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Rearrangement of Homoallylic Alcohols Induced by DAST

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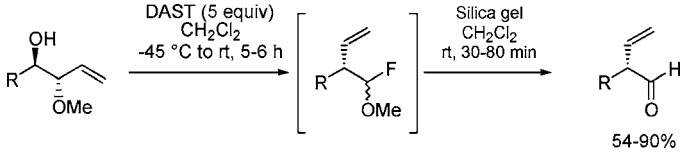
ABSTRACT

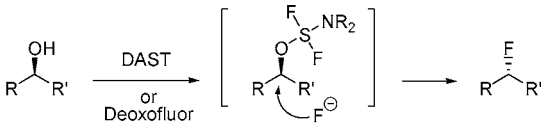


Treatment of β,γ-unsaturated monoprotected 1,2-diols with diethylaminosulfur trifluoride (DAST) allows the stereoselective formation of β,γ-unsaturated aldehydes in good yields and with a good transfer of chirality.

The introduction of fluorine in organic molecules strongly modifies their physical, chemical, and biological properties.[1] Although a variety of fluorinating reagents and methodologies have been developed to fulfill the increasing demand for site-selective fluorination of organic compounds, applications of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) and diethylaminosulfur trifluoride (DAST) continue to be used widely.[2] Simple alcohols are readily converted to the corresponding monofluorinated products using these reagents. Moderate to excellent yields were obtained with a variety of structurally diverse substrates such as primary, secondary, tertiary, allylic, and benzylic alcohols (Scheme 1).

The fluorination of optically active alcohols by using DAST generally proceeds with inversion of configuration[2] (S_N2 mechanism). In some hindered substrates, products with retained configuration may be obtained.[3] Retention of configuration and/or rearrangements have also been reported,[4]

Scheme 1



DAST: Et_2NSF_3
Deoxofluor: $(CH_3OCH_2CH_2)_2NSF_3$

especially in substrates having an electron-rich group at a vicinal position (e.g., in carbohydrates,[4a] in compounds with pyrrole[4b] or indole[4c] moieties, with azido[4a] or acetate[4d] groups,

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(1) (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier: Amsterdam, 1982. (b) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381−436. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (d) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (e) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. (f) Abeles, R. H.; Alston, T. A. *J. Biol. Chem.* **1990**, *265*, 16705-16708. (g) Special issue on fluorine chemistry. *Tetrahedron: Asymmetry* **1994**, *5*, 955−1126. (h) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645−652.

(2) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578. (b) Hudlický, M. *Org. React.* **1988**, *35*, 513−637.

(3) Zhou, G.-C.; Zhu, D.-Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2055−2057.

(4) (a) Vera-Ayoso, Y.; Borrachero, P.; Cabrera-Escribano, F.; Carmona, A. T.; Gómez-Guillén, M. *Tetrahedron: Asymmetry* **2004**, *15*, 429−444. (b) Boiadjiev, S. E.; Lightner, D. A. *J. Org. Chem.* **1997**, *62*, 399−404. (c) Giannini, G.; Marzi, M.; Moretti, G. P.; Penco, S.; Tinti, M. O.; Pesci, S.; Lazzaro, F.; De Angelis, F. *Eur. J. Org. Chem.* **2004**, 2411−2420. (d) Shiuey, S.-J.; Kulesha, I.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1990**, *55*, 243−247. (e) Burnell-Curty, C.; Faghih, R.; Pagano, T.; Henry, R. F.; Lartey, P. A. *J. Org. Chem.* **1996**, *61*, 5153−5154.

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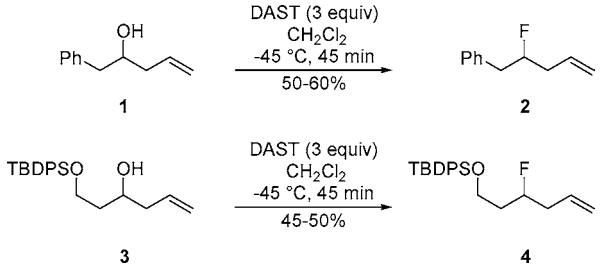
or with a double bond[4e]). These results can be explained in terms of neighboring group participation[2b] and are due to the carbonium ion character of the reaction of alcohols with DAST, as mentioned previously.[5]

To prepare homoallylic fluorides, the corresponding homoallylic alcohols were treated with DAST. When homoallylic alcohol **1** was treated with DAST (3 equiv) at −45 °C for 45 min in CH_2Cl_2, the homoallylic fluoride **2** was obtained as the major product in 50−60% yield (Scheme 2). Furthermore, compound **4** was isolated in 45−50% yield when the monoprotected 1,3-diol **3** was treated with DAST.

Scheme 2

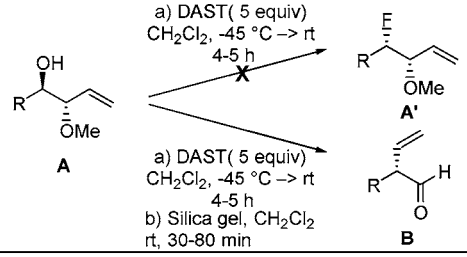


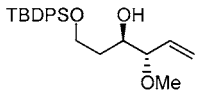
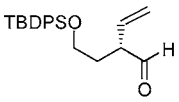
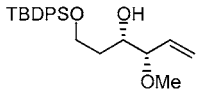
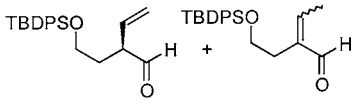
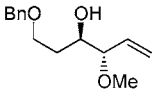
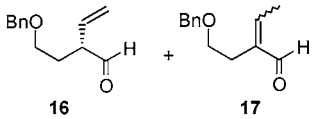
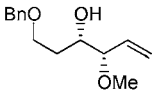
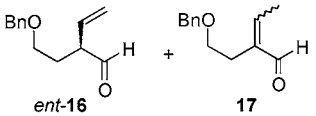
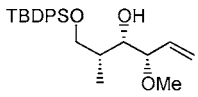
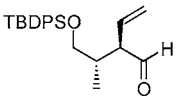
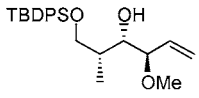
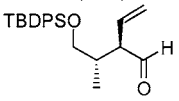
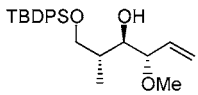
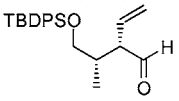
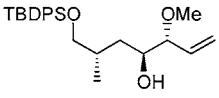
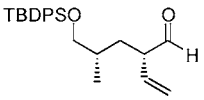
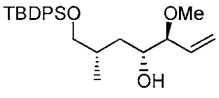
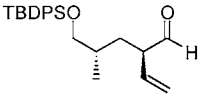
However, when the unsaturated monoprotected 1,2-diols of type **A** (Table 1) were treated with DAST, the expected fluoro compounds of type **A′** were not observed; instead, the β,γ-unsaturated aldehydes of type **B** were isolated in good yields. The reaction has been tested on several β,γ-unsaturated 1,2-diols, and the results are reported in Table 1.[6]

Diol (+)-**5** was first treated with DAST (5 equiv)[7] in dichloromethane from −45 °C to room temperature during 5 h. After workup, the reaction mixture was stirred with silica gel for 30 min at room temperature in CH_2Cl_2 and aldehyde **14** was isolated in 80% yield after filtration (Table 1, entry 1). Under the same conditions, compound (+)-**6**, a diastereomer of (+)-**5**, led to the enantiomeric vinyl aldehyde *ent*-**14**. In this case, the obtained β,γ-unsaturated aldehyde *ent*-**14** was isolated as an inseparable mixture with its isomerized α,β-unsaturated aldehyde **15**[8] (Scheme 3), with a global yield of 90% and a ratio *ent*-**14**/**15** ranging from 2:1 to 1:1 (Table 1, entry 2).

To determine the enantioselectivity of the rearrangement process, compounds **14** and *ent*-**14** were transformed, respectively, to the corresponding lactones (−)-**29** and (+)-**29**[10] (Scheme 3). Aldehyde **14** was first reduced to alcohol (−)-**22** ($NaBH_4$, MeOH, 44%) which was transformed to the lactone (−)-**29** after treatment with acryloyl chloride (DIPEA, CH_2Cl_2, quantitative) and ring-closing metathesis (RCM) with the second-generation Grubbs' catalyst **28**, [(4,5-dihydroIMES)(PCy_3)Cl_2Ru=CHPh][11] (10 mol %, CH_2Cl_2, 80%). The analytical data of the isolated

Table 1. Rearrangement of β,γ-Unsaturated Monoprotected 1,2-Diols Induced by DAST[9]



entry	alcohols	products (yield)[a]
1	 (+)-**5**	 **14** (80%)
2	 (+)-**6**	 *ent*-**14** + **15** (90%, *ent*-**14**/**15** = 2/1)
3	 (+)-**7**	 **16** + **17** (76%, **16**/**17** = 2.4/1)
4	 (+)-**8**	 *ent*-**16** + **17** (76%, **16**/**17** = 2.4/1)
5	 (+)-**9**	 **18** (86%)
6	 (-)-**10**	 **18** (80%)
7	 (+)-**11**	 **19** (90%)
8	 (-)-**12**	 **20** (90%)
9	 (+)-**13**	 **21** (79%)

[a] Crude isolated yields.

(5) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578.

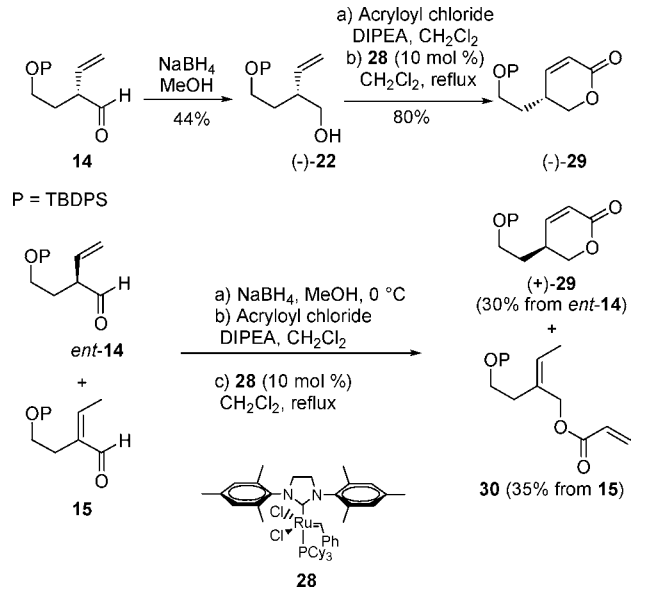
(6) The unsaturated aldehydes **14**−**21** formed during the rearrangement process could not be purified because of their instability. β,γ-Unsaturated aldehydes **14**, *ent*-**16**, and **18**−**21** were directly reduced into the corresponding primary alcohols **22**−**27** which were fully characterized.

(7) When less than 5 equiv was used, low conversion was observed possibly due to DAST decomposition during the reaction.

(8) The isomerization of the double bond of the β,γ-unsaturated aldehydes *ent*-**14**, **16**, and *ent*-**16** leading to the conjugated aldehyde **15** and **17** was impossible to avoid. For compounds **18**−**21**, the isomerization of the double bond seems to take place much more slowly and was avoided by controlling the treatment with silica gel.

(9) In the case of the silyl protecting group, no deprotection was observed in the presence of DAST. See, for example: Shiuey, S. J.; Kulesha, I.; Baggiolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1990**, *55*, 243−246.

Scheme 3



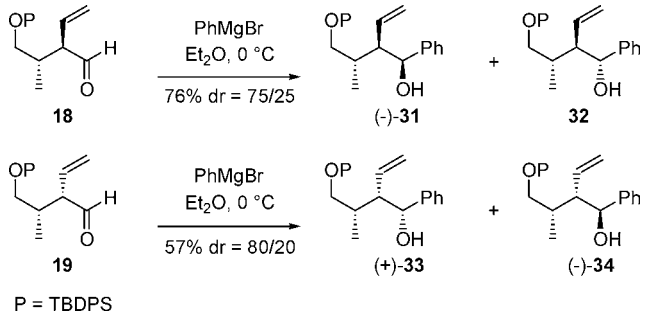
material were in agreement with those reported in the literature.[10] The comparison of the optical rotations allowed us to attribute the (*R*) configuration to the stereogenic center present in aldehyde **14** which was obtained with no apparent loss of chirality.[12] The same sequence of reactions was also applied to the mixture of compounds *ent*-**14** and **15**; lactone (+)-**29** was isolated with a global yield of 30% from *ent*-**14**, whereas acryloyl ester **30** did not react under RCM conditions.

When the primary alcohol is protected by a benzyl group as in compounds (+)-**7** and (+)-**8**, instead of by a TBDPS group as in (+)-**5** and (+)-**6**, the β,γ-unsaturated aldehydes **16** and *ent*-**16** were obtained as well as was the conjugated aldehyde **17** (**16**/**17** = 2.4:1 and *ent*-**16**/**17** = 2:1) with a global yield of, respectively, 76% and 87% (Table 1, entries 3 and 4).

To study the influence of the stereogenic centers on the stereoselectivity of the rearrangement, compounds (+)-**9** and (−)-**10** were treated with DAST. These two epimers, whose configurations differ only at the carbon bearing the methoxy group, were transformed to the same β,γ-unsaturated aldehyde **18**, obtained as a single diastereomer, in 86% and 80% yields, respectively (Table 1, entries 5 and 6). Furthermore, the homoallylic alcohol (+)-**11**, a diastereomer of (+)-**9** and (−)-**10**, was transformed to aldehyde **19** in 90% yield, and this compound was revealed to be the diastereomer of **18** (Table 1, entry 7). The relative and absolute configurations of aldehydes **18** and **19** were established by transformation of these compounds to the known alcohols (−)-**31** and (+)-**33**[13] by addition of phenylmagnesium bromide, as the major isomers should be the result of a Felkin−Anh attack of the nucleophile to the α-substituted aldehydes.

After treatment of **18** by phenylmagnesium bromide, alcohols (−)-**31** and **32** were isolated in 70% yield in a ratio of 75:25. The analytical and spectroscopic data of the major product (−)-**31** were in perfect agreement with those reported in the literature,[13] allowing us to attribute the *anti*/*syn* stereochemistry for the substituents present in (+)-**31** and the (*R*) configuration of the C2 stereogenic center of aldehyde **18**. When aldehyde **19** was treated with phenylmagnesium bromide, alcohols (+)-**33** and (−)-**34** were isolated in 57% yield in a ratio of 80:20. The major isomer (+)-**33** corresponds to the product issued from the Felkin−Anh addition of phenylmagnesium bromide to aldehyde **19**. The analytical and spectroscopic data of (+)-**33** match perfectly with those described in the literature.[13] The chemical transformation of **19** to the *syn*/*syn* product (+)-**33** allowed us to attribute the (*S*) configuration at the C2 position in aldehyde **19** (Scheme 4).

Scheme 4



The results obtained for the rearrangement of β,γ-unsaturated monoprotected 1,2-diols of type **A** (Table 1) and particularly the comparison of the transformation of compound (+)-**5** and (+)-**6** to the enantiomer **14** and *ent*-**14**, respectively, in addition to the transformation of compounds (+)-**9**, (−)-**10**, and (+)-**11** to the corresponding aldehydes **18** and **19**, proved that the hydroxy group may be the directing element in the rearrangement induced by DAST and that the methoxy group has no influence on it.

Diols (−)-**12** and (+)-**13** were also treated with DAST and led, respectively, to the β,γ-unsaturated aldehydes **20** (90%) and **21** (79%) in good yields (Table 1, entries 8 and 9).

It is worth noting that a fluorine intermediate can be isolated before treatment with silica gel. Compounds (+)-**5** and (+)-**9** were transformed quantitatively to the fluoroethers **35** and **36**, respectively. Each fluoroether was isolated as a mixture of two diastereomers in an equimolar ratio and was

(10) Lactone (+)-**29** of (*S*) configuration is described as enantiomerically pure ($[\alpha]^{19}_D = +50.6$ (*c* 0.54, $CHCl_3$)): Tanaka, D.; Yoshino, T.; Kouno, I.; Miyashita, M.; Irie, H. *Tetrahedron* **1993**, *49*, 10253−10262.

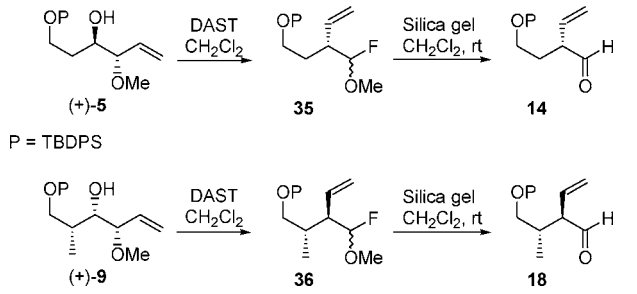
(11) Scholl, M.; Ding, S.; Woo Lee, S.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(12) Diol (+)-**5** was obtained with an enantiomeric excess of 85% (determined from the corresponding (*S*)- and (*R*)-*O*-methoxymandelic esters). Optical rotation obtained for lactone (−)-**29**, synthesized from (+)-**5** ($[\alpha]^{25}_D = -38.4$ (c 0.50 $CHCl_3$)), is consistent with more than 75% ee, confirming a good transfer of chirality. For the lactone of (*S*) configuration, see ref 9.

(13) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, C.; Bushmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 4218−4229.

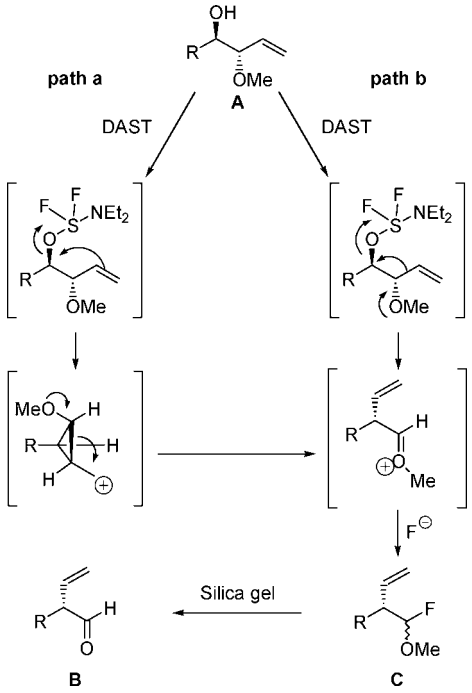
then transformed to the corresponding aldehyde, **14** from (+)-**5** and **18** from (+)-**9**, after treatment with silica gel (Scheme 5).

Scheme 5



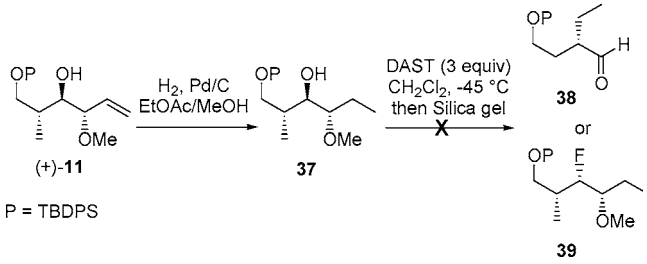
As the methoxy group present in compounds **5**−**13** does not seem to influence the stereoselectivity of the rearrangement of unsaturated monoprotected 1,2-diols of type **A** induced by DAST, the formation of β,γ-unsaturated aldehydes of type **B** can be explained either by a homoallylic participation[14] of the double bond present in compounds of type **A** (path a) or by a pinacolic-type rearrangement (path b). Both pathways could explain the formation of the fluoroethers of type **C** via the formation of an oxonium intermediate which could react with a fluoride anion present in the reaction media (Scheme 6).

Scheme 6



To verify the participation of the double bond in the rearrangement, compound (+)-**11** was hydrogenated and the resulting saturated product **37** was treated with DAST (3 equiv) and then with silica gel (chromatography). In this case, no traces of aldehyde **38** or fluorinated compound **39** were detected but the reaction led to a complex mixture of unidentified products (Scheme 7). The mechanism is certainly more complex than the one depicted in Scheme 6. Current efforts are underway to elucidate the mechanism of the rearrangement process.

Scheme 7



We have shown that DAST can induce a stereo- and enantioselective rearrangement of unsaturated monoprotected 1,2-diols and that α-substituted β,γ-unsaturated aldehydes can be formed stereoselectively in good yields.

Acknowledgment. One of us (S.C.) thanks the CNRS and Aventis Pharma for a grant.

Supporting Information Available: General experimental procedure and characterization data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060529M

(14) Nagasawa, T.; Handa, Y.; Onogushi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31−39.