Easy Access to 2-Fluoro- and 2-Iodo-2H-azirines via the Halex Reaction

Anastasiya V. Agafonova  
Ilia A. Smetenin  
Nikolai V. Rostovskii  
Alexander F. Khlebnikov  
Mikhail S. Novikov*

Saint Petersburg State University, Institute of Chemistry, 7/9 Universitetskaya nab., St. Petersburg, 199034, Russia  
m.novikov@spbu.ru

Abstract  
A simple gram-scale method for the preparation of esters and dialkylamides of 2-(fluoro/iodo)-2H-azirine-2-carboxylic acids via the halogen exchange (Halex) reaction of 2-bromo-substituted analogues is reported. The method operates with inexpensive and safe reagents, Bu4NF and potassium iodide, providing high product yields. Alternatively, 2-fluoro-2H-azirine-2-carboxylates can be prepared from 2-iodo- and 2-chloro-analogues. The latter compounds can be obtained in practically quantitative yield by treating the 2-iodo- and 2-bromo-2H-azirine-2-carboxylic esters with Bu4NI.

Key words  
azirines, halogen exchange reaction, fluorine, iodine, nucleophilic substitution

Fluorination and iodination are fundamental transformations in organic chemistry, and fluorinated1 and iodinated2 compounds are of extreme importance as building blocks in organic synthesis. In particular, organic iodides are considered among the best substrates for cross-coupling reactions,2 and the rapid development of modern coupling methods have greatly increased the demand for iodinated compounds as starting materials. Fluorinated compounds have found a variety of applications3 especially as pharmaceuticals.4 It is well known that the introduction of a fluorine atom into a certain position of a bioactive compound may remarkably reduce its toxicity, or improve its efficiency. Furthermore, both organic fluorides and iodides are used as imaging agents for positron emission tomography (PET) scanning.5 This method requires the use of a fluorine-containing agent enriched with the 18F nucleus6 or an iodine-containing agent enriched with the 123I, 124I, or 131I nucleus.7 These isotope have half-times of hours of minutes to several days, thus imposing strict requirements for the speed and operational simplicity of reactions used for the introduction of fluorine or iodine atoms into imaging probes. Such reactions, in particular, include nucleophilic substitution reactions, which can use commercially available isotopically labeled alkali metal fluorides and iodides as reagents.

One of the challenges of this chemistry is the introduction of halogen atoms into labile structures, which are easily destroyed by standard halogenating agents. It is particularly true for 2H-azirines, the strain energy of the three-membered ring of which makes them attractive building blocks for the synthesis of four-, five-, and six-membered heterocycles.8 Examples of the use of 2-bromoazirines for the preparation of the azete and oxazoline derivatives, proceeding with the preservation of the halogen atom in the product have also been reported.9 2-Fluoro- and 2-iodoazirines are much less accessible compounds, and their chemistry is practically unexplored. Besides, 2-iodo-2H-azirines are much more reactive in substitution reactions than 2-bromoazirines, and there are cases when less accessible iodides cannot be replaced by more accessible bromides.10

The known methods for the synthesis of these compounds are based on two strategies. In the framework of the first strategy, the 2-haloazirine ring is formed through the cyclization of halogenated open-chain precursor, for example, through thermal cyclization of a 2-halovinylazide. Some 2-iodo- and 2-fluorovinylazides can be obtained by dehydrohalogenation of 1-azido-2,2-dihalo derivatives11 or from a-oxoephosphonium ylides and N-iodosuccinimide in the presence of azidotrimethylsilane (Scheme 1, reaction 1).12 The reaction of β-carbonyl-substituted enamines with PhF2 generated in situ from PhI0 and Et3N·3HF was used for the preparation of 2-fluoroazirines, containing a carbonyl substituent at the C2 atom (reaction 4).13 Another strategy for the synthesis of 2-fluoro- and 2-iodoazirine-2-carbonyls is based on the metal-catalyzed ring contraction of 4-fluoro- and 4-iodoisoxazoles (reactions 2 and 3).14,15

Unfortunately, the methods noted above require either po-
tentially explosive compounds or expensive reagents. For the preparation of starting materials such as 4-fluoro- and 4-iodoisoxazoles, butyllithium is required. All of this calls into question the scalability of such protocols and stimulates the search for new methods for the preparation of 2-fluoro- and 2-iodoazirines.

One powerful method for the introduction of halogen atoms into a cyclic molecule is the halogen exchange (Hal-ex) reaction. A transition-metal-free version of this method is widely used for the preparation of haloarenes and, to a lesser extent, for the synthesis of haloheteroarenes, such as fluorotriazoles and fluoropyridines. In this work, a new method for the synthesis of 2-fluoro- and 2-iodoazirine-2-carboxyls based on the halogen exchange reaction is developed (Scheme 1, reaction 5). This method uses easily available 2-bromo-2H-azirine-2-carboxylic acid derivatives as starting materials and inexpensive and safe reagents for the introduction of fluorine and iodine into the azirine ring.

Recently, we have shown that a bromine atom in 2-bromo-2H-azirine-2-carboxylates can be easily substituted with acyloxy-, alkoxy-, alkenyloxy- and azolyl substituents under mild conditions. These transformations allow the nucleofugality of the reagent. Thus, aliphatic and aromatic carboxylic acids react with methyl 2-bromo-3-phenyl-2H-azirine-2-carboxylate (1a) in the presence of Et$_3$N to afford 2-acyloxy derivatives in high yields, while with substantially more acidic trichloroacetic acid the reaction does not occur. As far as we know, there is no information in the literature on the use of halide ions as nucleophiles in such reactions.

We began our study with the search for optimal conditions for the preparation of fluoroazirine 2a via the halogen exchange reaction of 2-bromooazirine 1a. The latter was chosen because of its synthetic accessibility and high reactivity in the substitution reactions.

It was found that 1a reacts with tetrabutylammonium fluoride hydrate (TBAF-H$_2$O) in toluene at ambient temperature to afford the target fluoride 2a in good yield (Table 1, entry 1). Screening of other sources of fluoride ion and solvents (entries 2–6) showed that the highest yield of fluoride 2a from bromide 1a was achieved using TBAF-H$_2$O (1.3 equiv) in dichloromethane (DCM) at room temperature (entry 2). These conditions were used in further experiments carried out to evaluate the substrate scope of the reaction.

### Table 1 Optimization of Azirine 2a Synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield of 2a (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF-H$_2$O (1.3)</td>
<td>toluene</td>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>TBAF-H$_2$O (1.3)</td>
<td>DCM</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>KF (1.5)</td>
<td>DMSO</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>CsF (1.5)</td>
<td>DMSO</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>CoF$_2$ (1.5)</td>
<td>DMSO</td>
<td>48</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>FeF$_3$ (1.5)</td>
<td>toluene</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Yield of isolated product.

Bromoazirines 1a–n required for the experiments were prepared from 5-(alkoxy/amino)isoxazoles 5a–n by bromination using N-bromosuccinimide (NBS) followed by FeSO$_4$-catalyzed isomerization of bromoisoxazoles 6a–n (Scheme 2). Isoxazoles 5 were synthesized from either 5-chloroisoxazoles 3 or isoxazol-5-ones 4. The substitution reaction worked well with 2-bromo-3-aryl-2H-azirine-2-carboxylic esters containing both electron-withdrawing (Scheme 3, compound 2e) and electron-donating (Scheme 3, compound 2g) aryl group and afforded the fluoroazirines in good to excellent yields. The reaction was also insensitive to steric hindrance introduced by bulky ortho-substituted aryl groups that could restrict the approach of the nucleophile (Scheme 3, compounds 2d,f,h). This simple protocol could also be applied to 2-bromo-3-aryl-2H-azirine-2-carboxamides, but the yields of the fluoroazirine-2-carboxamides were significantly lower (Scheme 3, compounds 2k,l). To test the ability to scale-up the synthesis of fluoroazirines 2, a gram-scale reaction of bromoazirine 1a (2.2 g, 8.66 mmol) with TBAF-H$_2$O (3.14 g, 11.26 mmol) was carried out to give fluoroazirine 2a in 80% (1.34 g) yield.
only 27%; after this the reaction stopped. Iodoazirines 7d,e were obtained in 90% yield only when a 15-fold excess of KI was used. This may be due to a significantly higher solubility of KBr, compared with KI in solutions containing ether compounds, to which can be attributed compounds 1m,n and 7d,e.

It was found that fluoroazirine 2a can be alternatively synthesized from iodoazirine 7a or chloroazirine 8a under the standard conditions (Scheme 5). The latter compound, in turn, can be obtained in practically quantitative yield by treating azirine 1a or 7a with tetrabutylammonium chloride in DCM. Unfortunately, the reverse transformation of chloroazirine 8a into bromoazirine 1a using tetrabutylammonium bromide (3 equiv) could not be carried out. This reaction does not occur at all. However, bromoazirine 1a was obtained by treating iodoazirine 7a with Bu4NBr (2 equiv) in DCM at room temperature in practically quantitative yield (Scheme 5).

Taking into account the results of the calculations and experimental data obtained for the halogen substitutions in 2-halo-2H-azirine-2-carboxylates with O- and N-nucleophiles,10,19 we believe that the halogen exchange reactions described above also proceed via a cascade S1→S2Jon mechan-ism.

All the newly synthesized haloazirines 1, 2, and 7 were characterized based on 1H, 13C NMR spectroscopic and HRMS data.

In summary, we have developed a simple synthesis of esters and dialkylamides of 2-(fluoro/iodo)-2H-azirine-2-carboxylic acids from much more synthetically accessible 2-bromo-analogues by the halogen exchange (Halex) reaction. The method operates with inexpensive and safe reagents, TBAF and potassium iodide, and provides high product yields. For the synthesis of the 2-fluoro-substituted azirine from the corresponding bromides, a small excess of TBAF is sufficient. A threefold excess of KI in acetone is required to replace bromine with iodine in most 3-aryl-2-
bromo-2H-azirine-2-carboxylates, with the exception of those that contain alkoxy groups in the aryl substituent. In the latter case, a 15-fold excess of the reagent enables high yields of the isoxazolines to be achieved. Alternatively, 2-fluoro-2H-azirine-2-carboxylates can be prepared from 2-ido- and 2-chloro-analogues. The latter compounds, in turn, can be obtained in practically quantitative yield by treating the 2-iodo- and 2-bromoazirines with Bu4NCl.

Melting points were determined with a SMP30 melting point apparatus. 1H (400 MHz) and 13C (100 MHz) NMR spectra were recorded with a Bruker AVANCE 400 spectrometer in CDCl3. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI), positive mode, mass spectra were measured with a Bruker MaXis mass spectrometer using acetonitrile for dilution of samples. Thin-layer chromatography (TLC) was conducted on Macherey-Nagel silica gel 60 M13C NMR (100 MHz, CDCl3): δ = 7.72–7.66 (m, 1 H), 7.66–7.60 (m, 1 H), 7.44–7.36 (m, 1 H), 7.36–7.29 (m, 1 H), 5.67 (s, 1 H), 4.07 (s, 3 H). HRMS (ESI): m/z [M + Na]+ calcd for C10H8BrN2O2+: 277.9610; found: 277.9606.

**Preparation of 3-(3,4-Dimethoxyphenyl)-5-methoxyisoxazole (5m)**

A solution of diazomethane (31.5 mmol) in Et2O, prepared from N-nitroso-N-methylurea and KOH, was added dropwise at 0 °C to a stirred suspension of 3-(3,4-dimethoxyphenyl)-5-methoxyisoxazolone (4a)21h (10.5 mmol) in anhydrous Et2O (50 mL). The resulting mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; hexane/EtOAc, 3:1), followed by crystallization from Et2O-hexane.

Yield: 1.20 g (99%) (from isoxazole 3b); colorless solid; mp 76–77 °C.

1H NMR (400 MHz, CDCl3): δ = 7.82–7.74 (m, 2 H), 7.48–7.42 (m, 3 H), 6.96–6.88 (m, 1 H), 5.50 (s, 1 H), 4.03 (d, J = 6.6 Hz, 2 H), 2.26–2.10 (m, 1 H), 1.07 (d, J = 6.7 Hz, 6 H).

13C NMR (100 MHz, CDCl3): δ = 174.0, 164.1, 129.9, 129.7, 128.8, 126.4, 78.4, 75.6, 28.1, 18.8.


**Bromoisoxazoles 6f and 6h; General Procedure**

A solution of the isoxazole 5f or 5h (2 mmol) and N-bromosuccinimide (392 mg, 2.2 mmol) in CHCl3 (25 mL) was stirred at ambient temperature for 3 h. The reaction mixture was diluted with 10% Na2S2O3 (60 mL) and extracted with CHCl3 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the product was purified by silica gel flash chromatography (hexane/EtOAc, 5:1), followed by crystallization from Et2O-hexane.

Yield: 0.50 g (90%) (from isoxazole 5f); colorless oil; mp 108–110 °C.

1H NMR (400 MHz, CDCl3): δ = 7.75–7.69 (m, 1 H), 7.48–7.34 (m, 3 H), 4.26 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 169.0, 164.5, 133.1, 131.5 (2C), 129.7, 127.3, 123.1, 68.9, 58.6.

4-Bromo-3-(2,4-dimethoxyphenyl)-5-methoxysoxazole (6h)
Yield: 440 mg (70%) (from isoxazole 5h); colorless solid; mp 71–73 °C.
1H NMR (400 MHz, CDCl3): δ = 7.37–7.31 (m, 1 H), 6.62–6.55 (m, 2 H), 4.21 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H).
13C NMR (100 MHz, CDCl3): δ = 168.6, 162.9, 162.7, 158.7, 131.7, 110.0, 104.7, 98.9, 69.4, 58.3, 55.6, 55.4.

Methyl 2-Bromo-3-[4-((tert-butyl)phenyl]-2H-azirine-2-carboxylate (1c)
Yield: 608 mg (98%) (from isoxazole 6c22); colorless solid; mp 85–86 °C.
1H NMR (400 MHz, CDCl3): δ = 7.94–7.88 (m, 2 H), 7.70–7.64 (m, 2 H), 3.82 (s, 3 H), 1.40 (s, 9 H).
13C NMR (100 MHz, CDCl3): δ = 167.4, 163.8, 159.5, 130.9, 126.8, 116.7, 54.1, 43.9, 35.6, 31.0.

Methyl 2-Bromo-3-(2,4-dimethylphenyl)-2H-azirine-2-carboxylate (1d)
Yield: 485 mg (86%) (from isoxazole 6d23); colorless solid; mp 60–61 °C.
1H NMR (400 MHz, CDCl3): δ = 7.75–7.68 (m, 1 H), 7.28–7.22 (m, 2 H), 3.83 (s, 3 H), 2.67 (s, 3 H), 2.46 (s, 3 H).
13C NMR (100 MHz, CDCl3): δ = 167.6, 162.9, 146.3, 142.6, 132.5, 132.3, 127.6, 115.8, 54.1, 43.5, 21.9, 19.7.

Methyl 2-Bromo-3-(2-bromophenyl)-2H-azirine-2-carboxylate (1f)
Yield: 619 mg (93%) (from isoxazole 6f); colorless solid; mp 83–84 °C.
1H NMR (400 MHz, CDCl3): δ = 8.07–8.00 (m, 1 H), 7.86–7.79 (m, 1 H), 7.65–7.55 (m, 2 H), 3.84 (s, 3 H).
13C NMR (100 MHz, CDCl3): δ = 167.0, 164.9, 136.0, 134.4, 133.8, 128.2, 126.3, 120.8, 54.2, 45.0.

Methyl 2-Bromo-3-(2,4-dimethoxyphenyl)-2H-azirine-2-carboxylate (1h)
Yield: 616 mg (98%) (from isoxazole 6h); colorless solid; mp 85–86 °C.
1H NMR (400 MHz, CDCl3): δ = 7.72–7.66 (m, 1 H), 6.71–6.65 (m, 1 H), 6.59–6.56 (m, 1 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.80 (s, 3 H).
13C NMR (100 MHz, CDCl3): δ = 167.9, 167.2, 162.8, 159.6, 134.7, 106.4, 101.4, 98.7, 56.1, 55.9, 53.9, 43.7.

Bromoazirines 1i,j,m; General Procedure
A solution of isoxazole 6i,j,m (2 mmol) and N-bromosuccinimide (392 mg, 2.2 mmol) in CHCl3 (25 mL) was stirred at ambient temperature for 3 h. The reaction mixture was diluted with 10% Na2S2O3 (60 mL), and extracted with CH2Cl2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na2SO4. The solvent was removed under reduced pressure, and the obtained bromoisoxazole 6i,j,m was used in the next step without further purification. A suspension of isoxazole 6i,j,m and FeSO4·7H2O (239 mg, 1.2 mmol, 60 mol%) in MeCN (15 mL) was stirred at ambient temperature for 5 h, then the solvent was removed under reduced pressure. In order to remove iron compounds, the product was purified by silica gel flash chromatography (hexane/EtOAc, 10:1), followed by crystallization from Et2O–hexane.

Isobutyl 2-Bromo-3-phenyl-2H-azirine-2-carboxylate (1i)
Yield: 539 mg (91%) (from isoxazole 5i); colorless oil.
1H NMR (400 MHz, CDCl3): δ = 8.02–7.93 (m, 2 H), 7.79–7.71 (m, 1 H), 7.69–7.60 (m, 2 H), 4.08–3.94 (m, 2 H), 2.06–1.88 (m, 1 H), 0.95–0.86 (m, 6 H).
13C NMR (100 MHz, CDCl3): δ = 166.7, 164.6, 135.0, 130.8, 129.6, 119.8, 73.2, 44.2, 27.6, 18.8.

Benzyl 2-Bromo-3-phenyl-2H-azirine-2-carboxylate (1j)
Yield: 594 mg (90%) (from isoxazole 5j); colorless solid; mp 60–61 °C.
1H NMR (400 MHz, CDCl3): δ = 7.98–7.92 (m, 2 H), 7.78–7.72 (m, 1 H), 7.67–7.61 (m, 2 H), 7.39–7.30 (m, 3 H), 5.28 (s, 2 H).
13C NMR (100 MHz, CDCl3): δ = 166.6, 164.4, 135.1, 134.9, 130.9, 129.6, 128.5, 128.4, 127.9, 119.6, 68.7, 43.9.

Methyl 2-Bromo-3-(3,4-dimethoxyphenyl)-2H-azirine-2-carboxylate (1m)
Yield: 597 mg (95%) (from isoxazole 5m); colorless solid; mp 102–103 °C.
1H NMR (400 MHz, CDCl3): δ = 7.61–7.49 (m, 1 H), 7.49–7.39 (m, 1 H), 7.13–7.03 (m, 1 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 3.82 (s, 3 H).
13C NMR (100 MHz, CDCl3): δ = 167.4, 163.3, 154.9, 150.0, 126.3, 111.9, 111.7, 111.4, 56.3, 56.2, 54.1, 44.6.

2-Fluoro-2H-azirines 2a–l; General Procedure
A solution of 2-bromo-2H-azirines 1a–l (1 mmol) and TBAF·H2O (363 mg, 1.3 mmol) in DCM (5 mL) was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane–EtOAc mixture) to give fluoroazirines 2a–l.

Methyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2a)
Yield: 155 mg (80%) (from azirine 1a); colorless solid; mp 58–59 °C.
Yield: 202 mg (81%) (from azirine 1c).  
Methyl 2-Fluoro-3-(4-nitrophenyl)-2-azirine-2-carboxylate (2f)  
Yield: 192 mg (76%) (from azirine 1h); colorless solid; mp 120–121 °C.  
HRMS (ESI): m/z [M + Na]+ calcd for C16H12FNNaO2+: 293.9536; found: 293.9529.  

Methyl 2-Fluoro-3-(4-methoxyphenyl)-2H-azirine-2-carboxylate (2g)  
Yield: 181 mg (81%) (from azirine 1g); colorless solid; mp 53–54 °C.  

Methyl 3-(2,4-Dimethoxyphenyl)-2-fluoro-2H-azirine-2-carboxylate (2h)  
Yield: 204 mg (75%) (from azirine 1f); colorless solid; mp 45–46 °C.  

Benzyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2i)  
Yield: 195 mg (83%) (from azirine 1i); colorless oil.  

Benzyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2j)  
Yield: 256 mg (95%) (from azirine 1j); colorless solid; mp 52–53 °C.  

(2-Fluoro-3-phenyl-2H-azirin-2-yl)(pyrrolidin-1-yl)methanone (2k)  
Yield: 149 mg (64%) (from azirine 1k); colorless solid; mp 67–68 °C.  

Isobutyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2l)  
Yield: 195 mg (83%) (from azirine 1l); colorless oil.  

Methyl 2-Fluoro-3-(4-nitrophenyl)-2H-azirine-2-carboxylate (2e)  
Yield: 256 mg (95%) (from azirine 1e); colorless solid; mp 115–116 °C.  

Methyl 2-Fluoro-3-(4-nitrophenyl)-2H-azirine-2-carboxylate (2e)  
Yield: 256 mg (95%) (from azirine 1e); colorless solid; mp 115–116 °C.  

Methyl 3-(2,4-Dimethylphenyl)-2-fluoro-2H-azirine-2-carboxylate (2d)  
Yield: 202 mg (81%) (from azirine 1c); colorless oil.  

Methyl 3-(2,4-Dimethylphenyl)-2-fluoro-2H-azirine-2-carboxylate (2d)  
Yield: 190 mg (86%) (from azirine 1d); colorless solid; mp 64–65 °C.  

Methyl 3-(2,4-Dimethylphenyl)-2-fluoro-2H-azirine-2-carboxylate (2d)  
Yield: 190 mg (86%) (from azirine 1d); colorless solid; mp 64–65 °C.  

Methyl 3-(2,4-Dimethylphenyl)-2-fluoro-2H-azirine-2-carboxylate (2d)  
Yield: 190 mg (86%) (from azirine 1d); colorless solid; mp 64–65 °C.  

Methyl 2-Fluoro-3-(p-toly1)-2H-azirine-2-carboxylate (2b)  
Yield: 170 mg (82%) (from azirine 1b); colorless solid; mp 44–45 °C.  

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Methyl 2-Fluoro-3-(p-toly1)-2H-azirine-2-carboxylate (2b)  
Yield: 170 mg (82%) (from azirine 1b); colorless solid; mp 44–45 °C.  
HRMS (ESI): m/z [M + H]+ calcd for C_{10}H_{7}IN_{2}NaO_{4}+: 233.1085; found: 233.1086.

(2-Fluoro-3-phenyl-2H-azirin-2-yl)(morpholino)methane (2l)
Yield: 99 mg (40%) (from azirine 1j); colorless solid; mp 87–88 °C.

1H NMR (400 MHz, CDCl3): δ = 7.89–7.81 (m, 2 H), 7.50–7.43 (m, 5 H), 5.25 (s, 2 H).

13C NMR (100 MHz, CDCl3): δ = 165.8, 165.3, 165.0, 164.2, 164.1, 149.7, 144.4, 125.1, 119.9, 118.8, 112.7, 112.6, 112.5, 112.4, 64.8, 64.0, 54.3, 14.6.

HRMS (ESI): m/z [M + Na]+ calcd for C_{10}H_{10}INNaO_{2}: 381.9547; found: 381.9547.

**Synthesis of Chloroaizirine 8a from Bromoaizirine 1a**
A solution of bromoaizirine 1a (301 mg, 1 mmol) and Bu_{4}NBr (645 mg, 2.0 mmol) in DCM (5 mL) was stirred at ambient temperature for 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/ EtOAc mixture) to give chloroaizirine 8a (205 mg, 98%).

**Funding Information**
We gratefully acknowledge the financial support of the Russian Science Foundation (Grant No. 17-13-01078).
Acknowledgment

This research used resources of the 'Magnetic Resonance Research Centre', the 'Chemical Analysis and Materials Research Centre', and the 'Chemistry Educational Centre' of the Research Park of St. Petersburg State University.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690200.

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