Ring enlargement and ring contraction induced by diethylaminosulfur trifluoride (DAST)

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This article is dedicated to our friends Bruce and Cynthia Maryanoff

Abstract
Diethylaminosulfur trifluoride (DAST) is a very powerful reagent that allows the conversion of various alcohols to fluorine-containing products which can possess interesting biological activities. The fluorination process can occur in unison with a ring-expansion and/or ring-contraction.

Keywords: Diethylaminosulfur trifluoride, DAST, alcohol, rearrangement, ring-expansion, ring-contraction, fluorine

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1. Introduction

The introduction of a fluorine atom into organic molecules modifies their physical, chemical and biological properties.[1] Selective fluorinations of organic compounds,[2] can be performed using a variety of reagents and methods which have been developed. Among the fluorinating reagents that have emerged, *N*,*N*-diethylaminosulfur trifluoride (DAST),[3] $(CH_3CH_2)_2NSF_3$ is probably one of the most popular and useful reagents to convert simple alcohols into the corresponding fluorinated products.[4] In general, the fluorination of optically active alcohols using DAST proceeds with inversion of configuration (S_N2 mechanism). Furthermore, when an electron-rich substituent (such as methoxy,[5] amine,[6] thioester,[7] epoxide,[8] azide,[9] double bond,[10] aromatic ring,[11] ester,[12] amide[13]) is vicinal to the hydroxyl group, rearrangements can proceed through anchimeric assistance of the electron-rich group. These rearrangements can be explained in terms of neighboring group participation and are the result of the formation of a very good leaving group coming from the reaction of an alcohol moiety with DAST. Herein, we will focus only on ring expansion and contraction induced by DAST (Scheme 1).

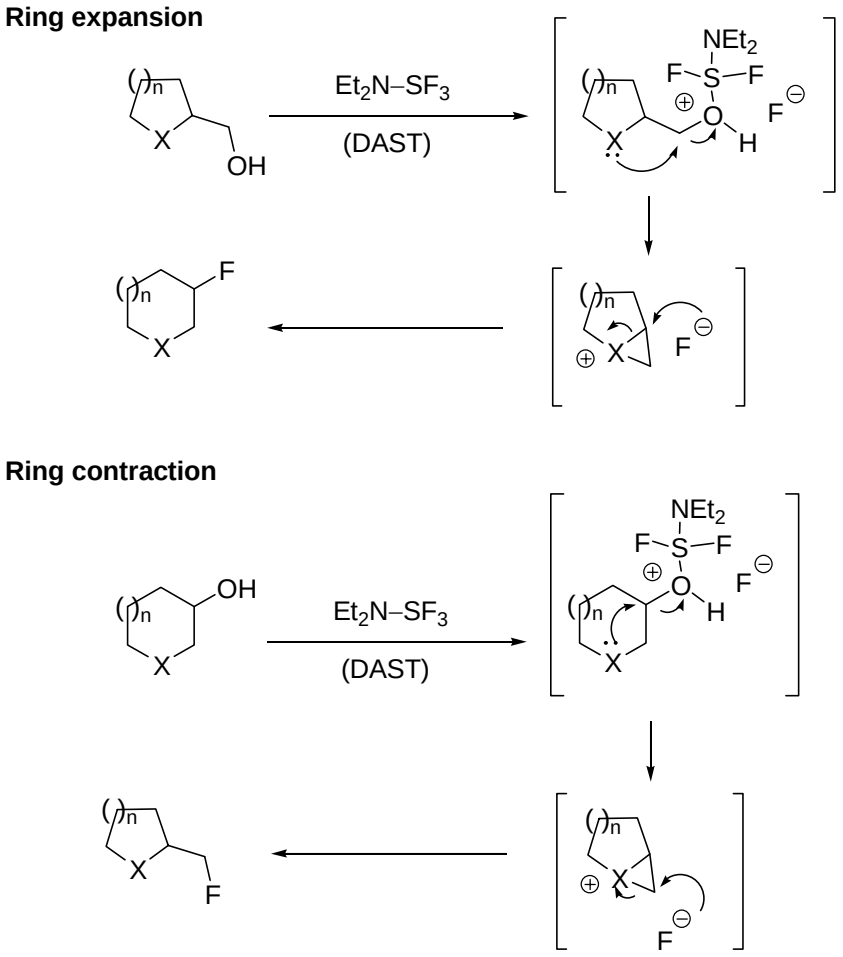
2. Ring Expansion

In considering the poor nucleophilicity of the fluoride anion, the ring expansion is under kinetic control. Ring expansion has been observed, *via* a carbocation intermediate, in carbocyclic systems when an homoallylic alcohol is present in the substrate. It has also been observed in *α*-epoxy-alcohols and in *β*-amino alcohols due to neighboring heteroatom participation. This ring expansion can be the result of the cleavage of a C–C or a C–heteroatom bond.

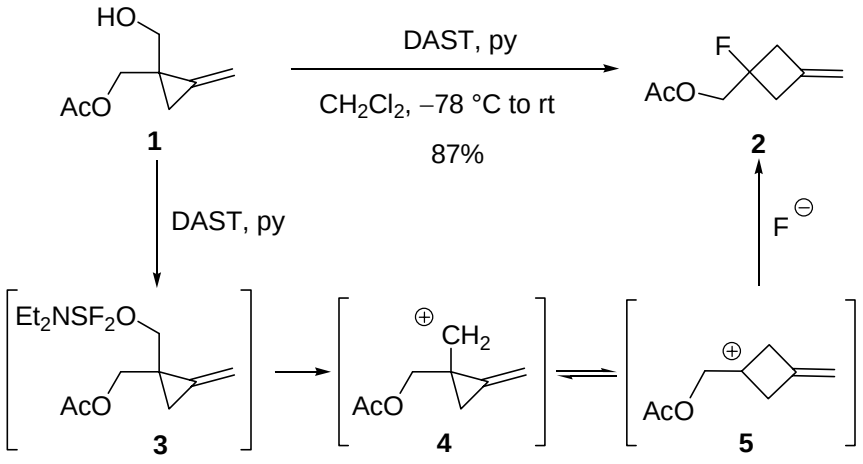
2.1. Carbocation induced rearrangements: Cyclic homoallylic alcohols

DAST can induce carbocation formation from homoallylic alcohols, which then can undergo ring expansion. These reactions are observed when substituted strained rings substituted by homoallylic alcohols are treated with DAST. Thus, fluoro-cyclobutane **2** (87%), the ring expansion product was the only observed product when hydroxymethyl methylenecyclopropane **1** was treated with DAST in a solution of pyridine in CH_2Cl_2 at temperatures between –78 °C and room temperature.[14] The reaction, induced by DAST, is initiated by the transformation of **1** to intermediate **3**. Then, a non-classical cyclopropylmethyl carbocation **4**, which exists in equilibrium with the cyclobutonium ion **5**, reacts with the fluorine anion to give **2** (Scheme 2).

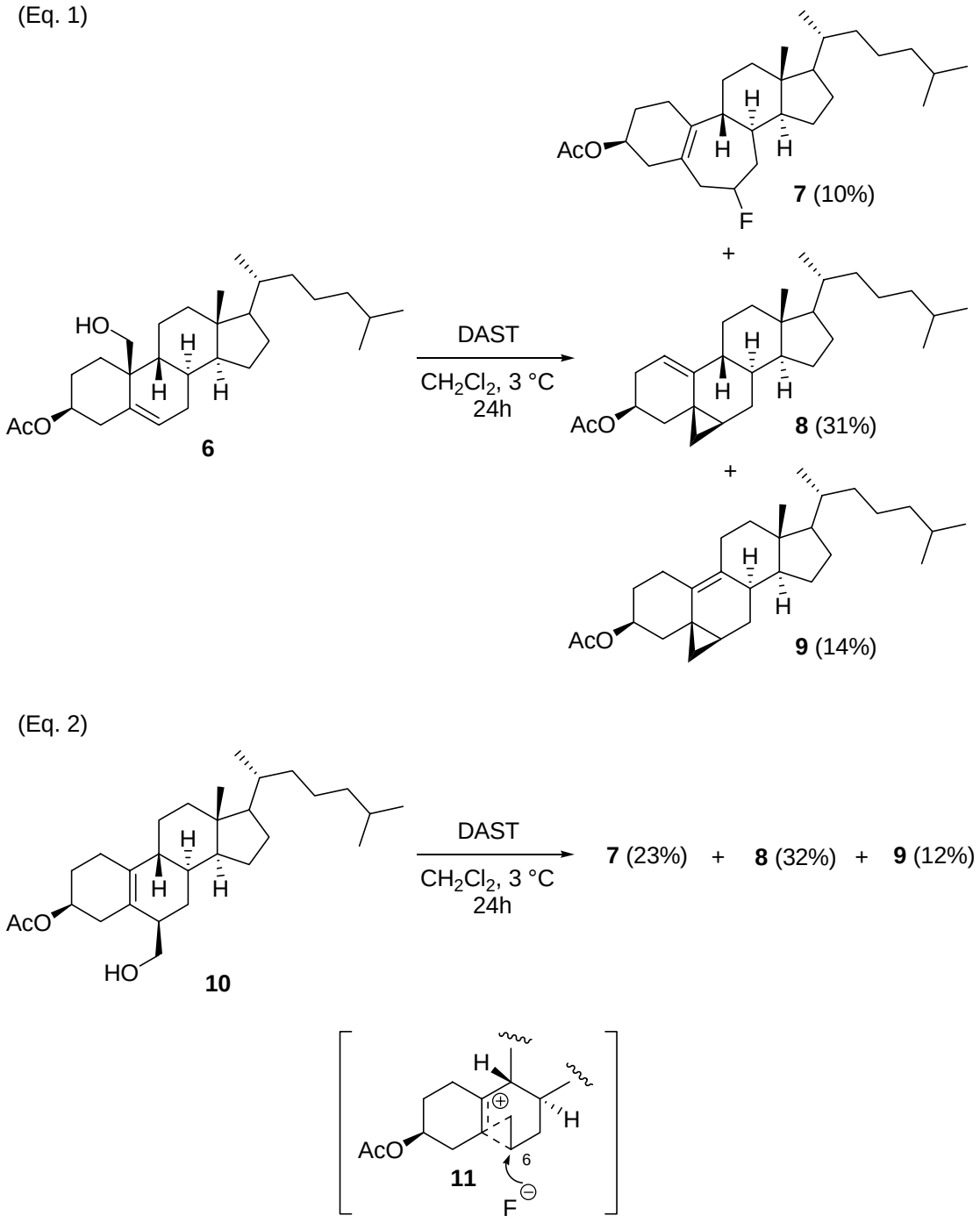
Ring expansions of carbocyclic compounds have also been observed in steroids.[15,16] When choles-5-en-3*β*-19-diol-3-acetate **6** was treated with DAST, three compounds **7**–**9** were formed, among which is compound **7**, the result of ring expansion (Scheme 3, Eq. 1). Furthermore, 6-*β*-hydroxymethyl-19-norcholest-5-(10)-en-3*β*-ol-3-acetate **10** was also transformed into the same three compounds **7**, **8** and **9** when treated with DAST (Scheme 3, Eq. 2).



Scheme 1. General scheme for ring expansion and ring contraction by DAST



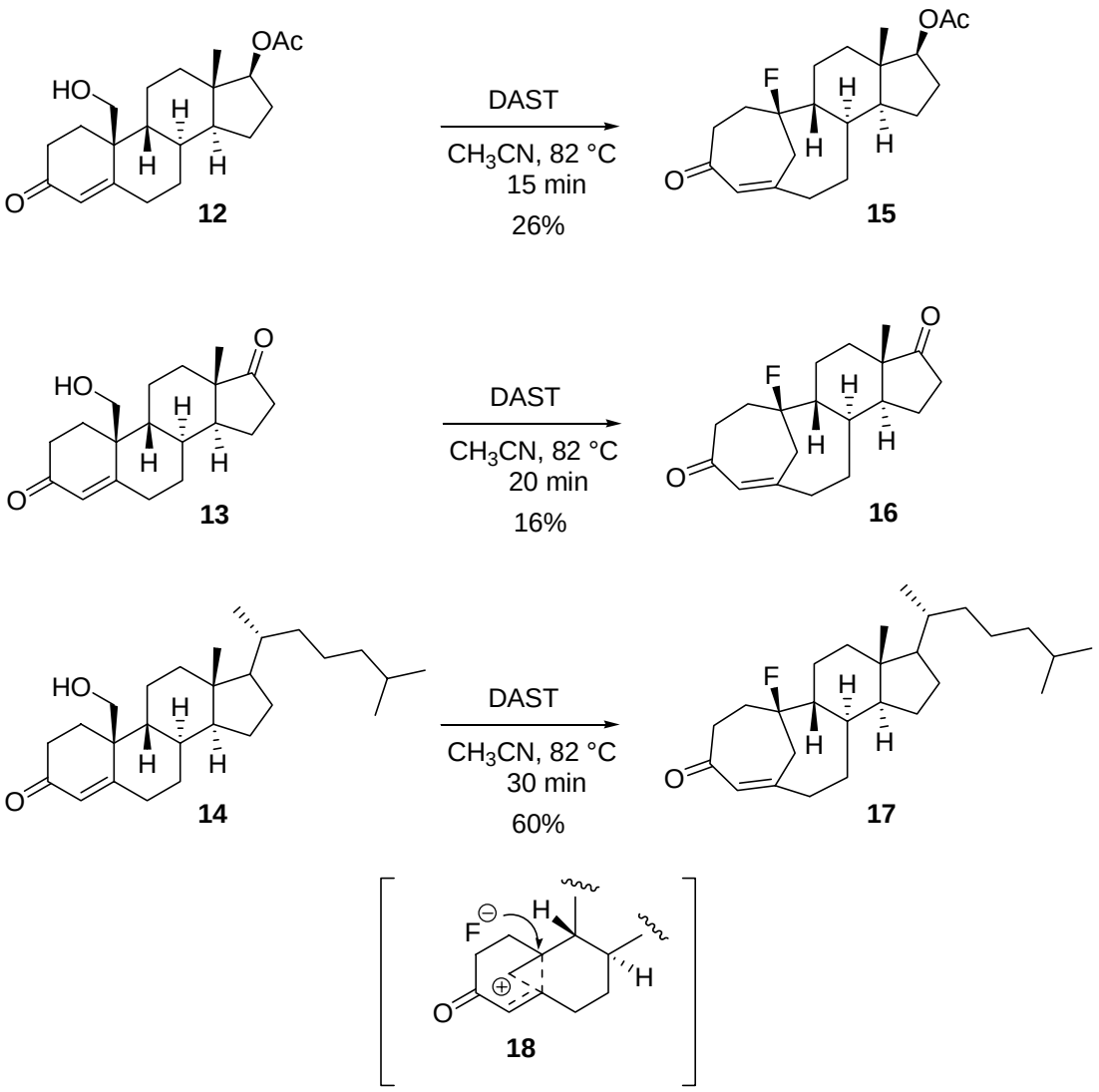
Scheme 2



Scheme 3

It is worth noting that the yield of **7** was slightly improved when starting from **10** rather than from **6** (23% *versus* 10%).[15] It is considered that a homoallylic cation such as **11** is formed as the intermediate. The formation of **7** can be explained by a low energy pathway involving the nucleophilic attack of the fluoride anion on the C6 position of intermediate **11** (Scheme 3).

In the cholest-4-en-3-one series, the yields in the ring-expanded products were quite similar to the yields in the cholesterol series as compounds **15** and **16** were obtained from **12** and **13** in 26% and 16% yield, respectively (Scheme 4). However, ring-expansion product **17** was isolated in a 60% yield, resulting from the treatment of **14** with DAST.[16] It is speculated that these compounds are probably proceeding *via* intermediate **18** and subsequent attack by the fluoride anion (Scheme 4).



Scheme 4

2.2. Neighboring heteroatom participation

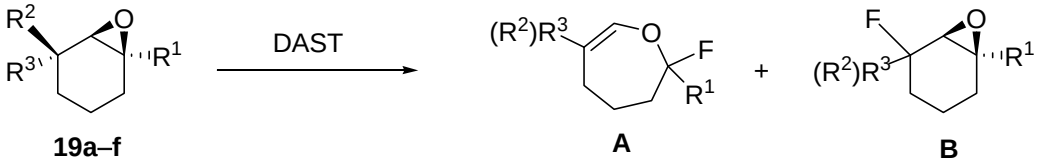
Cyclic epoxy-alcohols as well as cyclic β-amino-alcohols can be expanded when treated with DAST. This ring expansion takes place *via* an aziridinium or oxonium intermediate which can be formed, due to the presence of the epoxide or the amino group vicinal to the hydroxy group.

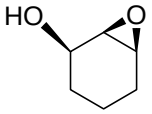
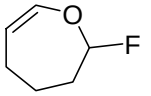
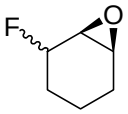
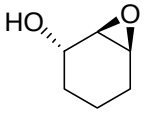
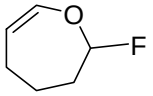
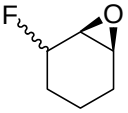
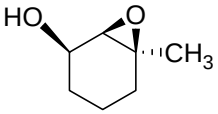
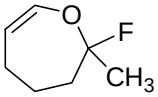
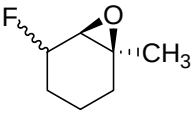
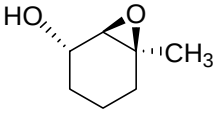
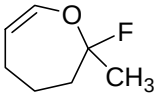
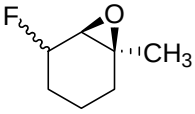
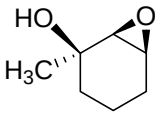
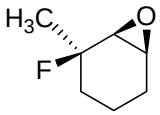
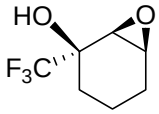
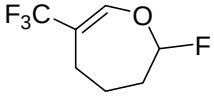
2.2.1 Oxygen participation: Epoxy-alcohols. Epoxides are highly versatile and reactive intermediates, due their easy access and their ring opening reaction which proceeds *via* cleavage of the C–O bond. The cleavage of the C–C bond of the epoxide is rare nevertheless observed when bicyclic epoxy-alcohols are treated with DAST, affording the ring-expansion product (Scheme 5).

Scheme 5.

During the ring enlargement process of epoxy-alcohols, the relative stereochemistry of the epoxide and hydroxyl group is of importance and effect the outcome of the reaction. The formation of the ring-expanded product involves a delicate balance between steric and electronic factors (Tables 1 and 2). When treated with DAST, the bicyclic *cis*-epoxy-alcohol **19a** was transformed to the fluorinated heterocyclic compound **20**, which corresponds to the ring-expanded product, and also to the fluoro-epoxide **24** as a mixture of *cis*- and *trans*- products. These two compounds, which could not be separated, were isolated in 58% yield in a ratio of 63/37 in favour of the ring-expanded product **20**. Interestingly, the *trans*-epoxy-alcohol **19b** showed reverse selectivity as the ratio **20**/**25** was in favour of the fluoro-epoxide **25** (31/69). The methyl substituted *cis*- and *trans*-derivatives **19c** and **19d** gave high ratio of the ring-expanded products (oxepanes) *versus* fluoro-epoxides (> 80%). In this later case, the stereochemical relationship between the functionalities was only of minor influence. On the contrary, the electronic nature of the substituents of the carbinol has a dramatic effect on the ring expansion as **19e**, possessing a methyl group, was transformed to the fluoro-epoxide **28** whereas **19f**, possessing a trifluoromethyl group, was transformed to the ring-expanded product **23** in 70% yield (Table 1).

Table 1. Ring expansion of 6-membered rings

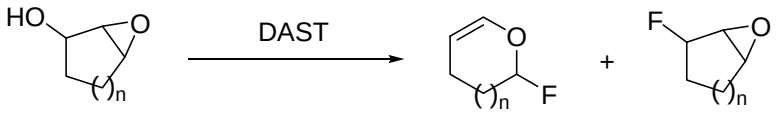


Substrate	Product **A**	Product **B**	Yield (%)	Ratio **A**/**B**
 **19a**	 **20**	 **24** (*cis*/*trans*:62/38)	58	63/37
 **19b**	 **20**	 **25** (*cis*/*trans*:10/90)	61	31/69
 **19c**	 **21**	 **26** (*cis*/*trans*:85/15)	–	83/17
 **19d**	 **22**	 **27** (*cis*/*trans*:85/15)	–	80/20
 **19e**	–	 **28**	73	–
 **19f**	 **23**	–	70	–

Similar results to those of the cyclohexane series were also observed for the cycloheptane series (Table 2). *Cis*-epoxy-alcohol **19g** gave a 70/30 mixture of fluoro-oxocene **29** and fluoro-epoxide **34**, while the *trans*-epoxy-alcohol **19h** showed a reverse selectivity as the ratio **30**/**35** is 30/70. Whereas for the cyclo-octane series, the reactivity of the *cis*-epoxy-alcohol **19i** is distinct, yielding only the ring-expansion product **31.** The cyclododecene alcohols appeared to be attractive substrates in terms of ring-expansion. The *cis*-epoxides **19j** and **19k** yielded only the

ring-expansion products, also only the *Z*-enol ether was formed when the hydroxyl group and the epoxide were *cis* (compound **19j** → **32**), however the reverse is true for the formation of the *E*-enol ether which was produced when the hydroxy group and the epoxide were *trans* (compound **19k** → **33**). The *trans*-epoxides **19l** and **19m** were transformed to the ring-expansion products with similar stereospecificity, yielding **32** and **33** respectively. However in both cases, the formation of fluoro-epoxides became predominant (Table 2).[8b]

Table 2. Ring expansion of 7-, 8-, and 12-membered rings



19g–m **C** **D**

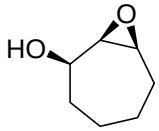
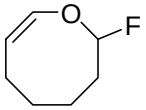
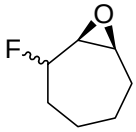
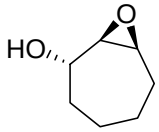
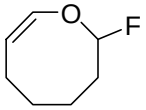
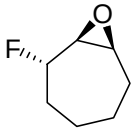
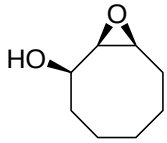
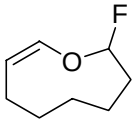
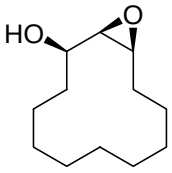
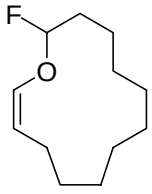
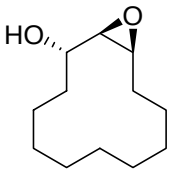
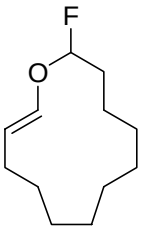
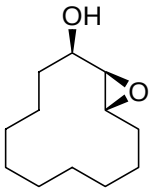
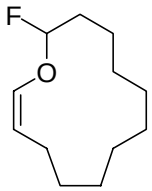
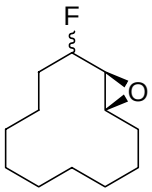
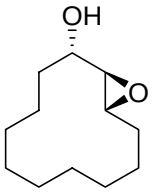
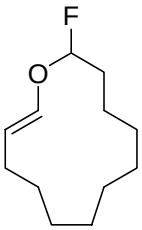
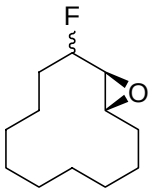
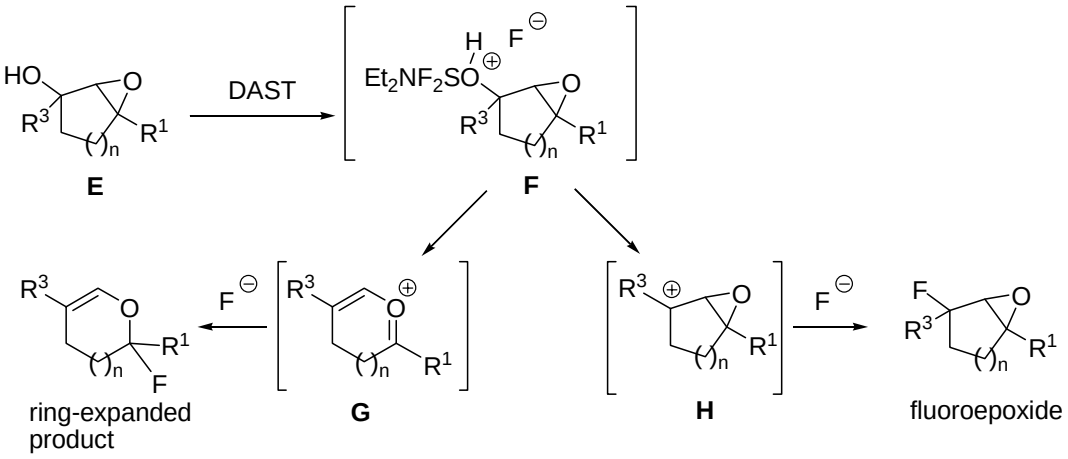
Substrate	Product **C**	Product **D**	Yield (%)	Ratio **C**/**D**
			63	70/30
19g	**29**	**34** (*cis*/*trans*:50/50)		
			65	30/70
19h	**30**	**35**		
		–	88	–
19i	**31**			
		–	86	–
19j	**32**			

Table 2. (continued)

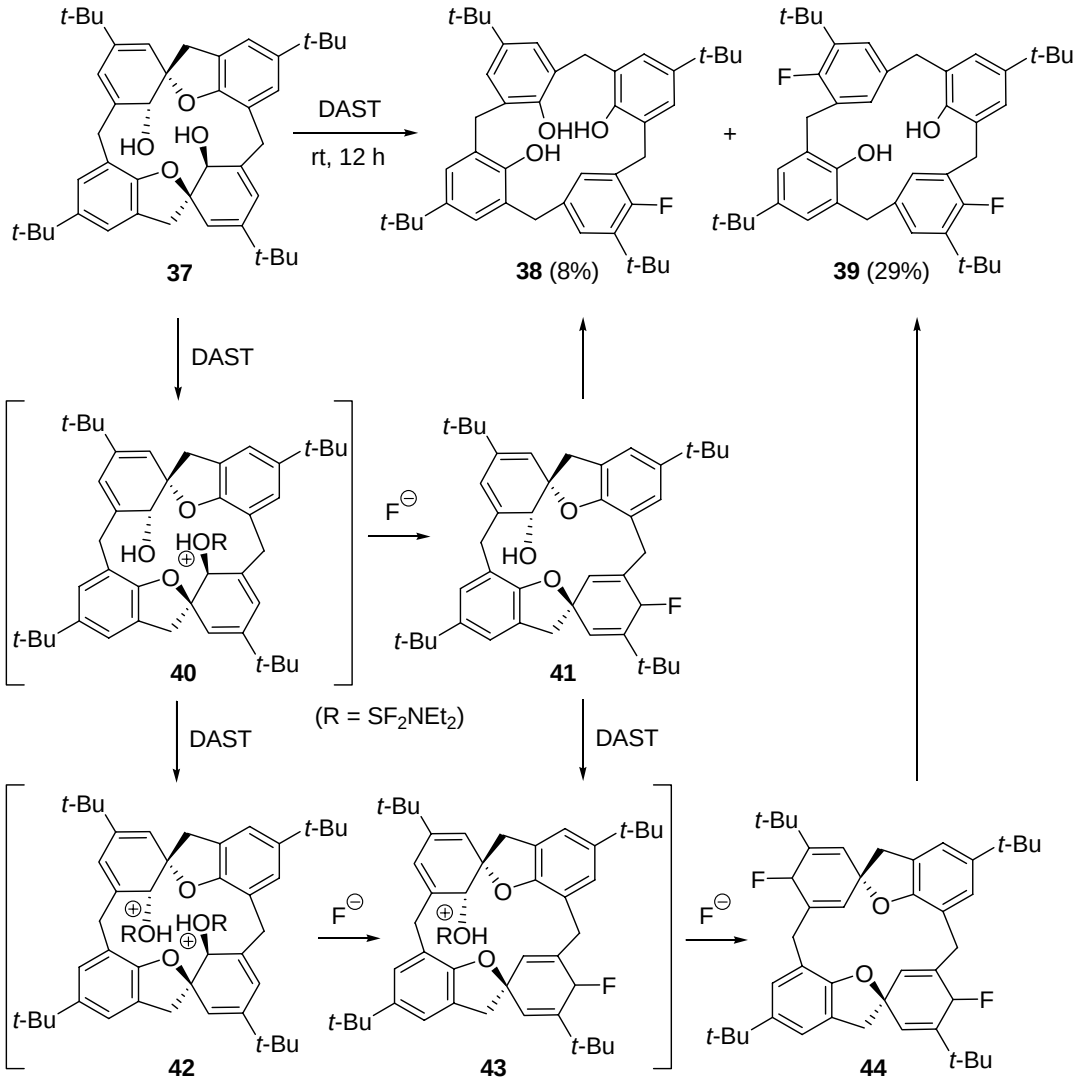
Substrate	Product **C**	Product **D**	Yield (%)	Ratio **C/D**
		–	90	–
19k	**33**			
			78	10/90
19l	**32**	**36** (*cis*/*trans*:73/27)		
			82	26/74
19m	**33**	**37** (*cis*/*trans*:11/89)		

As the electronic nature of the substituents present on cycloalkene alcohols has an important influence over the ratio between ring-expanded product and fluoro-epoxides, one can speculate that this results from the formation of both an oxonium ion **G** leading to the ring-expansion product (presence of a methyl group on the epoxide ring as well as a CF_3 on the carbinol) and an oxiranyl cation **H** leading to the fluorinated epoxides (presence of a methyl group on the vicinal carbinol) (Scheme 6).[8b] We have to point out that for the *cis*- and *trans*-epoxides of large ring systems such as **19j**–**19m**, the ratio between the ring-expansion products and the fluoro-epoxides is related to steric interactions between substituents on the carbocation center and those substituents vicinal to the epoxy carbon.

Ring enlargement by cleavage of C–O bonds has also been observed. When the *bis*-(spirodienol) calixarene **37** was treated with DAST, fluorinated calixarenes **38** and **39** were formed in 8% and 29% respectively, probably *via* intermediates **41** and **44** respectively (Scheme 7).[17]



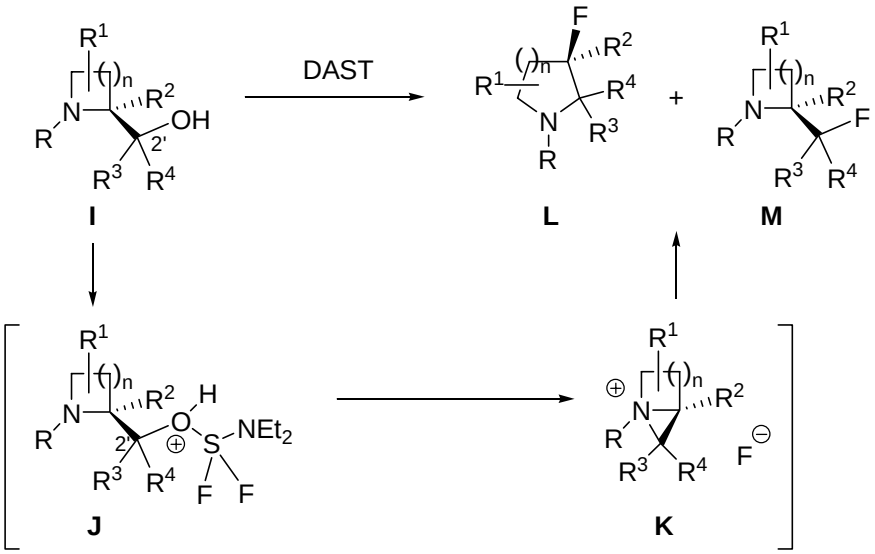
Scheme 6



Scheme 7

2.2.2 Nitrogen participation: *β*-amino alcohols

DAST is also able to induce ring enlargement of cyclic *β*-amino alcohols. Compounds of type **I** can be converted to the fluoro-amines **L** when treated with DAST, however synthesis of non-rearranged product **M** are also possible. The ring expansion of cyclic *β*-amino alcohols is supposed to proceed *via* an aziridinium intermediate **K**, resulting from an intramolecular nucleophilic substitution by the nitrogen atom displacing the leaving group evident in **J**. The product ratio **L**/**M**, depends mainly on the ring size of the cyclic *β*-amino alcohols, the steric hindrance of the *N*- and C2'-substituents (R and R^3, R^4 respectively) (Scheme 8).



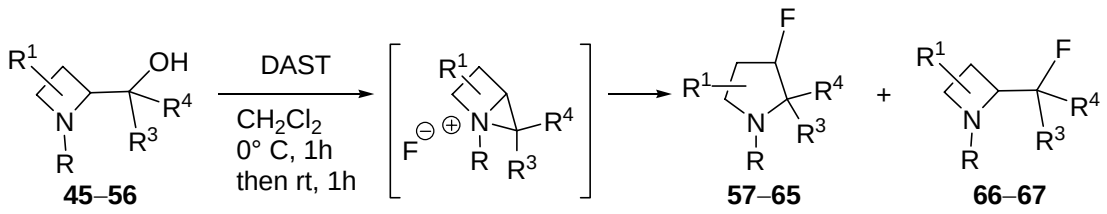
Scheme 8

The behavior of substituted azetidinols, prolinols, azepidinols, when treated with DAST, has also been studied.[18,19] Optically active azetidinols bearing a primary, secondary or tertiary alcohol and possessing different substituents on the azetidine ring were treated with DAST (Table 3). All primary and secondary alcohols **45**–**53** were rearranged into the corresponding fluoro-pyrrolidines **57**–**65**, regardless of the substituent present on the nitrogen atom. In each case, the 3-fluoro-pyrrolidines were isolated in fair to good yields and only one diastereoisomer was produced. However, the ring-expansion products were not detected when the azetidines possessed a tertiary alcohol at C2' as in compounds **54**–**56**. Only the fluorinated azetidines **66** and **67** were isolated in modest yields, together with significant amounts of the corresponding elimination product **66'** or **67'** (Table 3).

The rearrangement leading to fluoro-pyrrolidines **57**–**65** is stereospecific and involves a bicyclic 1-azoniabicyclo[2.1.0]pentane intermediate which is regioselectively opened by a fluoride anion. In the case of the azetidines with tertiary alcohols **54**–**56**, the absence of ring-expansion products can be attributed to the formation of an intermediate carbonium ion, which

occurs faster than the nucleophilic displacement leading to the bicyclic ammonium ion (Table 3).[18]

Table 3. Ring expansion of 2-hydroxyalkylazetidines



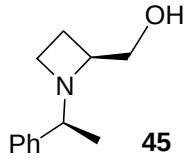
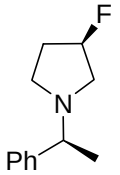
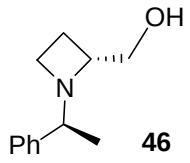
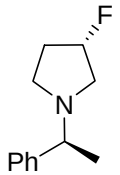
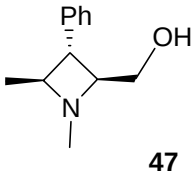
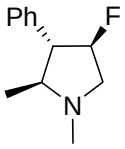
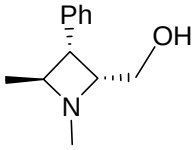
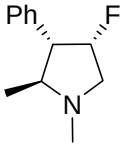
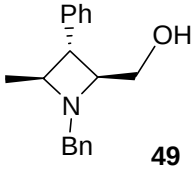
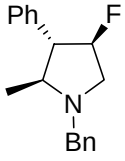
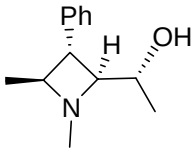
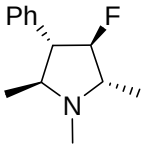
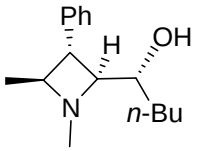
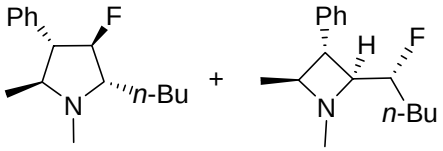
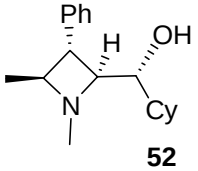
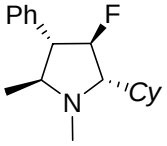
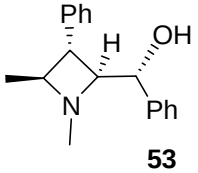
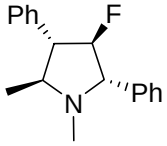
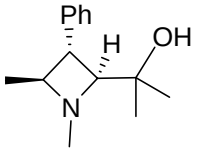
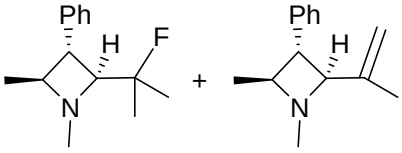
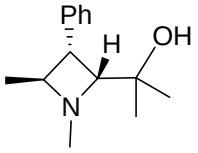
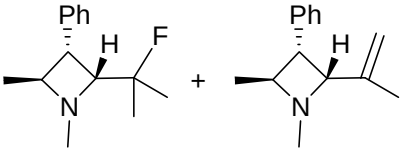
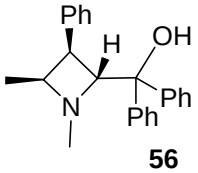
Substrate	Product(s)	Yield (%)
 **45**	 **57**	81
 **46**	 **58**	58
 **47**	 **59**	68
 **48**	 **60**	45
 **49**	 **61**	79
 **50**	 **62**	69

Table 3. (continued)

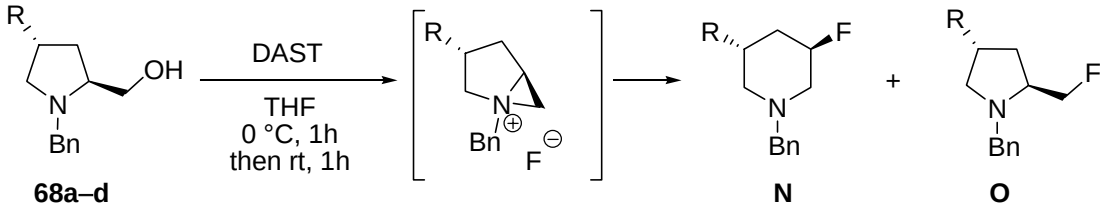
Substrate	Product(s)	Yield (%)
 **51**	 **63** + **63'**	78 (**63**) and 12 (**63'**)
 **52**	 **64**	80
 **53**	 **65**	62
 **54**	 **66** + **66'**	37 (**66**) and 37 (**66'**)
 **55**	 **67** + **67'**	32 (**67**) and 40 (**67'**)
 **56**	complex crude mixture in which **56** was the major product.	–

Rearrangement of optically active prolinols **68a–d** by treatment with DAST affords optically active piperidines of type **N** (Table 4). In contrast to the azetidine series, this group of compounds displays less regioselectivity in the nucleophilic attack of the fluoride anion, this can be explained by a less strained bicyclic 1-azoniabicyclo[3.1.0]hexane intermediate leading to fluoro-piperidines as well as to fluoro-pyrrolidines. The regioselectivity of the nucleophilic attack of the fluoride anion depends on the substitution pattern at C2 and C4 of the starting 2-hydroxymethylpyrrolidines as well as on the *N*-alkyl substituents (Tables 4–6).

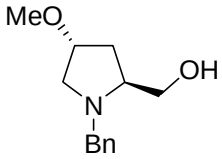
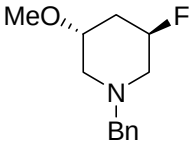
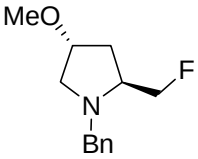
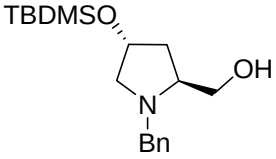
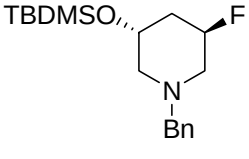
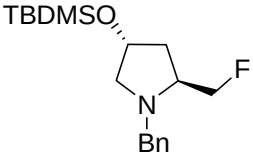
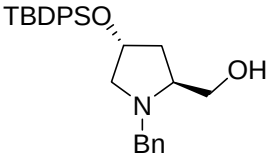
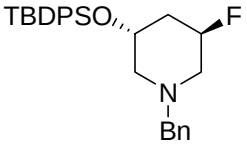
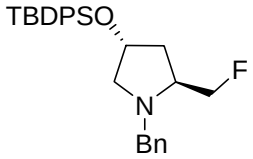
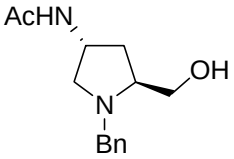
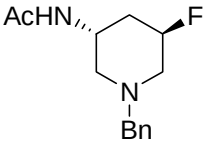
Increasing the bulkiness of the substituent at C4 improved the selectivity in favor of the ring-expansion product, as demonstrated by prolinol **68c**, which possesses *tert*-butyldiphenylsilyl ether at C4, and was transformed to piperidine **71** and pyrrolidine **75** in a ratio of 91/9 respectively. Whereas the corresponding methoxy ether **68a** was transformed to the ring-

expansion product **69** and fluoro-pyrrolidine **73** in a ratio of 55/45 (Table 4).[19] It is worth noting that prolinol **68d**, possessing an acetamide at C4, gave only the ring-expansion product **72**.[6c]

Table 4. Ring expansion of *N*-benzyl-2-hydroxypyrrolidines

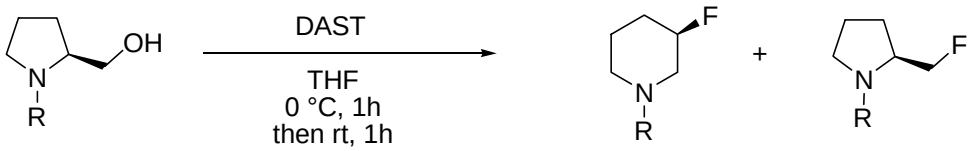


68a–d **N** **O**

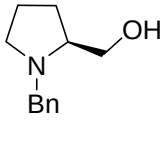
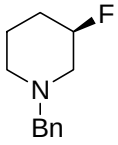
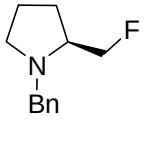
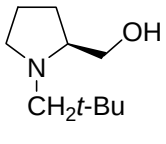
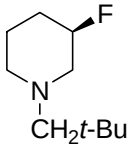
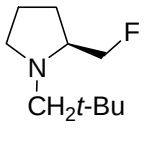
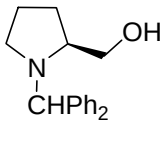
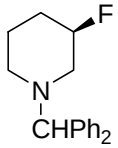
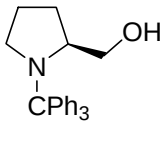
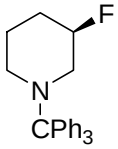
Substrate	Product **N**	Product **O**	Yield (%)	Ratio **N**/**O**
 **68a**	 **69**	 **73**	55	55/45
 **68b**	 **70**	 **74**	53 (**70**) and 8 (**74**)	80/20
 **68c**	 **71**	 **75**	61 (**71**) and 4 (**75**)	91/9
 **68d**	 **72**	–	–	100/0

Sterically hindered *N*-alkyl substituted pyrrolidines such as *N*-tritylprolinol **76d** are of great interest as they are transformed exclusively to fluoro-piperidine **80** (64%). On the contrary, a mixture of fluorinated five- and six-membered rings were obtained when a *N*-benzyl, *N*-*t*-butylmethyl or *N*-diphenylmethyl substituted derivatives **76a–c** were subjected to the same reaction conditions (ratio 6-/5-membered ring = 56/44 to 76/24) (Table 5).[19]

Table 5. Ring expansion of *N*-alkyl-2-hydroxymethylpyrrolidines

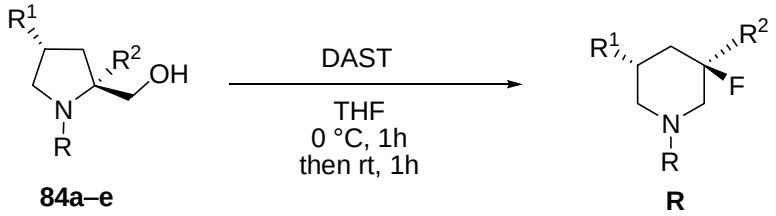


76a–d **P** **Q**

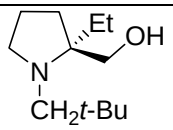
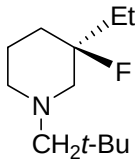
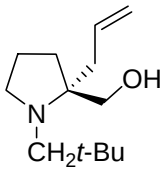
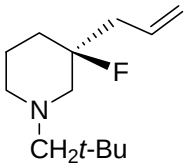
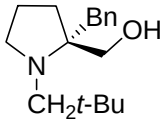
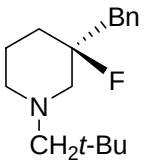
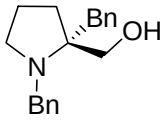
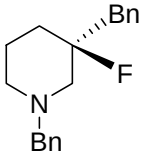
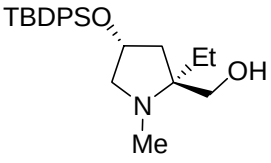
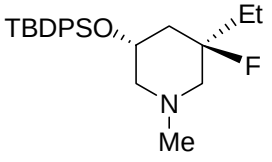
Substrate	Product **P**	Product **Q**	Yield (%)	Ratio **P**/**Q**
			60	56/44
76a	**77**	**81**		
			54	60/40
76b	**78**	**82**		
			71	76/24
76c	**79**	**83**		
		–	64	100/0
76d	**80**			

It is worth noting that when *N*-alkyl-2-alkylprolinols were treated with DAST, the ring expansion was very selective as only *N*-alkyl 3-fluoro-3-alkylpiperidines were observed. The optically active *N*-*tert*-butylmethyl-2-alkylprolinols **84a**–**c** were converted to 3-fluoro-piperidines **85**–**87** respectively in good yields (76–87%) with retention of their stereochemistry. The *N*-benzyl 3-fluoro-piperidines **88** and *N*-methyl 3-fluoro-piperidines **89** were respectively obtained from **84d** (30%) and **84e** (72%) (Table 6).[19] Noteworthy is the fact that all 3-fluoro-piperidines were obtained with excellent enantiomeric excesses.

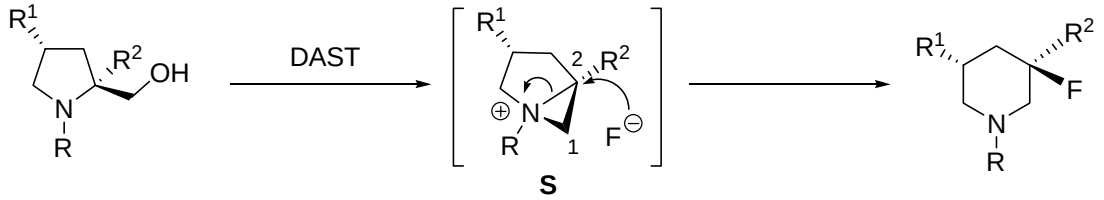
Table 6. Ring expansion of *N*-alkyl-2-alkyl-2-hydroxymethylpyrrolidines



84a–e **R**

Substrate	Product	Yield (%)
 **84a**	 **85**	76
 **84b**	 **86**	89
 **84c**	 **87**	87
 **84d**	 **88**	30
 **84e**	 **89**	72

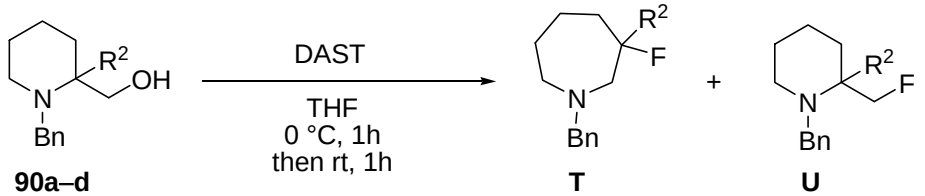
The selective attack of the fluoride anion at C2 (intermediate **S**), when substituted prolinols possess a C2 substituent, a bulky *N*-alkyl substituent or a bulky substituent of C4, can be explained by an increase of the length of the C2–N bond in the aziridinium intermediate **S**. As a result, the cleavage of the C2–N bond, occurs by nucleophilic attack of the fluoride anion on the more electrophilic carbon (Scheme 9).



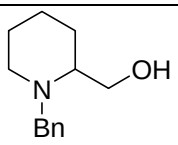
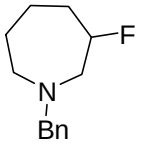
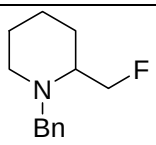
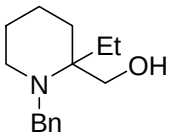
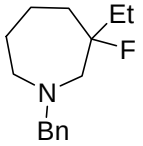
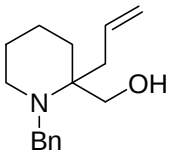
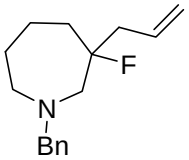
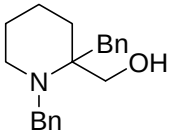
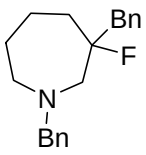
Scheme 9. Selectivity of the ring expansion.

These conditions of ring expansion were also implemented for the synthesis of 3-fluoro-azepanes from 2-hydroxymethylpiperidines (Table 7). When *N*-benzyl-2-hydroxy-methylpiperidine **90a** was treated with DAST, a mixture of 3-fluoroazepane **91** and 2-fluoro-methylpiperidine **95** was obtained in a ratio of 70/30 (total 63%). Similarly, to the prolinol series when a substituent is present at C2, a highly selective attack of the fluoride anion is observed as shown for **90b-d** which were transformed exclusively to their corresponding 3-fluoro-azepanes **92**–**94** (Table 7).[19b]

Table 7. Ring expansion of *N*-benzyl-2-hydroxymethylpiperidines



90a–d **T** **U**

Substrate	Product **T**	Product **U**	Yield (%)	Ratio **T**/**U**
 **90a**	 **91**	 **95**	51 (**91**) and 12 (**95**)	70/30
 **90b**	 **92**	–	63	100/0
 **90c**	 **93**	–	76	100/0
 **90d**	 **94**	–	76	100/0

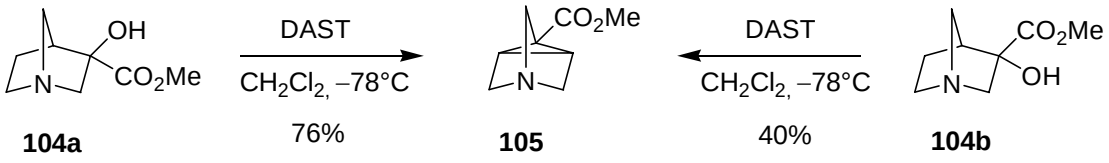
In summary, in the azetidine series, treatment with DAST results exclusively in ring expansion. On the contrary, in the pyrrolidine and piperidine series, a bulky *N*-alkyl substituent as well as the presence of an alkyl substituent at the C2 position are necessary for obtaining ring expansion exclusively.

3. Ring Contraction

3.1. Carbocation induced rearrangements

As DAST induces a strong carbocation character on the carbon bearing an hydroxy group, a number of cases are described whereby the fluorination only occurs after rearrangement of the carbon skeleton. When treated with DAST, tertiary cyclobutanols **96a–b**, can be transformed to their corresponding fluoro-cyclobutanes **V**, or undergo ring contraction to afford (fluoromethyl)cyclopropane **W** and/or homoallylic fluorides **X**, depending on the substituents (Table 8).[20] It is interesting to note that ring contraction mainly occurs when the formation of carbocation is disfavored when substituted by an electron-withdrawing group (compounds **96c–e**).

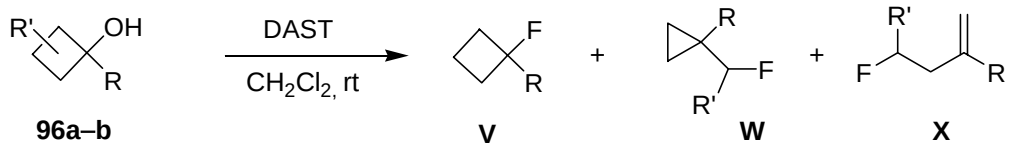
Another example of DAST-induced rearrangement, without subsequent fluorination, has been reported in the synthesis of the 4-azatricyclo[2.2.1.$0^{2,6}$]heptane **105** from bicyclic system **104**.[21] In this case, DAST generates a carbocation which after rearrangement led to **105**. It worth noting that the yield in **105** from the *exo*-hydroxy compound **104a** is 76%, while the compound **104b** with the *endo*-hydroxy group leads to **105** in only 40% yield (Scheme 10). These observations are fully in agreement with the $SbF_5{\cdot}SO_2$ initiated conversion of norborneol into nortricyclene *via* a carbocation intermediate.[22]



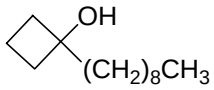
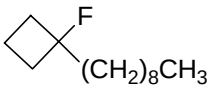
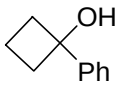
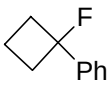
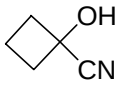
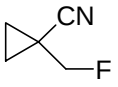
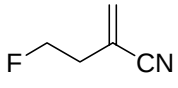
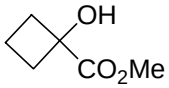
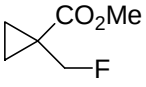
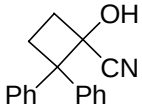
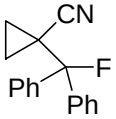
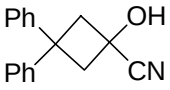
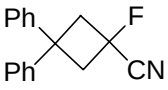
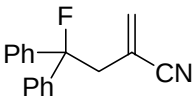
104a **105** **104b**

Scheme 10. Formation of 4-azatricyclo[2.2.1.$0^{2,6}$]heptane

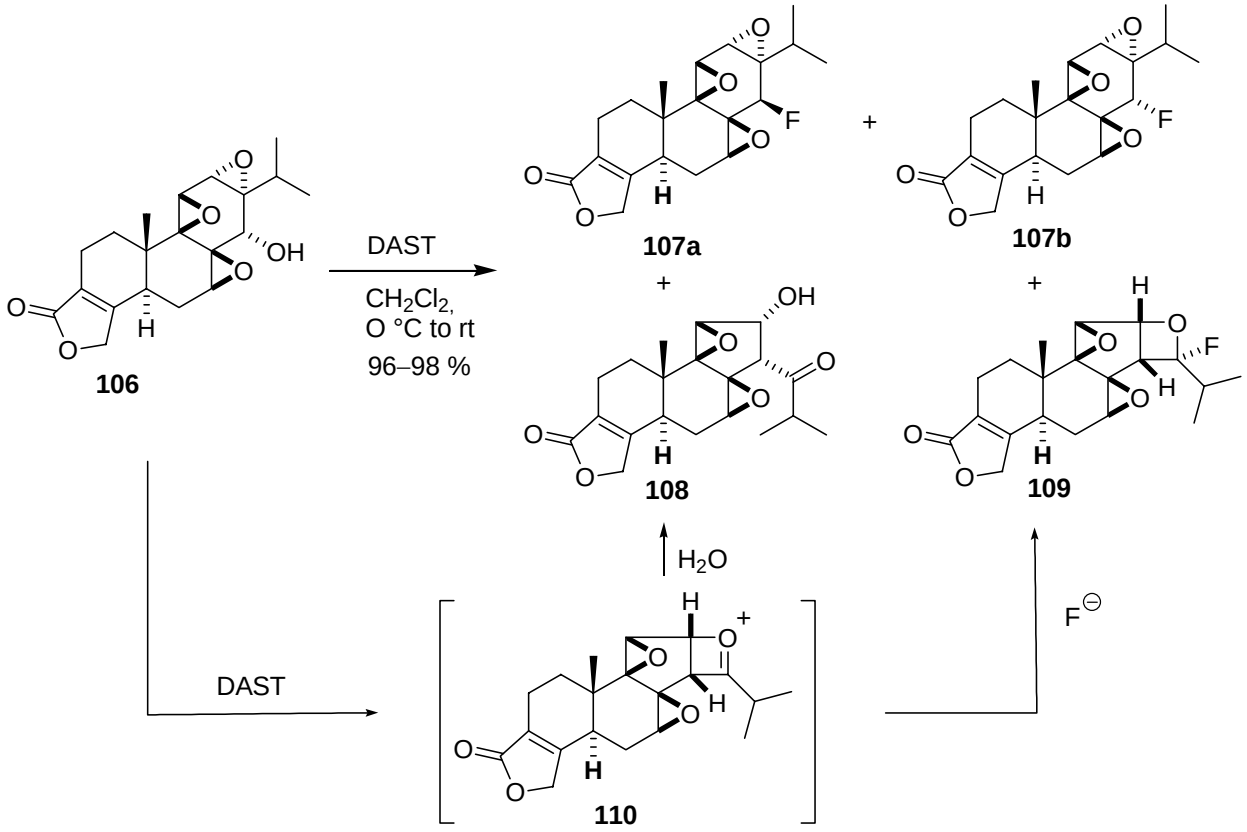
Table 8. Ring contraction of cyclobutanols



96a–b **V** **W** **X**

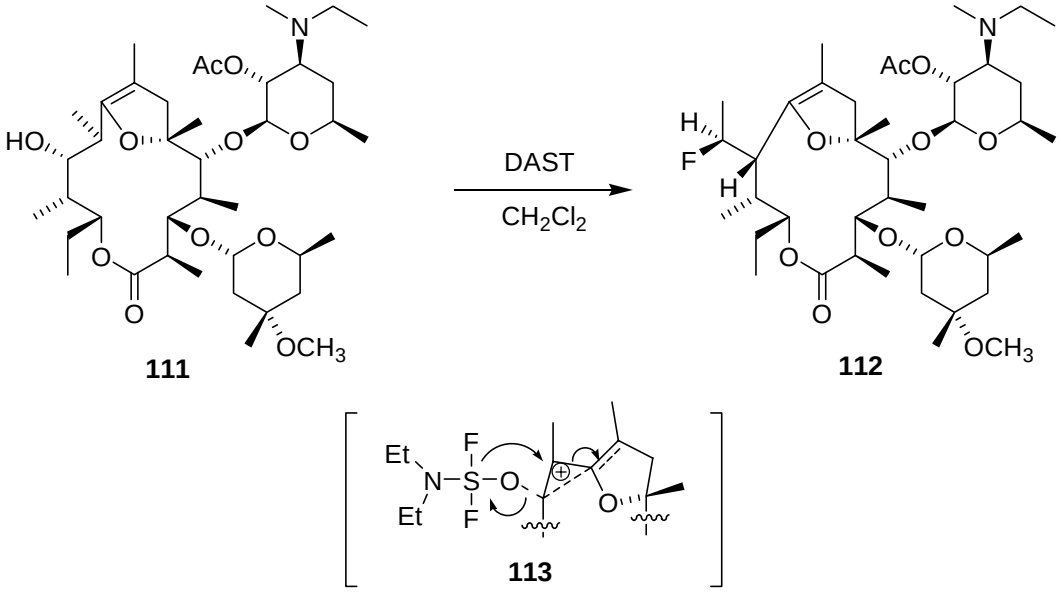
Substrate	Product **V**	Product **W**	Product **X**	Yield (%)
 **96a**	 **97**	–	–	72
 **96b**	 **98**	–	–	91
 **96c**	–	 **99**	 **100**	82 (**99**/**100** = 8/1)
 **96d**	–	 **101**	–	82
 **96e**	–	 **102**	–	82
 **96f**	 **103**	–	 **104**	17 (**103**) and 67 (**104**)

Very interesting DAST-induced rearrangements, leading to fluorinated biologically active natural products, were reported. Triptolide **106**, when reacted with DAST, led to a mixture of compounds, e.g. the desired fluoro derivatives **107a,b** and two derivatives produced by a ring contraction, *via* intermediate **110**, followed by a nucleophilic attack of either the fluoride anion, affording **109**, or by water to give **108**.[23] Yields are good, and the ratios of **108**/**109** are depending on the reaction conditions (Scheme 11).



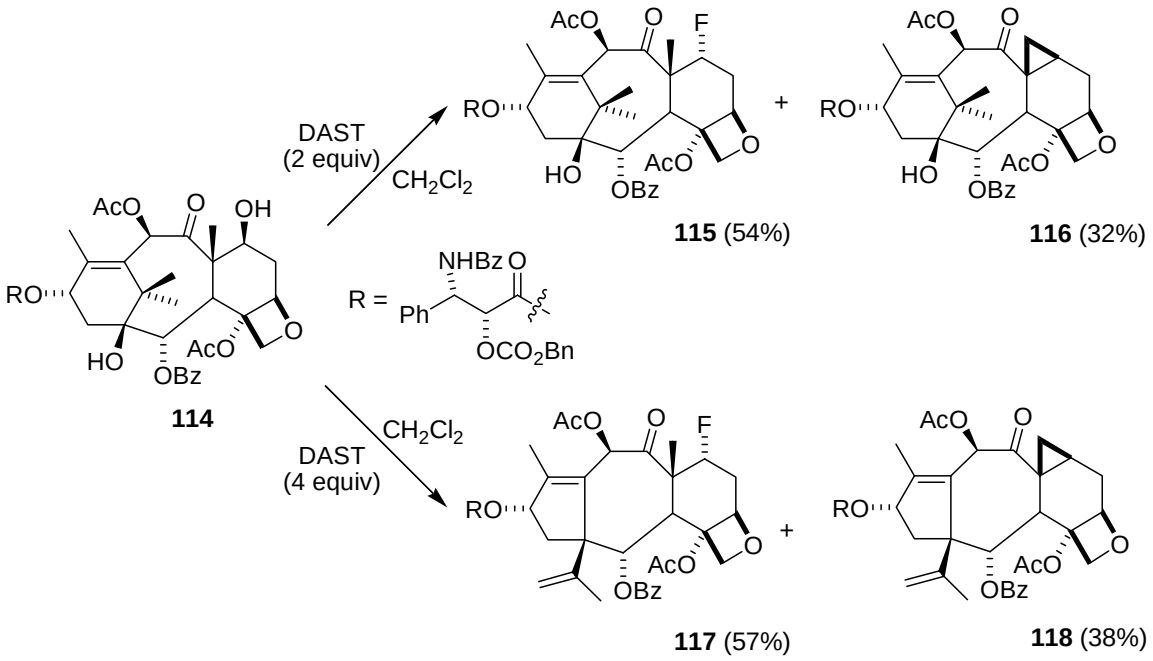
Scheme 11. DAST-induced rearrangement of triptolide **106**

A semi-synthetic erythromycin analog with agonist action on the motilin receptor, compound **111**, when treated with DAST was transformed to a novel 13-membered erythromycin analog **112** (Scheme 12).[24] As a mechanistic explanation, the neighboring group participation of the double bond of the dihydrofuran ring system, produces a non-classical homoallylic carbocation, as shown in intermediate **113**. The stereospecificity of the reaction leads the authors to propose an intramolecular delivery of fluorine atom at C10 and then, after anchimeric assistance of the double bond of the dihydrofuran, a ring contraction takes place to afford **112** (Scheme 12).



Scheme 12. DAST-induced ring contraction of an erythromycin analog.

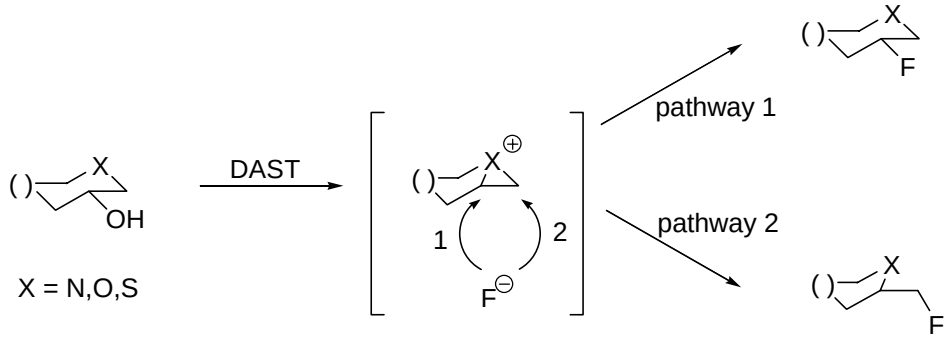
Treatment of the anti-cancer agent, taxol **114**, with DAST to obtain fluoro analogs at C7 has produced a number of very interesting rearrangements (Scheme 13).[25] Under mild conditions, only the C7 hydroxy group seems to react, leading to a cyclopropane derivative **116**, upon a postulated anchimeric participation of the angular methyl substituent. This substituent is perfectly antiperiplanar to the leaving group formed after the activation of the hydroxy group by DAST. Under longer, or more drastic conditions, the A-ring contraction seems to occur similar to the one described for taxol in refluxing acetyl chloride (Scheme 13).[26] A reaction mechanism based on a neighboring group participation from the double bond, similar to the one reported in Scheme 12 was proposed. It should be noted that this latter ring contraction has to be avoided, as the A-ring contracted products are devoid of biological activity.



Scheme 13. Reaction of taxol with DAST.

3.2. Neighboring heteroatom participation

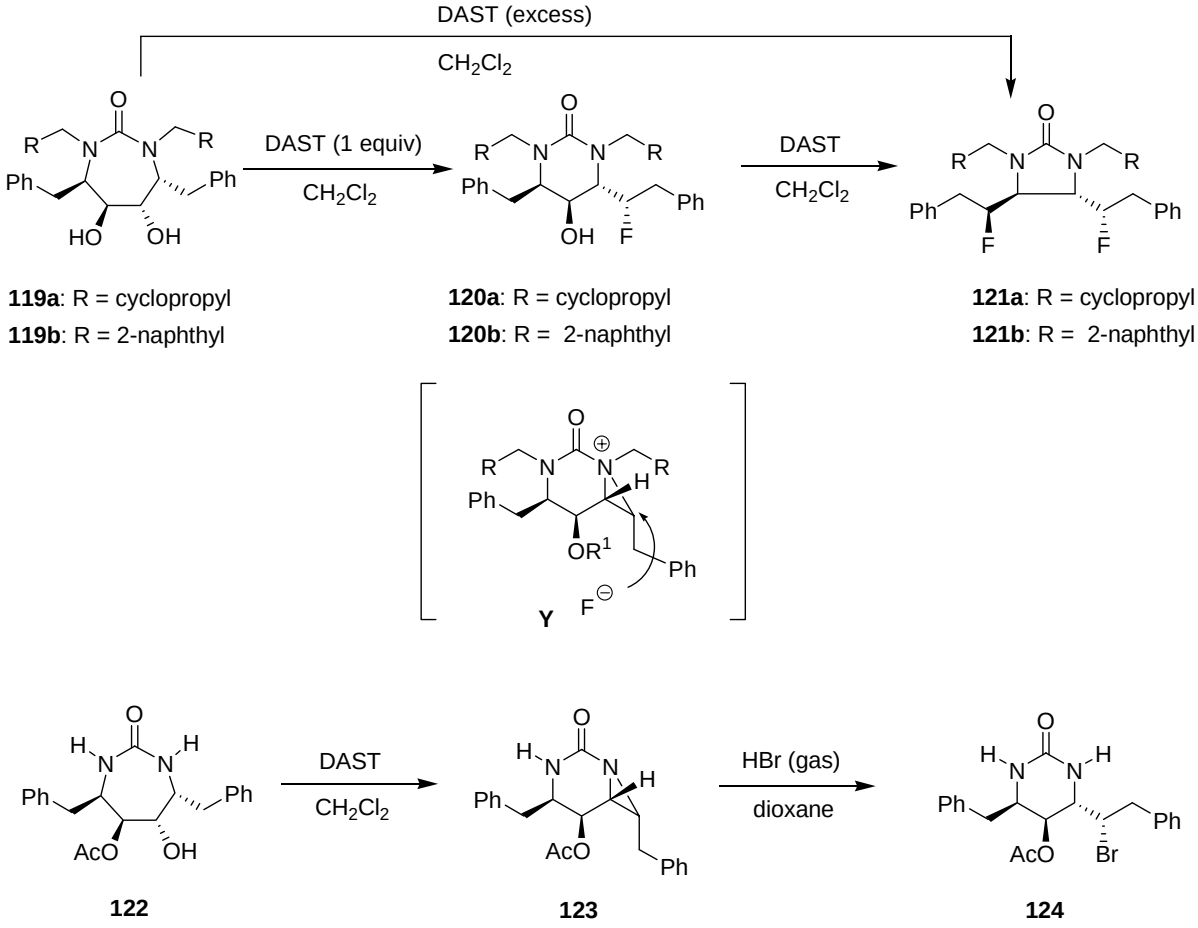
DAST is capable of inducing ring contractions, *via* a process similar to the one described in the ring expansion section, e.g. *via* an aziridinium, episulfonium or epoxonium intermediate. The opening of these strained species may produce either the desired transformation of the alcohol to the corresponding fluoro derivative possessing a configuration determined by the onium intermediate (pathway 1) or a ring-contracted product (pathway 2) (Scheme 14).



Scheme 14. Neighbouring heteroatom participation in the DAST –induced ring contraction and expansion.

3.2.1. Nitrogen participation

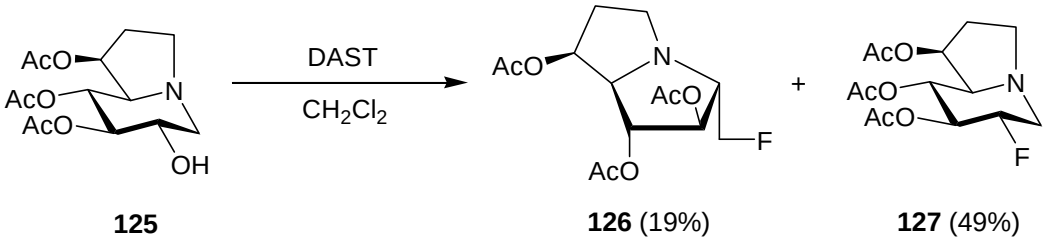
In the search for novel HIV inhibitors, a stereoselective rearrangement of hexahydro-1,3-diazepin-2-ones was developed.[27] When derivatives **119a,b** were treated with DAST, the desired and expected fluoro compound was not obtained. The only product observed was identified as tetrahydropyrimidin-2-one derivative **120a,b** (Scheme 15). The formation of this ring-contracted derivative can be simply explained by the formation of aziridinium intermediate **Y**, similar to the one described in Section 2.2.2. When more drastic conditions were used, the reaction proceeded further, using the same type of mechanism described previously, to afford the imidazolidin-2-ones **121a,b**. It is interesting to note that the *N*,*N*'-unsubstituted derivative **122**, when treated with DAST, did not provide the fluoro derivative but the aziridine **123**. This latter proved to be acid sensitive, affording the bromo derivative **124** upon treatment with hydrogen bromide gas (Scheme 15).



Scheme 15. Ring contraction *via* aziridinium species

Another nice example of nitrogen participation in ring-contraction induced by DAST, is the conversion of the hydroxy indolizine **125**, which provided the rearranged derivative **126**

accompanied with the fluoro derivative **127**, in an approximately 1/2.5 ratio (Scheme 16).[28] This ratio can be explained by a kinetic control due to the low nucleophilicity as well as by the poor leaving group character of the fluoride anion.

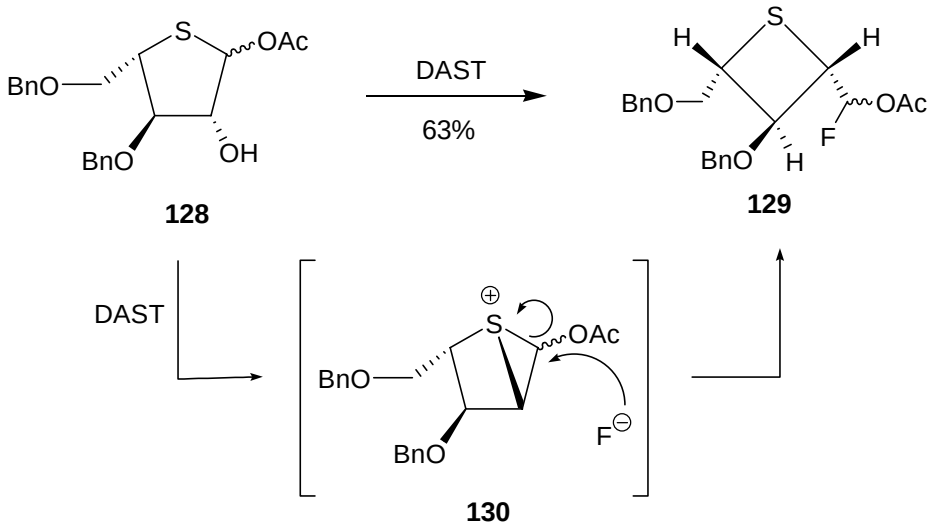


125 **126** (19%) **127** (49%)

Scheme 16. Ring contraction of an indolizine derivative

3.2.2. Sulfur participation

A number of ring contractions and/or rearrangements have been observed during DAST fluorination of 4-thiofuranose derivatives.[29] When the furanose derivative **128** was treated with DAST, the expected 3-fluoro derivative was not observed, but the ring contracted thioxetane **129** (Scheme 17). It is interesting to note that the sulfur atom possesses a more nucleophilic character than that of the oxygen of the benzyloxy group, leading to the episulfonium intermediate **130**, which was selectively attacked at the anomeric position by the fluorine anion (Scheme 17).



128 **129** **130**

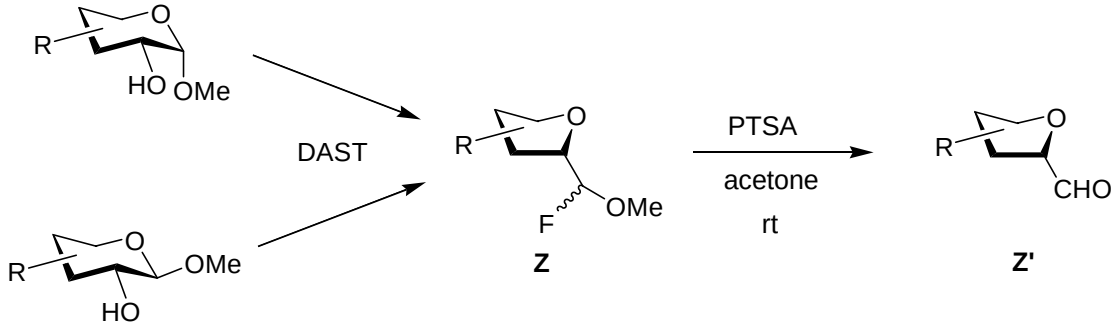
Scheme 17. Ring contraction *via* an epi-sulfonium intermediate

3.2.3. Oxygen participation

All the examples of DAST-induced ring contraction in this section involves carbohydrates (Table 9). Depending on the structures, the configuration of the reacting alcohol, and the substitution patterns, either the expected fluoro derivatives or the rearranged compounds, issued from the

participation of other heteroatoms than the intracyclic heteroatom, or the ring-contracted derivatives **Z** were obtained. This methodology proves to be an interesting entry into a diversity of substituted tetrahydrofuran-2-carboxaldehydes **Z'**.[30]

Table 9. Ring contraction of carbohydrate derivatives



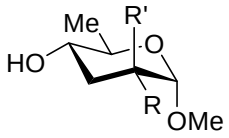
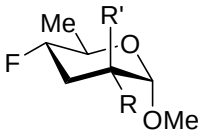
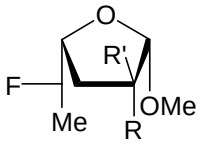
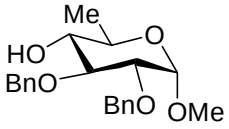
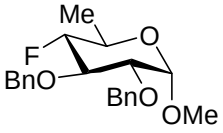
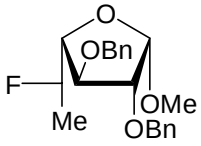
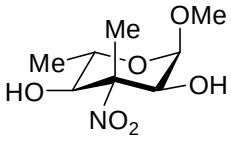
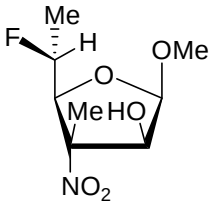
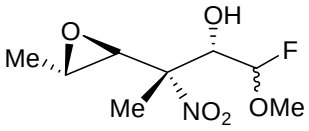
Educt	Reagent	Product(s) (Yield)		Ref.
 **131a**: R = OBn, R' = H **131b**: R = H, R' = OBn	DAST CH_2Cl_2	 **132a** (66%) **132b** (28%)	 **133a** (17%) **133b** (21%)	30a
 **134**	DAST CH_2Cl_2	 **135** (2%)	 **136** (38%)	30a
 **137**	DAST CH_2Cl_2	 **138** (46%)	 **139** (40%)	30g

Table 9. (continued)

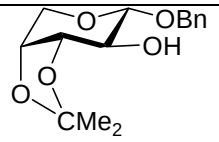
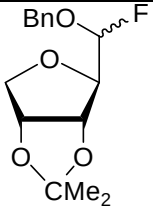
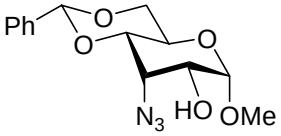
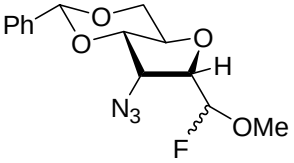
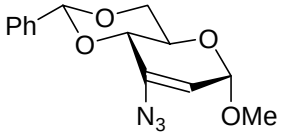
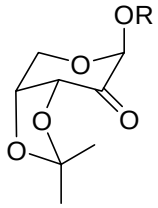
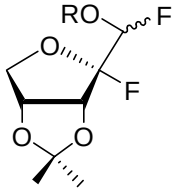
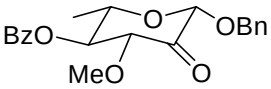
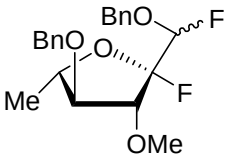
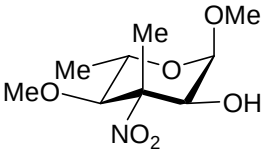
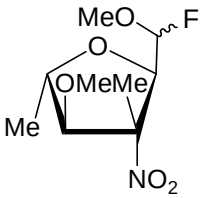
Educt	Reagent	Product(s) (Yield)	Ref.
 **140**	DAST CH_2Cl_2	 **141** (60%)	30a
 **142**	DAST CH_2Cl_2	 (1*R*)-**143** + (1*S*)-**143** (73%) [(1*R*)-**143** / (1*S*)-**143** = 1/3.3]  **144** (20%)	30c,d
 **145:** R=OMe **146:** R=OBn	DAST CH_2Cl_2	 **147:** R=OMe (72%) **148:** R=OBn (72%)	30h
 **149**	DAST CH_2Cl_2	 **150** (50%)	30h
 **151**	DAST CH_2Cl_2	 (1*R*)-**152** + (1*S*)-**152** (70%) [(1*R*)-**152** / (1*S*)-**152** = 3/1]	30g

Table 9. (continued)

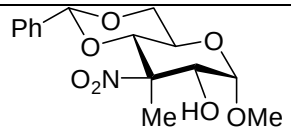
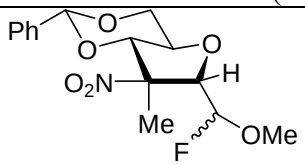
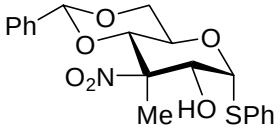
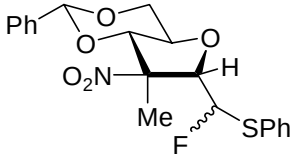
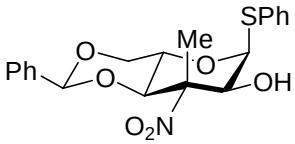
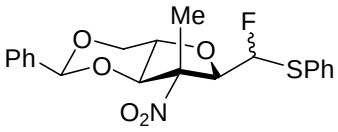
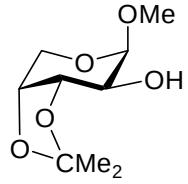
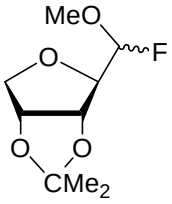
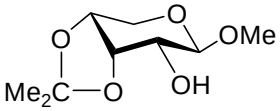
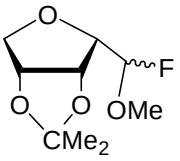
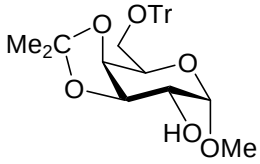
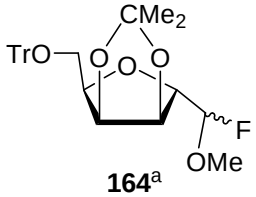
Educt	Reagent	Product(s) (Yield)	Ref.
 **153**	DAST diglyme	 (1*R*)-**154** + (1*S*)-**154** (23%) [mixture 2.5/1]	30f
 **155**	DAST CH_2Cl_2	 (1*R* or 1*S*)-**156** (9.5%)	30f
 **157**	DAST CH_2Cl_2	 (1*R* or 1*S*)-**158** (34%)	30f
 **159**	DAST CH_2Cl_2	 **160**[a]	30b
 **161**	DAST CH_2Cl_2	 **162**[a]	30b
 **163**	DAST CH_2Cl_2	 **164**[a]	30b

Table 9. (continued)

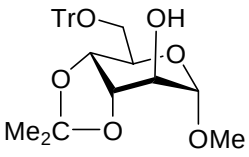
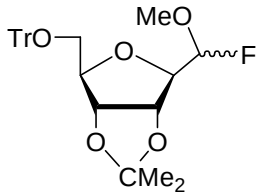
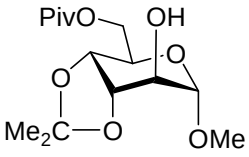
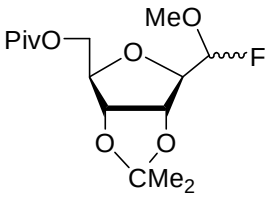
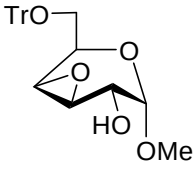
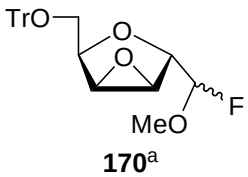
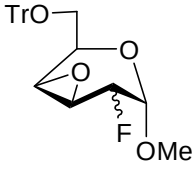
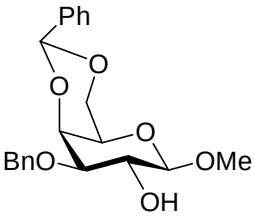
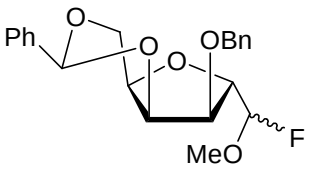
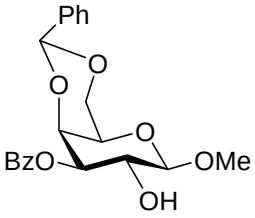
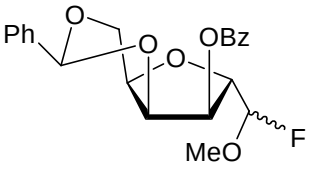
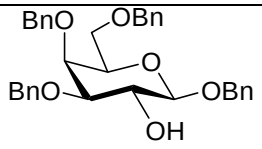
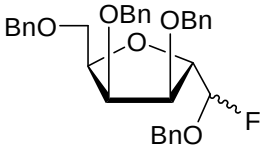
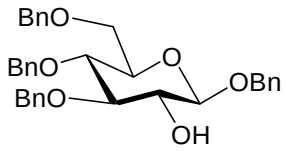
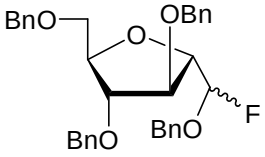
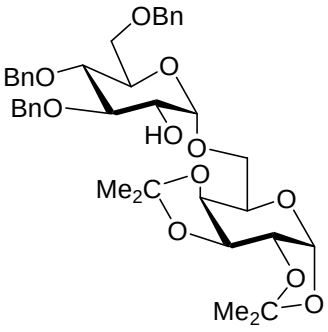
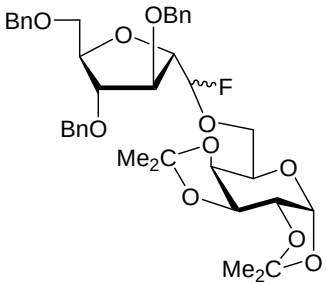
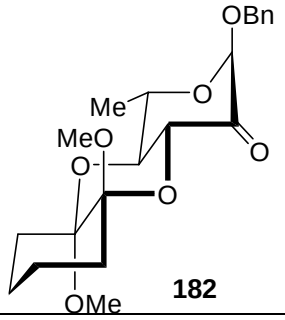
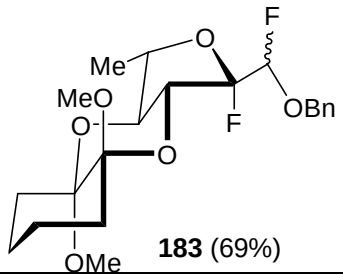
Educt	Reagent	Product(s) (Yield)		Ref.
 **165**	DAST CH_2Cl_2	 **166**[a]		30b
 **167**	DAST CH_2Cl_2	 **168**[a]		30b
 **169**	DAST CH_2Cl_2	 **170**[a]	 **171**[a]	30b
 **172**	DAST CH_2Cl_2	 **173**[a]		30b
 **174**	DAST CH_2Cl_2	 **175**[a]		30b

Table 9. (continued)

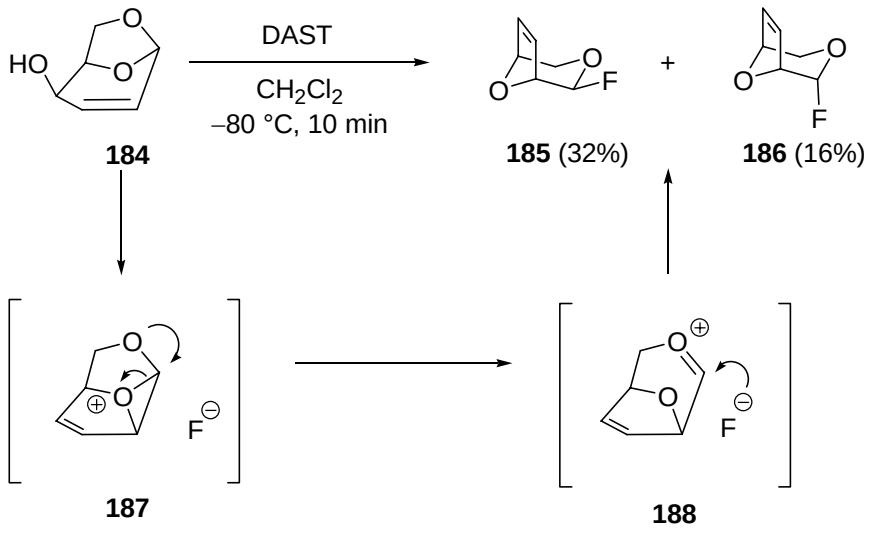
Educt	Reagent	Product(s) (Yield)	Ref.
 **176**	DAST CH_2Cl_2	 **177**[a]	30b
 **178**	DAST CH_2Cl_2	 **179**[a]	30b
 **180**	DAST CH_2Cl_2	 **181**[a]	30b
 **182**	DAST CH_2Cl_2	 **183** (69%)	30h

[a] The yield was not reported.

4. Ring contraction/ring expansion

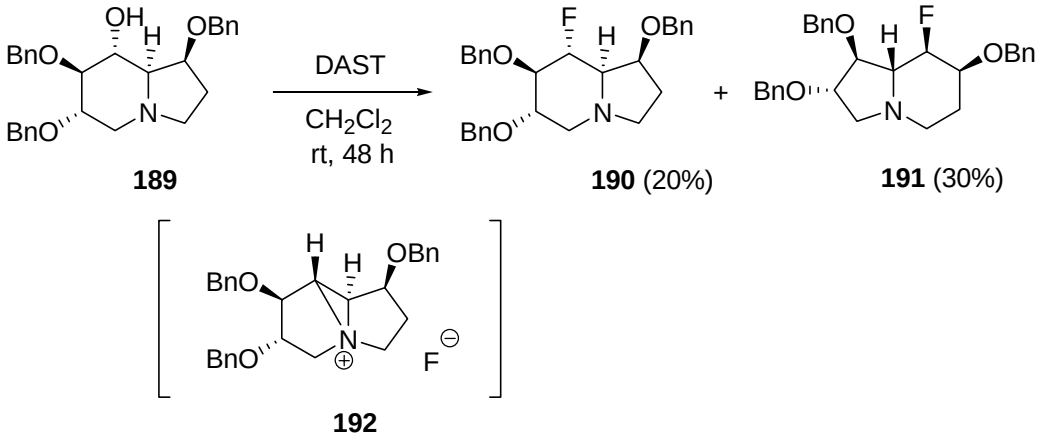
When bicyclic compounds are treated with DAST, a ring contraction/ring expansion process can occur. When compound **184** was reacted with DAST at low temperature (–80 °C), two diastereoisomeric fluoro-substituted dioxabicyclooctenes **185** and **186**, which

correspond to a ring contraction/ring expansion process, were obtained. These compounds are probably issued from intermediates **187** and **188** (Scheme 18).[31]



Scheme 18

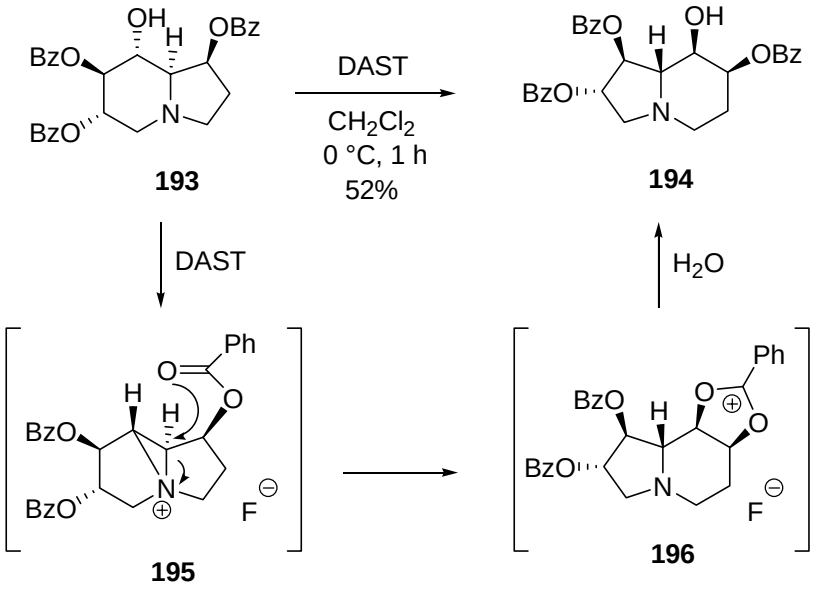
In the series of hydroxylated indolizines, two fluoro-indolizines were obtained when treated with DAST, and the major compounds corresponds to the ring-contracted/ ring-expanded products. In the case of **189**, its treatment with DAST led to the fluoro-indolizidines **190** and **191**. It is worth noting that **191** is the result of a nucleophilic attack of the fluoride anion on the aziridinium intermediate **192** and corresponds to the ring-contracted/ring-expanded product (Scheme 19).[6d]



Scheme 19

The reaction is very selective in favor of the ring-contracted/ring-expanded product when a double anchimeric assistance is possible. Thus, when **193** was treated with DAST, **194** was the

only product formed *via* the aziridinium intermediate **195** which was attacked intramolecularly by the benzoyl group to form intermediate **196** (Scheme 20).[6d]



Scheme 20

5. Conclusions

DAST is a very powerful reagent that allows the conversion of various substrates to fluorine-containing products. In a one-pot process, ring-expansion and/or ring-contraction can occur involving either a carbocation or an anchimeric assistance of neighboring groups. A variety of fluoro derivatives can be obtained and has been revealed to have interesting biologically activity.

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