Fluorine as a Regiocontrol Element in the Ring Opening of Bicyclic Aziridiniums

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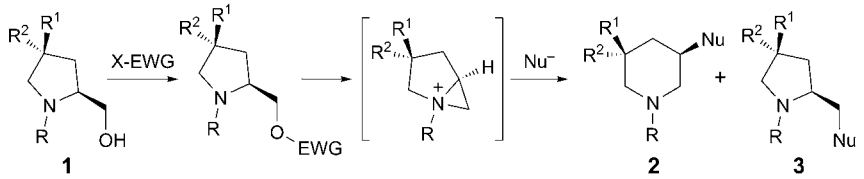
Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

The origin of the variation in the regioselectivity of the nucleophilic ring opening of a series of bicyclic aziridinium ions derived from *N*-alkylprolinols was investigated by quantum-chemical computations (M06-2X/6-31 + G(d,p)-SMD). These aziridiniums differ only in the degree and the configurations of F-substitution at C(4). With the azide ion as nucleophile, the ratio of the piperidine to the pyrrolidine product was computed. An electrostatic *gauche* effect influences the conformation of the adjoining five-membered ring in the fluorinated bicyclic aziridinium. This controls the regioselectivity of the aziridinium ring opening.

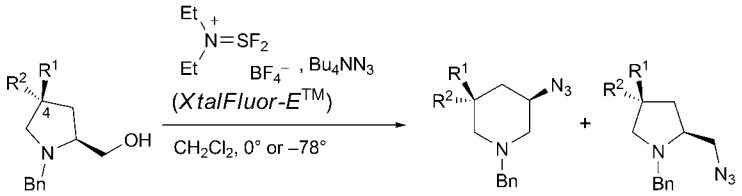
1. Introduction. – Many 3-aminopiperidine derivatives are bioactive compounds. The enantioselective synthesis of these substances is an area of active research [1]. A longstanding strategy for the preparation of 3-substituted piperidines **2** is ring expansion of *N*-protected prolinols **1** by a regioselective nucleophilic attack on bicyclic aziridinium intermediates generated by judicious activation of the OH group (*Scheme*) [2][3].

Scheme. *Nucleophilic Addition to an Aziridinium Intermediate Derived from* N-*Protected Prolinol* **1**



Recently, *Cossy* and co-workers reported that 3-azidopiperidines could be accessed by this strategy starting from prolinols such as **1a**–**1d** (*Table 1*) by utilizing

Table 1. *Ring Expansion of Nonfluorinated and Fluorinated Prolinol Derivatives,* **1a** *and* **1b**–**1d**, *Respectively*



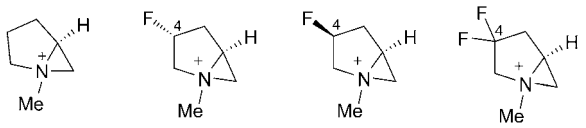
1a – 1d **2a – 2d** **3a – 3d**

Entry	Prolinol	R^1	R^2	Yield [%]	**2a**–**2d**/**3a**–**3d**
1	**1a**	H	H	70	50 : 50
2	**1b**	H	F	66	93 : 7
3	**1c**	F	H	58	50 : 50
4	**1d**	F	F	66	91 : 9

tetrabutylammonium azide in the presence of (diethylamino)difluorosulfonium tetrafluoroborate (*XtalFluor-E*™) as the activating reagent. The target amines can then be obtained by a *Staudinger* reduction [4][5]. Remarkably, among the fluorinated prolinols studied, the regioselectivity of the ring opening of the corresponding bicyclic aziridinium is highly dependent on the extent of fluorination and the configuration of the F-atoms at C(4) (*Table 1*). Thus, while the reaction of **1b** yields the piperidine product with high selectivity (93 : 7; *Entry 2*) the reaction of the epimeric compound **1c** is nonselective (*Entry 3*). Difluorinated prolinol **1d** gives rise to the piperidine product as the major product with a ratio of 91 : 9 *vs.* the pyrrolidine (*Entry 4*), a much higher selectivity than its nonfluorinated counterpart **1a**, whose ring opening is nonselective (*Entry 1*).

As reviewed recently by *De Kimpe* and co-workers [6] and *Cossy* and co-workers [7], the regiochemistry of the ring opening of nonactivated aziridiniums, *i.e.*, aziridiniums without an electron-withdrawing group on the N-atom, is more sensitive to factors besides the substitution pattern on the ring than activated aziridiniums, including [8][9] the nature of the nucleophile [10–14] and the method of activation [4][15]. Nevertheless, we were drawn to the intriguing problem posed by the product distributions of the ring opening of the aziridiniums in *Table 1*, as the regioselectivity displays a wide variation that depends only on the degree and the configuration of the F-atoms at C(4) of the prolinol precursors **1a**–**1d**. Although we previously showed that the regioselectivity of the ring opening of bicyclic aziridiniums derived from prolinols could be enhanced to some extent by the use of bulky substituents at N and C(4) [4], it was less obvious how the F-atoms, with their minimal steric impact, exert such a dramatic influence on the product outcome. Moreover, while the regiochemistry of the ring opening of aziridines fused to six-membered rings has been reported [16][17], the regioselectivity of the nucleophilic attack of the bicyclic aziridinium ions of type **1a**–**1d** has yet to be systematically investigated. We now present a computational analysis of these reactions, focusing on the influence of F-substitution on the conformation of the prolinols and the regioselectivity of the nucleophilic attack.

2. Computational Method. – All of the computations were performed on *Gaussian 09* [18]. The aziridinium and the transition structures (TSs) for the reactions with an azide ion were modeled computationally. *Cossy* and co-workers have demonstrated the intermediacy of the aziridinium in these reactions [5]. The reactions of **1a**–**1d** proceed under kinetic rather than thermodynamic control [4][17]. The geometries were optimized at the M06-2X/6-31 + G(d,p) level of theory [19][20] in conjunction with the SMD continuum solvation model [21] using CH_2Cl_2 as solvent. Each structure was characterized as either an energy minimum or a transition structure by a frequency computation. To study the influence of the substituent at C(4) of the prolinol on product outcome, the nonfluorinated, monofluorinated, and difluorinated bicyclic aziridiniums, **4a**, **4b**–**4c**, and **4d**, respectively, were studied (see below). The *N*-Bn groups in the experimental substrates were replaced by *N*-Me groups in the modeling.



4a **4b** **4c** **4d**

3. Results and Discussion. – Two conformations of **4a**–**4d** were found (*Fig. 1*). The conformers in which the five-membered ring exhibits the ^4E and the E_4 conformations are termed the boat and the chair, respectively. To fully understand the conformational energetics of the azabicycles, we also studied the boat and the chair forms of the carba analogs **4e**–**4h**. The computations show that for **4a**, **4c**, and **4d**, the boat conformers are more stable than the chairs by 1.5–4.5 kcal/mol, whereas **4b** shows the opposite preference, if slightly, with the chair being the more stable. The carba analogs, on the other hand, favor the boat forms regardless of F-substitution. The computed preferences for the boat conformation in structures analogous to **4c**, where C(4) bears an electronegative atom [22], and in the bicyclo[3.1.0]cyclohexanes [23–26] are supported by several X-ray crystallographic structures, some of which are illustrated in *Fig. 2*.

The chair conformers of the nonfluorinated aziridinium **4a** and the fused carbocyclic rings in **4e**–**4h** are disfavored by eclipsing strain which is not found in the boat forms. The chair conformers of these bicyclic rings contain two pairs of eclipsing interactions between a pseudoaxial C–H bond in the five-membered ring (as shown in *Fig. 3*,*a*, for **4a**) and either an N^+–R bond or a C–H bond at one of the ring junctions (not shown), as documented previously [27–29]. When C(4) is fluorinated, the so-called electrostatic *gauche* effect [30][31], *i.e.*, the preference of the F-atom to be *gauche,* rather than *anti*, to the quaternary ammonium N-atom, constitutes the second important conformation-determining factor. Thus, in **4c**, F-substitution enhances the stability of the boat form (shown in *Fig. 3*,*c*) relative to the chair (4.5 kcal/mol, compare with 3.3 kcal/mol in favor of the boat for nonfluorinated **4a**) due to the synclinal disposition of the pseudoaxial F-atom to the ammonium N-atom in the boat, while in **4b**, the *gauche* effect is found in the chair (*Fig. 3*,*b*) and causes this conformer to be less unfavorable, diminishing the energy difference between the conformers compared with that in **4a**. Both the boat and the chair forms of **4d**

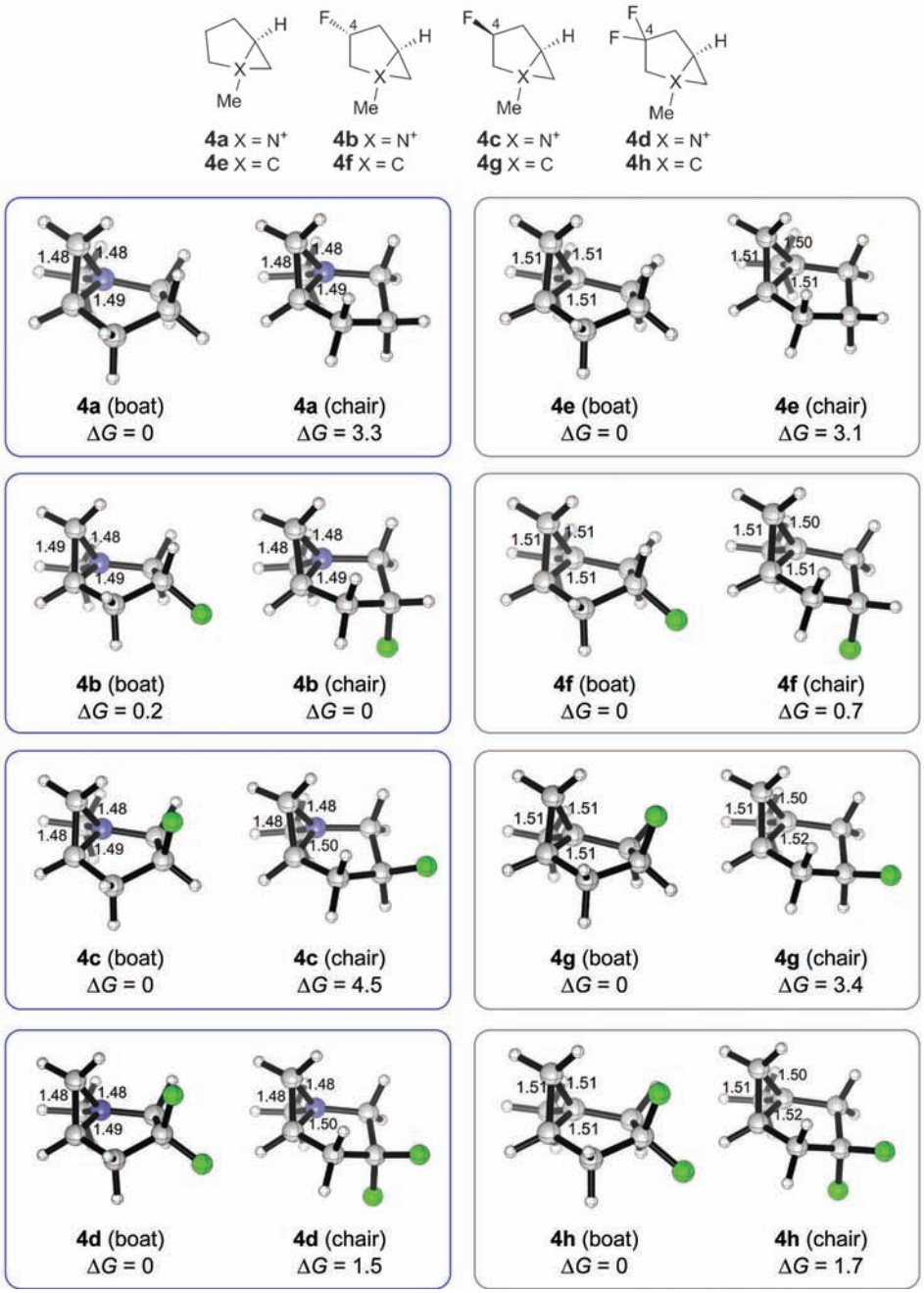


Fig. 1. *Structures and free energies of the boat and chair conformers of aziridinium ions* **4a**–**4d** (boxed in blue) *and their carba analogs* **4e**–**4h** (boxed in grey). The relative *Gibbs* free energies of the two conformers are given in kcal/mol.

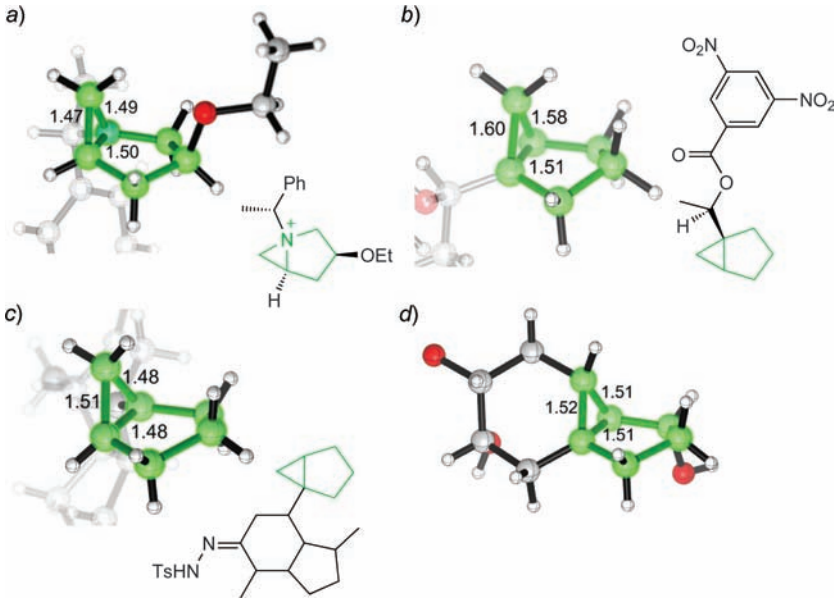


Fig. 2. *Crystallographic structures of molecules or ions containing the bicyclo[3.1.0]cyclohexane ring* (*b* – *d*) *or its 1-aza analog* (*a*)*, retrieved from the* Cambridge Crystallographic Structural Database. For *a*, the mirror image of the reported structure is shown to maintain comparability with the structure of **4c**. Reference codes: *a*) QOZDEO ([22]); *b*) HEBCHN ([23]); *c*) KIXSAL ([24]); *d*) EBUXAB ([25]).

accommodate one *gauche* F–C–C–N^+ interaction, and the intrinsic boat preference of the fused ring system dictates the conformational equilibrium. The role of the *gauche* effect in biasing the conformation of the fluorinated bicyclic aziridiniums here is directly analogous to that in influencing the conformational behavior of 4-fluoroproline [32][33], 3-fluoropiperidine, and its derivatives [34], and four- and eight-membered ring systems [35].

The transition structures for the nucleophilic ring opening step of **4a**–**4d** by the azide ion leading to 3-azidopiperidine and 2-(azidomethyl)pyrrolidine were then studied. These were optimized by starting from both the boat and the chair conformations, as well as different dihedral angles at which the azide approaches the aziridinium. The lowest-energy chair and boat forms of the regioisomeric transition structures are illustrated in *Fig. 4*.

For all of the aziridiniums studied, good agreement was found between the relative free energies of the regioisomeric transition structures and the experimental selectivity (*Table 2*). For the non-fluorinated **4a**, the energy difference of 0.5 kcal/mol between the **TS-5a** and **TS-5c** predicts a low selectivity of 72:28 in favor of the piperidine product, comparing well with the experimental ratio of 50:50 for reaction of prolinol **1a**. The dependence of the regioselectivity on the configuration of the fluorinated stereogenic center C(4) was also accounted for by the computations. Thus, the nonselective reaction from **1c** was reproduced, as **TS-7a** and **TS-7c**, derived from **4c**, were found to be isoenergetic. Inverting the configuration at C(4) of **4c** widens the

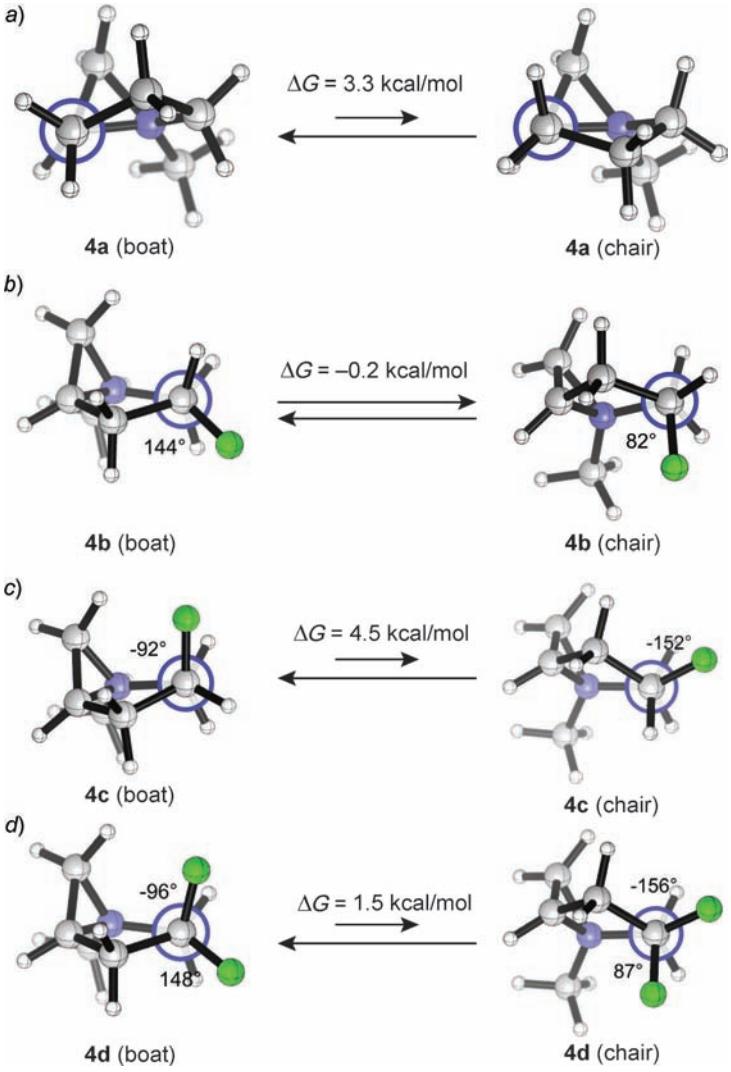


Fig. 3. a) Newman *Projection of* **4a** *along C(3)–C(2) bond, showing one of the two eclipsing interactions in the chair conformation.* b–d) Newman *Projections along the C(4)–C(5) bond of* **4b**, **4c**, *and,* **4d**, *respectively.* The F–C(4)–C(5)–N^+ dihedral angles are annotated.

energy difference between the transition structures, as **TS-6b** is now more stable than **TS-6d** by 1.4 kcal/mol, corresponding to a selectivity of 97:3 favoring the piperidine product at $-78°$. The high regioselectivity for difluorinated **4d** was also reproduced computationally.

The results compiled in *Fig. 4* reveal two points of consideration that shed light on the origin of the regioselectivity. First, the same conformation was adopted by the aziridinium in the reactant and in the lowest-energy transition structures, except in the

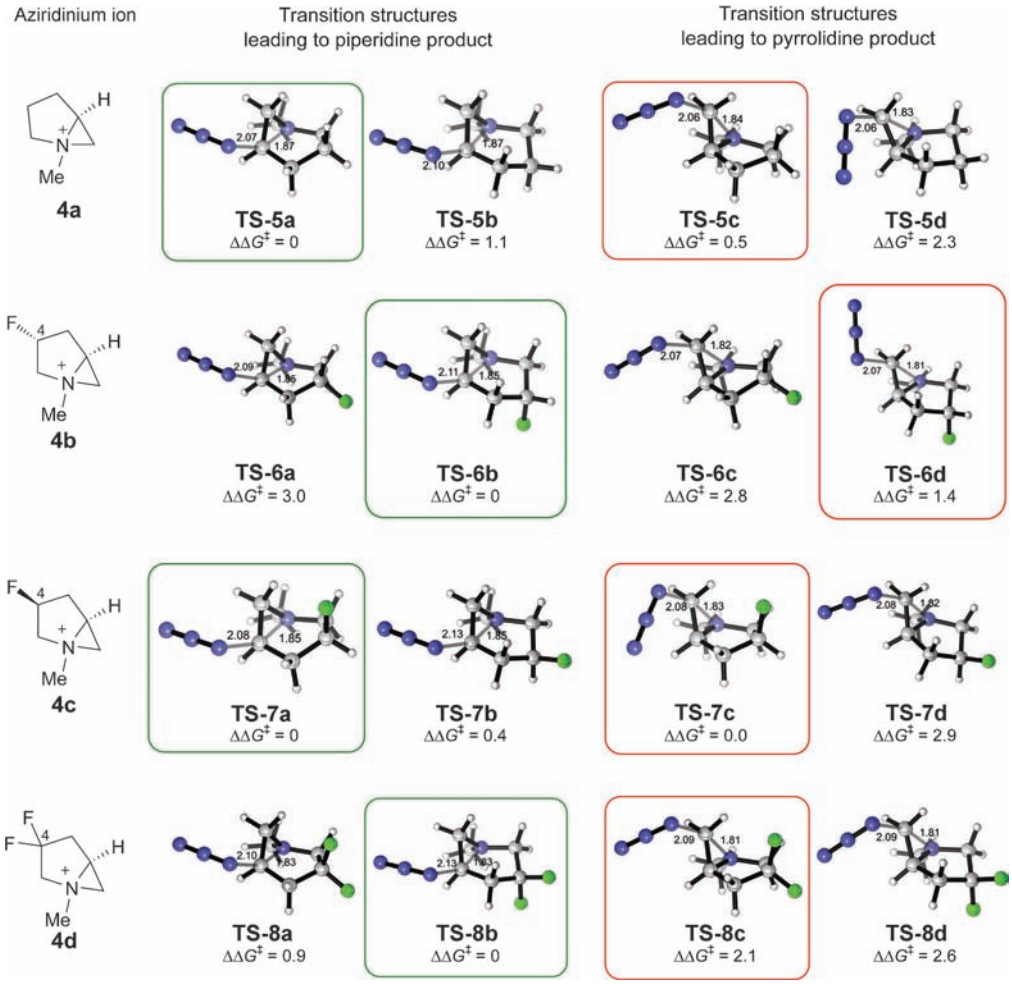


Fig. 4. *Optimized geometries and relative free energies* ($\Delta\Delta G^{\ddagger}$, in kcal/mol) *of the lowest-energy transition structures for the nucleophilic ring opening reactions of aziridinium ions* **4a**–**4d** *by azide.* Type **a** and type **c** structures feature the azabicycle in a boat-like conformation, while type **b** and type **d** structures are chair-like. The lowest-energy transition structures leading to the piperidine and the pyrrolidine products are boxed in green and red, respectively.

case of **4d**. Thus, the non-regioselective ring opening of **4a** (and **4c**) was predicted to proceed through **TS-5a** (**TS-7a**) and **TS-5c** (**TS-7c**), which features a boat-like conformation of the aziridinium analogous to that of **4a** (**4c**). Bicyclic aziridinium **4b** also reacts predominantly *via* the chair-like **TS-6b** and **TS-6d**. The boat-like **TS-6a** and **TS-6c** are at least 2.8 kcal/mol less stable than **TS-6b**, representing an amplified difference in conformational energy compared with that found for the reactant (0.2 kcal/mol, *Fig. 2*). The conformational preferences of **4d** and its derived transition structures are less uniform. The most stable transition structure was found to be the

Table 2. *Free Energies of Activation* ($\Delta G^{\ddagger}$) *for the Formation of the Piperidine Product and the Regioselectivities of the Nucleophilic Ring-Opening Step of* **4a**–**4d**. The regioselectivities were computed using the boxed transition structures in *Fig. 4* at the experimental temperature (0° for **4a**, −78° for **4b**–**4d**).

Entry	Aziridinium ion	$\Delta G^{\ddagger}$ [kcal/mol]	Piperidine/pyrrolidine ratio	
			Experimental	Computed
1	**4a**	16.4	50 : 50	72 : 28
2	**4b**	12.0	93 : 7	98 : 2
3	**4c**	14.5	50 : 50	50 : 50
4	**4d**	12.0	91 : 9	> 99 : 1

chair-like **TS-8b**, which differs from the boat-like **TS-8a** by 0.9 kcal/mol, although the lowest-energy transition structure leading to the pyrrolidine, **TS-8c**, preserves the boat conformation. Second, all of the chair-like transition structures (types **b** and **d**) open preferentially to give the piperidine product with high selectivity, while the boat-like structures (types **a** and **c**) are nonselective except for **4d**. Thus, the chair conformer **TS-5b** for the piperidine product is 1.2 kcal/mol more stable than **TS-5d**, and the corresponding difference between **TS-7b** and **TS-7d** is 2.5 kcal/mol. The computations, therefore, revealed that no regioselectivity was experimentally observed with prolinols **1a** and **1c**, because the chair conformers of these aziridiniums are energetically inaccessible, being at least 3.3 and 4.5 kcal/mol higher in energy than the most stable boat conformer.

Why do the chair conformers of the bicyclic aziridiniums open regioselectively at the more substituted end? The preference of the azide nucleophile to react at the more substituted C-atom of **4a**–**4d** may seem surprising[1]). To understand the role of the adjoining five-membered ring in influencing the regioselectivity of the nucleophilic attack of the bicyclic aziridinium, we have computed the transition structures for the ring opening of the model aziridinium ion **8** (*Fig. 5*). This monocyclic compound preserves the Me substitution at N- and C(2)-atoms. **TS-9a**, in which the azide ion

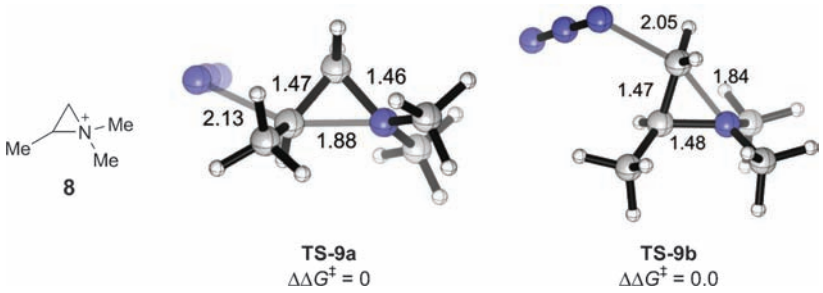


Fig. 5. *The structure of model aziridinium* **8**, *and the optimized transition structures* **TS-9a** *and* **TS-9b** *for the nucleophilic ring opening step by azide*

[1]) Ring opening of 2-(alk-1-enyl)-substituted aziridiniums is known to occur preferentially at the more substituted C-atom (see [36]).

reacts at the Me-substituted C(2), is analogous to the transition structures leading to the piperidine products, and **TS-9b** corresponds to transition structures giving rise to the pyrrolidine products. The computations show that these transition structures are isoenergetic. Thus, contrary to expectations from steric effects, the basic bicyclic aziridinium moiety in **4a**–**4d** has no intrinsic regioselectivity with azide as the nucleophile. Presumably, the longer length of the partial bond between C(2) and the nucleophilic N-atom in **TS-9a** (2.13 Å), compared with that in **TS-9b** (2.05 Å), reduces the steric strain experienced by the approaching nucleophile, making **TS-9a** less disfavored than expected.

Since the model aziridinium **8** opens non-regioselectively, any regioselectivity in the ring opening of the bicyclic aziridinium must be due to the presence of the pyrrolidine ring. To understand why the piperidine TSs are lower in energy than the pyrrolidine TSs when the bicycle is in the chair conformation, it proved instructive to examine the *Newman* projections of these TSs along the C–C bond geminal to the breaking C–N^+ bond of the aziridinium moiety. These *Newman* projections are shown in *Fig. 6* for the chair-like **TS-6b** and **TS-8b**, which, being lower in energy than the chair-like **TS-6d** and **TS-8d** by 1.4 and 2.6 kcal/mol (*Fig. 4*), are responsible for the formation of the piperidine as the major product. In the optimized structures of **TS-6b** and **TS-8b**, the C(3)–C(4) bond is placed antiperiplanar to the partially formed C–N bond as highlighted. This stereoelectronic effect might serve to stabilize **TS-6b** and **TS-8b** with respect to **TS-6d** and **TS-8d**, which do not have these interactions.

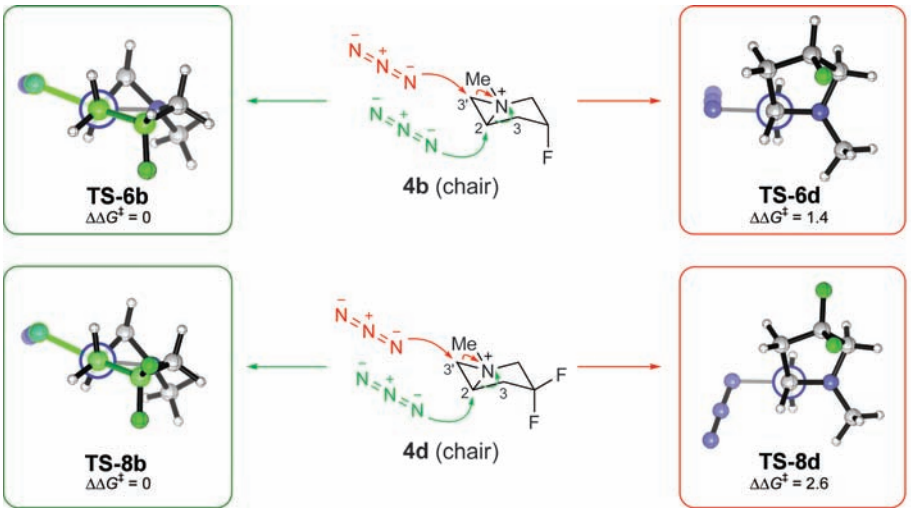


Fig. 6. Newman *Projections along the C–C bond geminal to the breaking C–N^+ bond of the ring-opening transition structures of* **4b** (chair) *and* **4d** (chair). The transition structures for ring opening at C(2), leading to piperidine, and C(3′), leading to pyrrolidine, are colored green and red, respectively.

It is also of interest to note that the chair-like **TS-6b** and **TS-8b** are more stable than their boat-like conformers **TS-6a** and **TS-8a** (*Fig. 7*), although these differences do not impact the product outcome, since both type **a** and type **b** TSs lead to the same piperidine product. The geometries in the vicinity of the partial bonds as revealed by

the *Newman* projections in *Fig. 7* reveal a more staggered arrangement in **TS-6b** and **TS-8b**. This is reminiscent of the effect of transition-state staggering, or torsional steering, which originates from the preference for a maximally staggered arrangement of bonds in transition structures (as well as reactants and products). This effect is responsible for inducing contra-steric stereoselectivity [37] (see also [27]), not least in the well-known case of the totally stereoselective additions to 2,6-disubstituted 1,3-dioxin-4-ones reported by *Seebach et al.* [37a].

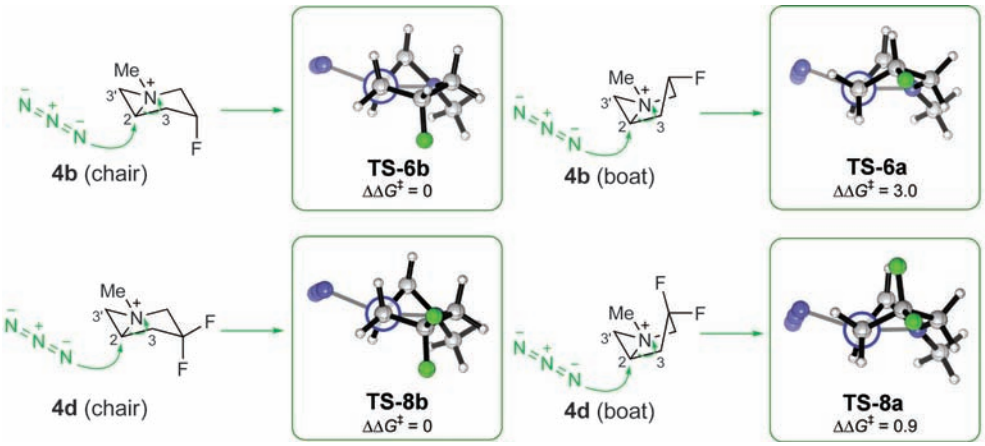


Fig. 7. Newman *Projections along the C(3)–C(2) bond of the boat-like conformers* **TS-6a** *and* **TS-8a** *and the chair-like conformers* **TS-6b** *and* **TS-8b** *of the ring-opening transition structure of* **4b** *and* **4d**. These *Newman* projections show that the bonds around the reacting C-atom (C(2)) are more staggered in the chair-like conformers (type **b**) than in the boat-like conformers (type **a**).

In summary, the computations reported here have delineated the effect of F-substitution at C(4) of prolinols **1a**–**1d** on the regioselectivities of the nucleophilic ring opening of bicyclic aziridinium ions derived from the prolinols. The azabicycle normally prefers the boat conformation, but the F-ammonium *gauche* effect can arise as an additional factor that tips the energy balance to the chair if the F-atom at C(4) is incorporated with the appropriate configuration. The computed transition structures show that, for **4a**–**4c**, the chair conformers of the bicyclic aziridiniums are more discriminating than the boats in their ring opening to give the piperidine products, regardless of F-substitution. The high regioselectivity observed with fluorinated prolinol **1b** arises from the predominance of chair-like transition structures due to the favorable *gauche* effect. The nonselectivities in the ring opening of the bicyclic aziridinium starting from epimeric **1c** and nonfluorinated **1a** are attributed to the prevalence of boat-like transition structures. Fluorine, therefore, acts as a device for conformational control through the electrostatic *gauche* effect. The exploitation of these effects in organic and biological chemistry is currently an emerging area [38–41]. Our experimental and theoretical work illustrates how these effects result in enhanced regiocontrol in the ring opening chemistry of bicyclic aziridiniums, complementing much of the research to date on the stereoelectronic effects of fluorine, which mostly focuses on their stereochemical ramifications [42] (see also [30–35]).

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REFERENCES

[1] K. Berggren, R. Vindebro, C. Bergström, C. Spoerry, H. Persson, T. Fex, J. Kihlberg, U. von Pawel-Rammingen, K. Luthman, *J. Med. Chem.* **2012**, *55*, 2549; R. Sakurai, K. Sakai, K. Kodama, M. Yamaura, *Tetrahedron: Asymmetry* **2012**, *23*, 221; G. Kumaraswamy, A. Pitchaiah, *Tetrahedron* **2011**, *67*, 2536; J. Gonzalez Rodriguez, B. Vidal Juan, L. Vidal Gispert, J. Bach Taña, PCT Int. Appl. 2012, WO2012069202A1; P. A. Blomgren, K. S. Currie, S. A. Mitchell, D. R. Brittelli, PCT Int. Appl. 2010, WO2010068788A1; T. Kuroita, Y. Imaeda, K. Iwanaga, N. Taya, H. Tokuhara, Y. Fukase, PCT Int. Appl. 2009, WO2009154300A2; R. J. Christopher, C. Paul, S. African Pat. 2009, ZA2008002857A; H. Nakahira, H. Hochigai, Y. Ikuma, M. Takamura, PCT Int. Appl. 2008, WO2008136457A1; K. Robins, U. Bornscheuer, M. Hoehne, PCT Int. Appl. 2008, WO2008028654A1; E. Martini, C. Ghelardini, S. Dei, L. Guandalini, D. Manetti, M. Melchiorre, M. Norcini, S. Scapecchi, E. Teodori, M. N. Romanelli, *Bioorg. Med. Chem.* **2008**, *16*, 1431.

[2] D. O. Tymoshenko, *Arkivoc* **2011**, (*i*), 329.

[3] J. L. Bilke, S. P. Moore, P. O'Brien, J. Gilday, *Org. Lett.* **2009**, *11*, 1935; I. Déchamps, D. Gomez Pardo, J. Cossy, *Arkivoc* **2007**, (*v*), 38; A. Dondoni, B. Richichi, A. Marra, D. Perrone, *Synlett* **2004**, 1711; J. Cossy, O. Mirguet, D. Gomez Pardo, J.-R. Desmurs, *Eur. J. Org. Chem.* **2002**, 3543; J. Cossy, D. Gomez Pardo, *Chemtracts – Org. Chem.* **2002**, *15*, 579; J. Cossy, O. Mirguet, D. Gomez Pardo, *Synlett* **2001**, 1575; J. Lee, T. Hoang, S. Lewis, S. A. Weissman, D. Askin, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **2001**, *42*, 6223; J. Cossy, O. Mirguet, D. Gomez Pardo, J.-R. Desmurs, *Tetrahedron Lett.* **2001**, *42*, 5705; J. Cossy, C. Dumas, D. Gomez Pardo, *Eur. J. Org. Chem.* **1999**, 1693.

[4] A. Cochi, D. Gomez Pardo, J. Cossy, *Eur. J. Org. Chem.* **2012**, 2023.

[5] A. Cochi, D. Gomez Pardo, J. Cossy, *Org. Lett.* **2011**, *13*, 4442.

[6] S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, H.-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643.

[7] T.-X. Métro, B. Duthion, D. Gomez Pardo, J. Cossy, *Chem. Soc. Rev.* **2010**, *39*, 89.

[8] H. D. Banks, *J. Org. Chem.* **2006**, *71*, 8089.

[9] H. Helten, T. Schirmeister, B. Engels, *J. Org. Chem.* **2005**, *70*, 233.

[10] M. D'hooghe, S. Catak, S. Stanković, M. Waroquier, Y. Kim, H.-J. Ha, V. Van Speybroeck, N. De Kimpe, *Eur. J. Org. Chem.* **2010**, 4920.

[11] S. Y. Yun, S. Catak, W. K. Lee, M. D'hooghe, N. De Kimpe, V. Van Speybroeck, M. Waroquier, Y. Kim, H.-J. Ha, *Chem. Commun.* **2009**, 2508.

[12] Y. Kim, H.-J. Ha, S. Y. Yun, W. K. Lee, *Chem. Commun.* **2008**, 4363.

[13] E. M. van Oosten, M. Gerken, P. Hazendonk, R. Shank, S. Houle, A. A. Wilson, N. Vasdev, *Tetrahedron Lett.* **2011**, *52*, 4114.

[14] S. Catak, M. D'hooghe, N. De Kimpe, M. Waroquier, V. Van Speybroeck, *J. Org. Chem.* **2010**, *75*, 885.

[15] S. Catak, M. D'hooghe, T. Verstraelen, K. Hemelsoet, A. Van Nieuwenhove, H.-J. Ha, M. Waroquier, N. De Kimpe, V. Van Speybroeck, *J. Org. Chem.* **2010**, *75*, 4530.

[16] J. Karban, J. Kroutil, M. Buděšínský, J. Sýkora, I. Císařová, *Eur. J. Org. Chem.* **2009**, 6399.

[17] J. Kroutil, T. Trnka, M. Buděšínský, M. Černý, *Eur. J. Org. Chem.* **2002**, 2449.

[18] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S.

Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, 'Gaussian 09' (Revision C.01), Gaussian, Inc., Wallingford, CT, 2010.

[19] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[20] Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.

[21] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378; R. F. Ribeiro, A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2011**, *115*, 14556.

[22] M. A. Graham, A. H. Wadsworth, M. Thornton-Pett, C. M. Rayner, *Chem. Commun.* **2001**, 966.

[23] N. G. Steinberg, G. H. Rasmusson, G. F. Reynolds, J. P. Springer, B. H. Arison, *J. Org. Chem.* **1979**, *44*, 3416.

[24] L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841.

[25] D. M. Hodgson, Y. K. Chung, J.-M. Paris, *J. Am. Chem. Soc.* **2004**, *126*, 8664.

[26] M. F. Grostic, D. J. Duchamp, C. G. Chidester, *J. Org. Chem.* **1971**, *36*, 2929.

[27] P. H.-Y. Cheong, H. Yun, S. J. Danishefsky, K. N. Houk, *Org. Lett.* **2006**, *8*, 1513.

[28] P. Kang, J. Choo, M. Jeong, Y. Kwon, *J. Mol. Struct.* **2000**, *519*, 75.

[29] V. S. Mastryukov, E. L. Osina, L. V. Vilkov, R. L. Hilderbrandt, *J. Am. Chem. Soc.* **1977**, *99*, 6855.

[30] N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer, R. J. Young, *Angew. Chem.* **2007**, *119*, 6008; N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer, R. J. Young, *Angew. Chem., Int. Ed.* **2007**, *46*, 5904.

[31] C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta, J. A. K. Howard, *Org. Biomol. Chem.* **2004**, *2*, 732.

[32] J. T. Gerig, R. S. McLeod, *J. Am. Chem. Soc.* **1973**, *95*, 5725.

[33] M. L. DeRider, S. J. Wilkens, M. J. Waddell, L. E. Bretscher, F. Weinhold, R. T. Raines, J. L. Markley, *J. Am. Chem. Soc.* **2002**, *124*, 2497.

[34] A. Sun, D. C. Lankin, K. Hardcastle, J. P. Snyder, *Chem. – Eur. J.* **2005**, *11*, 1579; D. C. Lankin, N. S. Chandrakumar, S. N. Rao, D. P. Spangler, J. P. Snyder, *J. Am. Chem. Soc.* **1993**, *115*, 3356.

[35] N. E. J. Gooseman, D. O'Hagan, A. M. Z. Slawin, A. M. Teale, D. J. Tozer, R. J. Young, *Chem. Commun.* **2006**, 3190.

[36] S. B. D. Jarvis, A. B. Charette, *Org. Lett.* **2011**, *13*, 3830; M. D'hooghe, V. Van Speybroeck, A. Van Nieuwenhove, M. Waroquier, N. De Kimpe, *J. Org. Chem.* **2007**, *72*, 4733; B. K. Lee, M. S. Kim, H. S. Hahm, D. S. Kim, W. K. Lee, H.-J. Ha, *Tetrahedron* **2006**, *62*, 8393.

[37] a) D. Seebach, J. Zimmermann, U. Gysel, R. Ziegler, T.-K. Ha, *J. Am. Chem. Soc.* **1988**, *110*, 4763; b) R. G. Iafe, K. N. Houk, *Org. Lett.* **2006**, *8*, 3469; c) K. Ando, N. S. Green, Y. Li, K. N. Houk, *J. Am. Chem. Soc.* **1999**, *121*, 5334; d) M. J. Lucero, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 6973; e) M. J. Martinelli, B. C. Peterson, V. V. Khau, D. R. Hutchison, M. R. Leanna, J. E. Audia, J. J. Droste, Y.-D. Wu, K. N. Houk, *J. Org. Chem.* **1994**, *59*, 2204; f) Y. D. Wu, K. N. Houk, B. M. Trost, *J. Am. Chem. Soc.* **1987**, *109*, 5560; g) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, R. J. Loncharich, *Science* **1986**, *231*, 1108.

[38] L. Hunter, K. A. Jolliffe, M. J. T. Jordan, P. Jensen, R. B. Macquart, *Chem. – Eur. J.* **2011**, *17*, 2340.

[39] L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem.* **2011**, *123*, 12062; L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem., Int. Ed.* **2011**, *50*, 11860.

[40] L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, doi: 10.3762/bjoc.6.38.

[41] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308.

[42] P. W. Chia, M. R. Livesey, A. M. Z. Slawin, T. van Mourik, D. J. A. Wyllie, D. O'Hagan, *Chem. – Eur. J.* **2012**, *18*, 8813; E. Durantie, C. Bucher, R. Gilmour, *Chem. – Eur. J.* **2012**, *18*, 8208; E.-M. Tanzer, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Chem. – Eur. J.* **2012**, *18*, 2006; J. M. Um, D. A. DiRocco, E. L. Noey, T. Rovis, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 11249; C. Sparr, E. Salamanova, W. B. Schweizer, H. M. Senn, R. Gilmour, *Chem. – Eur. J.* **2011**, *17*, 8850; N. H. Campbell, D. L. Smith, A. P. Reszka, S. Neidle, D. O'Hagan, *Org. Biomol. Chem.* **2011**, *9*, 1328; I. Yamamoto, G. P. Deniau, N. Gavande, M. Chebib, G. A. R. Johnston, D. O'Hagan, *Chem. Commun.* **2011**, *47*, 7956; C. Bucher, R. Gilmour, *Angew. Chem.* **2010**, *122*, 8906; C. Bucher,

R. Gilmour, *Angew. Chem., Int. Ed.* **2010**, *49*, 8724; C. Sparr, R. Gilmour, *Angew. Chem.* **2010**, *122*, 6670; C. Sparr, R. Gilmour, *Angew. Chem., Int. Ed.* **2010**, *49*, 6520; J. Díaz, J. M. Goodman, *Tetrahedron* **2010**, *66*, 8021; S. Paul, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Organometallics* **2010**, *29*, 4424; C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111; C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem., Int. Ed.* **2009**, *48*, 3065; M. Tredwell, J. A. R. Luft, M. Schuler, K. Tenza, K. N. Houk, V. Gouverneur, *Angew. Chem.* **2008**, *120*, 363;
M. Tredwell, J. A. R. Luft, M. Schuler, K. Tenza, K. N. Houk, V. Gouverneur, *Angew. Chem., Int. Ed.* **2008**, *47*, 357; R. I. Mathad, B. Jaun, O. Flögel, J. Gardiner, M. Löweneck, J. D. C. Codée, P. H. Seeberger, D. Seebach, M. K. Edmonds, F. H. M. Graichen, A. D. Abell, *Helv. Chim. Acta* **2007**, *90*, 2251; R. I. Mathad, F. Gessier, D. Seebach, B. Jaun, *Helv. Chim. Acta* **2005**, *88*, 266.

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