Lim, J. *Tetrahedron Lett.* **2000**, *41*, 5915.
(7) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *J. Org. Chem.* **2007**, *72*, 1604.
(8) Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. *J. Org. Chem.* **2005**, *70*, 519.
(9) Van Brabandt, W.; Vanwalleghem, M.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7083.
(10) (a) Narimatsu, S.; Arai, T.; Watanabe, T.; Masubuchi, Y.; Horie, T.; Suzuki, T.; Ishikawa, T.; Tsutsui, M.; Kumagai, Y.; Cho, A. K. *Chem. Res. Toxicol.* **1997**, *10*, 289. (b) Bair, K. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1990**, *33*, 2385. (c) Bair, K. W.; Andrews, C. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1991**, *34*, 1983.
(11) Shanklin, J. R., Jr.; Johnson, C. P. Eur. Pat. Appl. 1988, EP 279707 A2; *Chem. Abstr.* **1988**, *109*, 230821.
(12) Fernández-García, C.; McKervey, M. A. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2905.
(13) Naranjo, L.; Martin de Valmaseda, E.; Bañuelos, O.; Lopez, P.; Riaño, J.; Casqueiro, J.; Martin, J. F. *J. Bacteriol.* **2001**, *183*, 7165.
(14) Thurkauf, A.; Mattson, M. V.; Huguenin, P. N.; Rice, K. C.; Jacobson, A. E. *FEBS Lett.* **1988**, *238*, 369.
(15) Sax, M.; Ebert, K.; Schepmann, D.; Wibbeling, B.; Wünsch, B. *Bioorg. Med. Chem.* **2006**, *14*, 5955.
(16) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647. (b) Sulmon, P.; De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synthesis* **1986**, 192.
(17) Saulnier, M. G.; Zimmermann, K.; Struzynski, C. P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D. B. *Tetrahedron Lett.* **2004**, *45*, 397.
(18) Dejaegher, Y.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 5974.
(19) (a) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, *37*, 3325. (b) Decazes, J.; Luche, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1970**, *11*, 3365.
(20) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.
(21) Li, B.; Wang, Y.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 990.

SCHEME 1



SCHEME 2

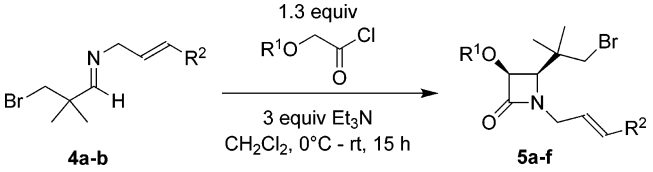


TABLE 1. Synthesis of *cis*-1-(2-Alkenyl)azetidin-2-ones 5 under Staudinger Conditions

entry	R^1	R^2	compd	yield (%)[a]
1	Me	H	**5a**	90
2	Ph	H	**5b**	76
3	Bn	H	**5c**	90
4	Me	Ph	**5d**	63
5	Ph	Ph	**5e**	73
6	Bn	Ph	**5f**	78

[a] Yields after purification by column chromatography.

hydride.[22,23] Treatment of 1-allylazetidin-2-ones **5a**−**c** and 1-(3-phenylallyl)azetidin-2-ones **5d**−**f** with 1.5 equiv of tributyltin hydride and 0.7 equiv of azoisobutyronitrile (AIBN) in refluxing toluene afforded bicyclic 7-alkoxy-5,5-dimethyl-1-azabicyclo-[4.2.0]octane-8-ones **6** for the first time as single diastereomers in 28−37% yield after purification by means of column chromatography or recrystallization from Et_2O (Scheme 3, Table 2).[24] Besides bicyclic compounds **6**, the corresponding monocyclic 4-(*tert*-butyl)-*β*-lactams **7** were also formed in substantial amounts (sometimes >50%), explaining the lower yields of the bicycles **6**. After purification by means of column chromatography, 4-(*tert*-butyl)-*β*-lactams **7** were isolated in 6−11% yield (Scheme 3, Table 2). The low material balance of this radical reaction is mainly due to decomposition of the 4-(*tert*-butyl)-*β*-lactams **7** during the chromatographic purification on silica gel. The use of triethylborane as a radical initiator at −78 or 0 °C in tetrahydrofuran was unsuccessful and the starting materials were recovered.[25]

When the radical cyclization of a chloro derivative, *cis*-1-allyl-4-(2-chloro-1,1-dimethylethyl)-3-phenoxyazetidin-2-one **8**, was evaluated applying the same reaction conditions, the reaction could not be driven to completion, resulting in the formation of the contemplated bicyclic compound **6b** besides the presence of monocyclic 4-(*tert*-butyl)-*β*-lactam **7b** and unreacted starting material **8** in a 36/58/6 ratio (Scheme 4). Therefore, preference was given to the use of 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **5** as substrates for the radical cyclization toward bicyclic *β*-lactams **6**, as in these cases no starting material was recovered afterward. *β*-Lactam **8** was synthesized using the same reaction conditions as described for the preparation of 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **5** (Scheme 2).[18]

The above-described method led to the formation of carbacephams **6** as the sole bicyclic products via radical cyclization of the methyl radical **9**, derived from the corresponding bromo compound **5** through the action of Bu_3SnH/AIBN. Although both 6-*exo*-*trig* and 7-*endo*-*trig* are favored according to the Baldwin rules,[26] only the 6-*exo*-*trig* product was obtained after cyclization giving rise to intermediates **10** (Scheme 5). When R^2 is a phenyl group, the radical in intermediate **10b** is located at a benzylic position, favoring the 6-*exo*-*trig* step. Also for R^2 = H, the formation of a six-membered ring via a primary radical intermediate **10a** is preferred over the formation of a seven-membered ring via a more stable secondary radical intermediate **11**. Since the yields with R^2 = H are similar to those with R^2 = Ph, the transition state must be quite early and the cyclization is controlled by the best alignment of the orbitals involved, which appears to be better for a 6-*exo*-*trig* than for a 7-*endo*-*trig* cyclization.

Besides the observed regioselectivity, the merit of this radical cyclization approach comprises the stereoselective synthesis of functionalized 1-azabicyclo[4.2.0]octan-2-ones **6** as single diastereomers bearing three stereogenic centers. The relative stereochemistry at positions 6 and 7 is a direct result from the diastereoselective Staudinger reaction affording *cis*-*β*-lactams **5**. During the subsequent radical cyclization step, the preformed geometry of the azetidin-2-one ring accounts for the observed stereoselectivity. Several attempts were performed in order to elucidate the relative configuration at C-3 with respect to the 7-alkoxy group. Nuclear Overhauser effect (NOE) experiments were unsuccessful due to proton overlap, making selective irradiation impossible. Fortunately, X-ray analysis of the bicyclic azetidin-2-one **6b** revealed that the methyl substituent at C3 accommodates a pseudoequatorial position at the six-membered ring, which is folded in a chairlike conformation (see the Supporting Information). Thus, it could be derived that the C-3 substituents and the 7-alkoxy group in compounds **6** are in a *trans*-disposition.

The observed relative stereochemistry can be explained considering the transition states involved in the radical cyclization process (Scheme 6). On the basis of a 3D-model, the transition states **TTS 1** and **TTS 2** are disfavored because of spacial interaction (electronic repulsion) between the methylene radical and one of the electron pairs of oxygen of the alkoxy substituent. In transition states **TTS 3** and **TTS 4**, however,

(22) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1. (b) Davis, A. G. *J. Chem. Res.* **2006**, *3*, 141.

(23) Parsons, A. F. *An introduction to free radical chemistry*; Blackwell Science Ltd: Oxford, UK, 2000; Vol. 1.

(24) Van Brabandt, W.; Dejaegher, Y.; De Kimpe, N. *Pure Appl. Chem.* **2005**, *77*, 2061.

(25) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.

(26) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738. (d) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233.

SCHEME 3

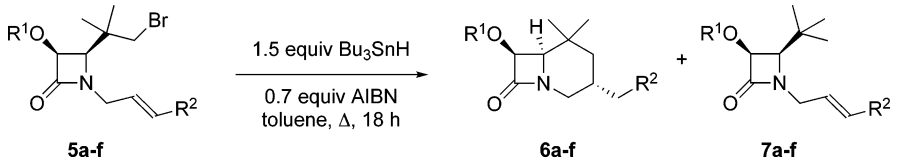


TABLE 2. Synthesis of Bicyclic β-Lactams 6 through Radical Cyclization

entry	R^1	R^2	compd	yield (%)[a]	compd	yield (%)[a]
1	Me	H	**6a**	36	**7a**	11
2	Ph	H	**6b**	29	**7b**	6
3	Bn	H	**6c**	28	**7c**	7
4	Me	Ph	**6d**	35	**7d**	9
5	Ph	Ph	**6e**	28	**7e**	6
6	Bn	Ph	**6f**	37	**7f**	10

[a] Yields after purification by column chromatography or recrystallization from Et_2O.

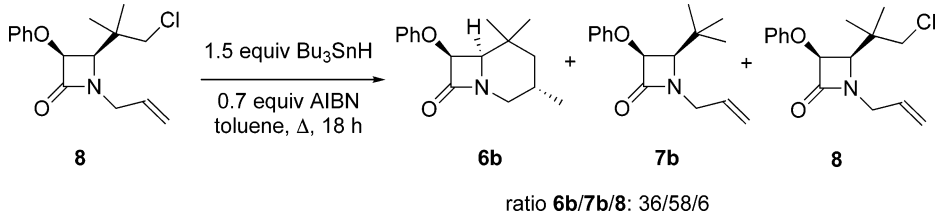
the radical center and the alkoxy group are oriented away from each other. In **TTS 3**, the double bond is pointed pseudoaxial, resulting in a considerable steric hindrance with the lactam moiety. On the other hand, the pseudoequatorial position of the double bond in **TTS 4** minimizes the latter steric repulsion. On the basis of these arguments, the diastereoselective formation of azabicycles **6** can be explained via the most favorable transition state **TTS 4**, resulting in the observed stereochemistry.

Next, the influence of a substituent at the 2′-position of the *N*-allyl group was examined. For this purpose, 4-(2-bromo-1,1-dimethylethyl)-1-(2-methylallyl)azetidin-2-ones **12** were synthesized under Staudinger reaction conditions. The starting *N*-(3-bromo-2,2-dimethylpropylidene)-2-methylallylamine **4c** was prepared via condensation of 3-bromo-2,2-dimethylpropanal **3** with the hydrobromide salt from 2-methylallylamine (Scheme 1). Treatment of this β-bromoimine **4c** with an alkoxy- or phenoxyacetyl chloride in dichloromethane in the presence of Et_3N furnished *cis*-1-(2-methylallyl)azetidin-2-ones **12** in 71−90% yield (Scheme 7, Table 3).

When these novel brominated azetidinones **12** were reacted with 1.5 equiv of tributyltin hydride and 0.7 equiv of azoisobutyronitrile (AIBN) in refluxing toluene, novel bicyclic azetidinones **13** were obtained as a mixture of stereoisomers through intramolecular cyclization (Scheme 8, Table 4). After purification by means of column chromatography or recrystallization from Et_2O, the mixtures of 3,6,6-trimethyl-1-azabicyclo[5.2.0]-nonane-9-ones *trans*-**13** (major) and *cis*-**13** (minor) were isolated in 16−21% yield. All attempts to separate the diastereomers from each other failed. Also in this approach, the formation of monocyclic 4-*tert*-butyl-β-lactams **14** as side products in yields of 7−11% was observed.

In contrast with the synthesis of 1-azabicyclo[4.2.0]octan-8-ones **6**, a seven-membered ring is fused to the β-lactam ring in compounds **13** instead of a six-membered ring. These results indicate that the radical cyclization of 1-(2-methylallyl)-substituted β-lactams **12** proceeds through a 7-*endo-trig* cyclization protocol via a stable intermediate tertiary radical **17** (Scheme 9). Steric hindrance at the 6-*exo-trig* cyclization center is probably the main factor orienting the cyclization to a 7-*endo-trig* selectivity in the case of bicyclic β-lactams **13**. On the basis of the rationalization discussed in Scheme 5, it can also be assumed that a similar favorable transition state is involved,

SCHEME 4



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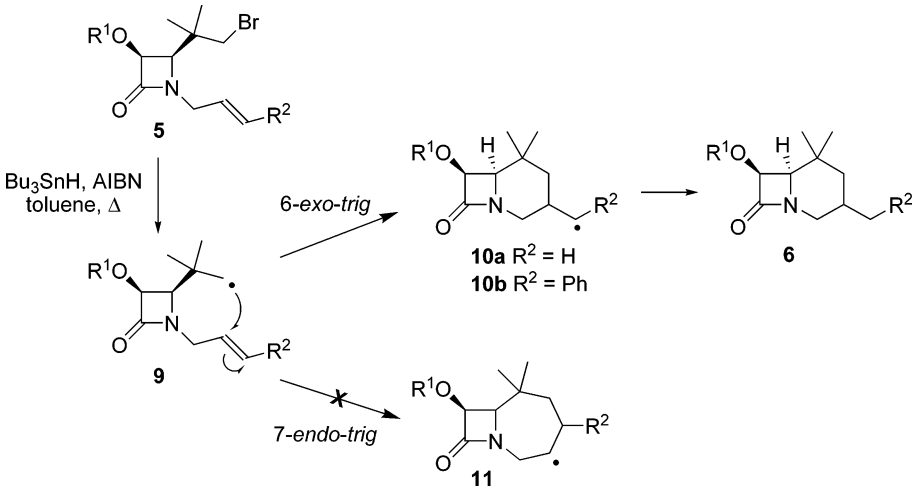
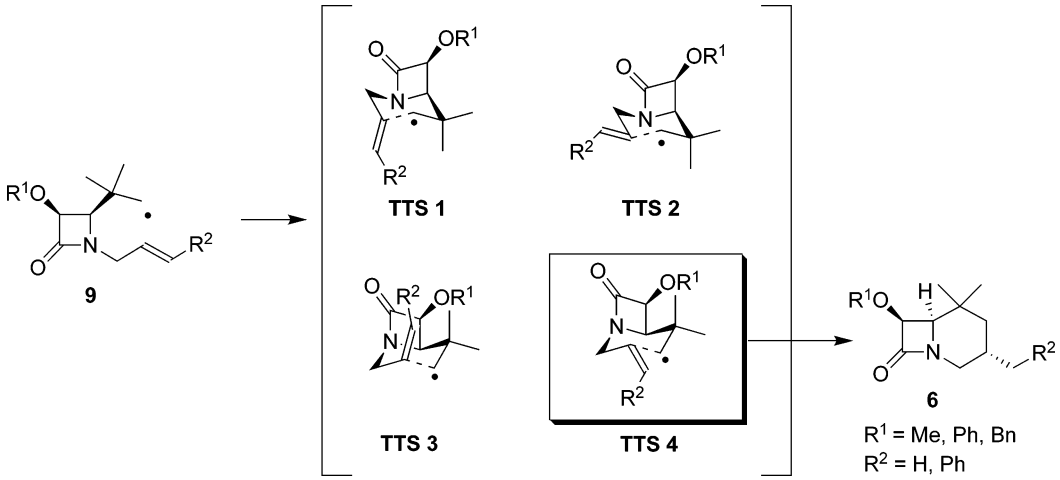


SCHEME 6



SCHEME 7

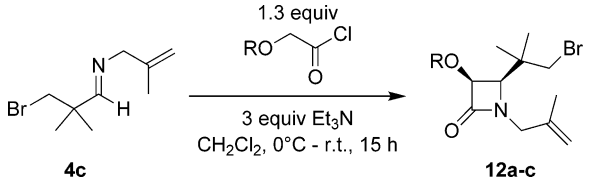


TABLE 3. Synthesis of *cis*-1-(2-Methyl-2-propenyl)azetidin-2-ones 12

entry	R	compd	yield (%)[a]
1	Me	**12a**	90
2	Ph	**12b**	76
3	Bn	**12c**	71

[a] Yields after purification by column chromatography.

TABLE 4. Synthesis of Bicyclic β-Lactams 13

entry	R	compd	ratio[a] *trans*-**13**:*cis*-**13**	yield (%)[b]	compd	yield (%)[b]
1	Me	**13a**	87:13	20	**14a**	10
2	Ph	**13b**	89:11	21	**14b**	11
3	Bn	**13c**	88:12	16	**14c**	7

[a] Ratio determined by means of ^{1}H NMR. [b] Yields after purification by column chromatography or recrystallization from Et_2O.

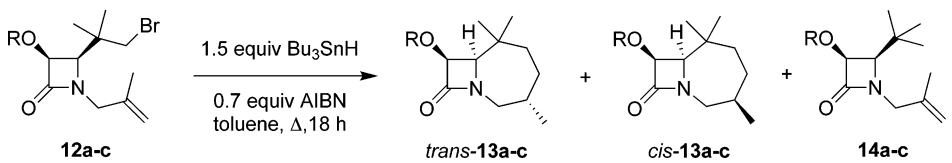
affording 3-methyl-1-azabicyclo[5.2.0]nonan-9-ones *trans*-**13** as the major stereoisomers (87−89%). Since this transition state comprises a puckered seven-membered ring, the stereoselectivity is less pronounced as compared to the synthesis of the corresponding 1-azabicyclo[4.2.0]octan-8-ones **6**, explaining the formation of compounds *cis*-**13** as minor constituents (11−13%).

The second objective of this research was the stereoselective synthesis of 2-(1-alkoxy-2-hydroxyethyl)piperidines and 2-(1-alkoxy-2-hydroxyethyl)azepanes via reductive ring opening of the corresponding bicyclic precursors. 7-Alkoxy-1-azabicyclo[4.2.0]octane-8-ones **6** were reduced by means of 2 equiv of lithium aluminum hydride in ether, affording 2-(1-alkoxy-2-hydroxyethyl)piperidines **18** in good yields after 16 h at reflux (Scheme 10, Table 5). Only two similar compounds have been reported to date, i.e., 2-(2-hydroxy-1-phenoxyethyl)-7-methyl-6-oxa-3,7-diazabicyclo[3.2.1]octane and 2-(1-benzyloxy-2-hydroxyethyl)-7-methyl-6-oxa-3,7-diazabicyclo[3.2.1]octane, in which the proton C*H*OPh of the former was described as a quadruplet at 4.35 ppm and the CH_2OH protons as two times a d×d at 3.81 and 4.07 ppm (^{1}H NMR, $CDCl_3$).[27,28] The chemical shifts obtained for piperidines **18** were comparable to those mentioned in the literature.

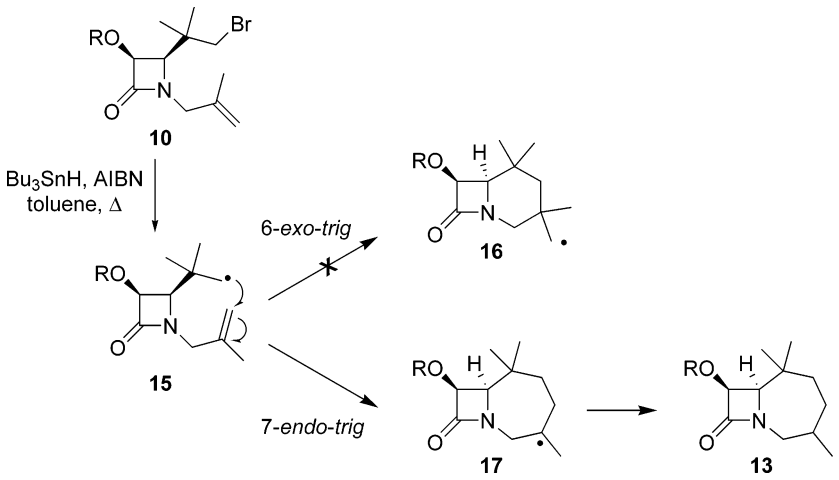
In an analogous reaction, the reduction of 8-alkoxy-3,6,6-trimethyl-1-azabicyclo[5.2.0]nonane-9-ones **13** (as mixtures of *trans* and *cis* isomers) with lithium aluminum hydride was evaluated. Treatment of the latter bicycles **13** with 2 equiv of $LiAlH_4$ in diethyl ether afforded the corresponding 2-(1-alkoxy-2-hydroxyethyl)azepanes **19**, again as mixtures of *trans* and *cis* isomers. After purification by column chromatography on silica gel, the major compounds *trans*-2-(1-alkoxy-2-hydroxyethyl)-azepanes **19** were isolated as single stereoisomers (Scheme 11, Table 6). In literature, no precedents of the analogous azepanes **19** have been reported.

In summary, the radical cyclization of 1-allyl-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones and 1-(3-phenylallyl)-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones by means of *n*-tributyltin hydride and AIBN has been described for the first time as an elegant approach toward the synthesis of 3-substituted 7-alkoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octane-8-ones with excellent diastereocontrol. The relative configuration of the latter compounds was determined by using X-ray analysis. On the other hand, the radical cyclization of 4-(2-bromo-1,1-dimethylethyl)-1-(2-methylallyl)azetidin-2-ones furnished 8-alkoxy-3,6,6-trimethyl-1-azabicyclo[5.2.0]nonan-9-ones in good but lower diastereomeric excess (75−78%). Finally, 1-azabicyclo-[4.2.0]octane-8-ones and 1-azabicyclo[5.2.0]nonan-9-ones were subjected to an efficient reductive ring opening with lithium

SCHEME 8



SCHEME 9



SCHEME 10

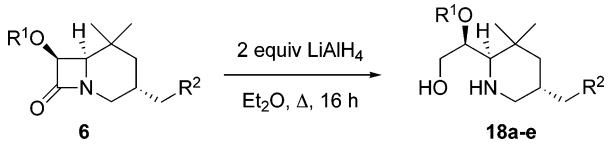


TABLE 5. Synthesis of Piperidines 18 via Reductive Ring Opening of Bicyclic β-Lactams 6

entry	R^1	R^2	compd	yield (%)[a]
1	Me	H	**18a**	72
2	Ph	H	**18b**	78
3	Bn	H	**18c**	82
4	Me	Ph	**18d**	81
5	Bn	Ph	**18e**	76

[a] Yields after purification by column chromatography or recrystallization.

TABLE 6. Synthesis of Azepanes 19 via Reductive Ring Opening of Bicyclic β-Lactams 13

entry	R	compd	yield (%)[a]
1	Me	*trans*-**19a**	81
2	Ph	*trans*-**19b**	83
3	Bn	*trans*-**19c**	79

[a] Yields after purification by column chromatography.

aluminum hydride toward novel 2-(1-alkoxy-2-hydroxyethyl)-piperidines and 2-(1-alkoxy-2-hydroxyethyl)azepanes, which were isolated as single isomers.

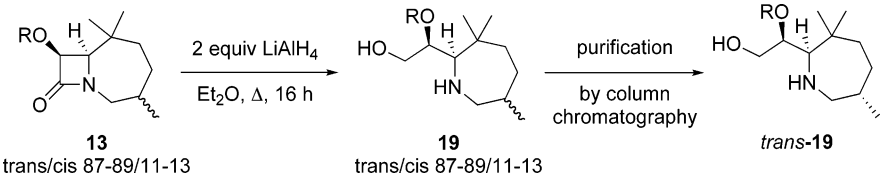
Experimental Section

Synthesis of 4-(2-Bromo-1,1-dimethylethyl)azetidin-2-ones 5 and 12. As a representative example, the synthesis of *cis*-4-(2-bromo-1,1-dimethylethyl)-3-phenoxy-1-(2-methylallyl)azetidin-2-one **12b** is described here. To a stirred, ice-cooled solution of imine **4c** (1.50 g, 6.88 mmol) and Et_3N (2.09 g, 21.65 mmol) in CH_2Cl_2 (20 mL) was added phenoxyacetyl chloride. After being stirred for 15 h at room temperature, the reaction mixture was poured into water (50 mL) under vigorous stirring and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish *cis*-1-allyl-4-(2-broom-1,1-dimethylethyl)-3-phenoxyazetidin-2-one **12b**, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 3/1).

***cis*-4-(2-Bromo-1,1-dimethylethyl)-3-phenoxy-1-(2-methylallyl)azetidin-2-one 12b.** Yellow oil. Yield 76%. R_f 0.48 (petroleum ether/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (6H, s), 1.74 (3H, s), 3.41 (1H, d, J = 10.0 Hz), 3.64 (1H, d, J = 15.3 Hz), 3.69 (1H, d, J= 10.0 Hz), 4.00 (1H, d, J = 5.5 Hz), 4.16 (1H, d, J = 15.3 Hz), 4.91 (1H, s), 4.99 (1H, s), 5.31 (1H, d, J = 5.5 Hz), 6.97−7.33 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3 (CH_3), 22.8 (CH_3), 24.6 (CH_3), 37.3 (C), 43.7 (CH_2), 48.4 (CH_2), 64.1 (CH), 81.5 (CH), 114.8 (CH_2), 116.1 (CH), 122.5 (CH), 129.6 (CH), 139.2 (CH), 157.7 (C), 167.7 (C). IR (NaCl, cm^{-1}) ν_{max} 1597, 1760, 2971, 3501. MS m/z (%) 352/4 (M^+ + H, 100). Anal. Calcd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.29; N, 3.98. Found: C, 58.33; H, 6.11; N, 3.75.

Synthesis of 5,5-Dimethyl-1-azabicyclo[4.2.0]octan-8-ones 6 and 3,6,6-Trimethyl-1-azabicyclo[5.2.0]nonan-9-ones 13. As a representative example, the synthesis of 3-benzyl-7-methoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octan-8-one **6d** is described here. *n*-Bu_3SnH (1.37 mL, 5.11 mmol) and AIBN (0.39 g, 2.38 mmol) were added to a refluxing solution of *cis*-4-(2-bromo-1,1-dimethylethyl)-3-phenoxy-1-(3-phenylallyl)azetidine-2-one **5d** (1.20 g, 3.41 mmol) in toluene (10 mL) in 3 portions, the interval between each addition being 1 h. Afterward, the reaction mixture was stirred for an additional 8 h at reflux temperature. After cooling to room temperature, an aqueous sodium hydroxide solution (20 mL, 2 N) was added to the resulting mixture, followed by a period of stirring of 1 h at room temperature. The suspension was then filtered over Celite, and the organic phase was separated and washed with a sodium hydroxide solution (10 mL, 2 N) and with brine. The organic layer was dried ($MgSO_4$), and the crude reaction product was obtained after filtration and evaporation of the solvent. The tin hydroxides were removed by column chromatography on silica gel (hexane/EtOAc 3/1), yielding pure 3-benzyl-7-methoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octan-8-one **6d**.

SCHEME 11



3-Benzyl-7-methoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octan-8-one 6d. Yellow crystals. Yield 35%. R_f 0.14 (hexane/EtOAc 3/1). Mp 102.3−103.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.02 (3H, s), 1.01−1.09 (1H, m), 1.45 (1H, d × d, J = 13.5, 2.2 Hz), 1.99−2.14 (1H, m), 2.28 (1H, d × d × d, J = 13.1, 11.3, 1.7 Hz), 2.44 (1H, d × d, J = 13.6, 6.7 Hz), 2.50 (1H, d × d, J = 13.6, 7.7 Hz), 3.10 (1H, d, J = 4.8 Hz), 3.49 (1H, s), 3.75 (1H, d × d, J = 13.1, 4.8 Hz), 4.48 (1H, d × d, J = 4.8, 1.7 Hz), 7.09−7.31 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (CH_3), 28.3 (CH_3), 32.7 (CH), 33.1 (C), 41.0 (CH_2), 42.5 (CH_2), 46.1 (CH_2), 59.3 (CH_3), 61.5 (CH), 85.5 (CH), 126.3 (CH), 128.5 (CH), 128.9 (CH), 138.9 (C), 166.3 (C). IR (KBr, cm^{-1}) ν_{max} 1736, 2981. MS m/z (%) 274 (M^+ + H, 100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 73.57; H, 8.20; N, 4.93.

***trans*-3,6,6-Trimethyl-8-phenoxy-1-azabicyclo[5.2.0]nonan-9-one *trans*-13b (signals derived from the mixture of *trans*-13b and *cis*-13b).** White crystals. R_f 0.12 (hexane/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, d, J = 7.2 Hz), 1.07 (3H, s), 1.15 (3H, s), 1.18−1.67 and 1.72−1.83 (4H, m), 2.11−2.22 (1H, m), 3.24 (1H, d × d, J = 13.5, 4.7 Hz), 3.57 (1H, d × d, J = 13.5, 3.9 Hz), 3.77 (1H, d, J = 4.7 Hz), 5.24 (1H, d, J = 4.7 Hz), 6.97−7.33 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (CH_3), 20.3 (CH_3), 26.8 (CH_3), 30.4 (CH), 30.6 (CH_2), 36.6 (C), 40.4 (CH_2), 48.4 (CH_2), 66.9 (CH), 81.6 (CH), 115.9 (CH), 122.0 (CH), 129.5 (CH), 158.1 (C), 167.0 (C). IR (KBr, cm^{-1}) ν_{max} 1739, 2917. MS m/z (%) 274 (M^+ + H, 100).

Synthesis of 2-(1-Alkoxy-2-hydroxyethyl)piperidines 18 and 2-(1-Alkoxy-2-hydroxyethyl)azepanes 19. As a representative example, the synthesis of 2-(1-phenoxy-2-hydroxyethyl)-3,3,5-trimethylpiperidine **18b** is described here. To a stirred, ice-cooled solution of 7-phenoxy-3,5,5-trimethyl-1-azabicyclo[4.2.0]octan-8-one **6b** (0.20 g, 0.77 mmol) in diethyl ether (15 mL) was added lithium aluminum hydride (0.06 g, 1.54 mmol) in small portions, and the resulting mixture was stirred at room temperature for 16 h. Afterward, water was added dropwise at 0 °C until all residual lithium aluminum hydride was consumed completely. The resulting suspension was filtered over Celite, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered and crude 2-(1-phenoxy-2-hydroxyethyl)-3,3,5-trimethylpiperidine **18b** was obtained after removal of the solvent in vacuo, which was purified by recrystallization from Et_2O.

2-(1-Phenoxy-2-hydroxyethyl)-3,3,5-trimethylpiperidine 18b. Colorless crystals. Recrystallization from Et_2O. Yield 78%. Mp 139.0−139.4 °C. ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.79 (3H, d, J = 6.6 Hz), 0.93 (3H, s), 0.95 (3H, s), 1.03 (1H, t, J = 13.1 Hz), 1.46 (1H, d × d × d, J = 13.1, 3.3, 2.2 Hz), 1.61−1.74 (1H, m), 2.21 (1H, d × d, J = 13.5, 11.6 Hz), 2.69 (1H, s_{br}), 3.09 (1H, d × d × d, J = 13.5, 4.3, 2.2 Hz), 3.81 (1H, d × d, J = 11.6, 1.7 Hz), 4.07 (1H, d × d, J = 11.6, 2.4 Hz), 4.48 (1H, s_{br}), 6.80−7.31 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (CH_3), 21.0 (CH_3), 28.5 (CH), 29.5 (CH_3), 33.1 (C), 49.9 (CH_2), 53.5 (CH_2), 65.9 (CH_2), 67.5 (CH), 72.7 (CH), 116.2 (CH), 121.2 (CH), 129.6 (CH), 156.8 (C). IR (KBr, cm^{-1}) ν_{max} 1242, 1494, 1598, 2948, 3294. MS m/z (%) 264 (M^+ + H, 100). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.76; H, 9.84; N, 5.18.

2-(2-Hydroxy-1-methoxyethyl)-3,3,6-trimethylazepane 19a. Colorless oil. Yield 81%. R_f 0.26 (CH_2Cl_2/MeOH 17/3). ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.81 (3H, d, J = 6.3 Hz), 0.91 (3H, s), 0.92 (3H, s), 1.20−1.29 (1H, m), 1.44−1.48 (2H, m), 1.54−1.64 (2H, m), 2.23 (1H, d × d, J = 14.2, 11.3 Hz), 2.57 (1H, s_{br}), 3.16 (1H, s_{br}), 3.17 (1H, d × d × d, J = 14.2, 5.1, 1.7 Hz), 3.35 (3H, s), 3.62 (1H, d × d, J = 11.4, 1.7 Hz), 4.10 (1H, d × d, J = 11.4, 3.0 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ 19.8 (CH_3), 25.0 (CH_3), 28.7 (CH_3), 30.1 (CH_2), 38.5 (C), 38.7 (CH), 41.2 (CH_2), 55.9 (CH_3), 57.8 (CH_2), 64.5 (CH_2), 70.4 (CH), 77.3 (CH). IR (NaCl, cm^{-1}) ν_{max} 1463, 2920, 2944, 3350. MS m/z (%) 216 (M^+ + H, 100).

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Supporting Information Available: Spectroscopic data of compounds **5b**,**e**, **6a**−**c**,**e**,**f**, **10c**, **11a**,**c**, **15a**,**c**−**e**, and **16b**,**c** and crystallographic data for **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Alcaide, B.; Sáez, E. *Eur. J. Org. Chem.* **2005**, 1680.
(28) Alcaide, B.; Pardo, C.; Sáez, E. *Synlett* **2002**, 85.