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Stereospecific mono- and difluorination of the C_7-bridge of norbornenes

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ABSTRACT

Fluorinated norbornenes are very desirable monomers in the semiconductor and high-temperature polyimide industries. We describe herein a synthetic strategy for the stereospecific mono- or difluorination of the C_7-carbon in norbornene systems beginning with 7-ketonadic anhydride **1**. In particular, *anti*-7-fluoro methyl diester **4** and its 7,7-difluoronadic analog **7** can be prepared from **1** in 3 or 4 steps: saponification, reduction (for **4**), esterification, fluorination with DAST. In addition, *anti*-7-fluoro-*syn*-7-fluoromethylnadic diester **16** is obtained from epoxide **14**, and dimethyl 7,7-difluorobicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate (**17**) from ketone **15**. Anchimeric assistance of the norbornene double bond guides the introduction of attacking fluoride anions stereospecifically *anti* to the olefinic linkage.

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1. Introduction

Fluorination has been widely used in the synthetic polymer field for the development of tough membranes for fuel cells, coatings for ships, and resist materials in 157 nm laser microlithography [1]. Fluorinated norbornenes are very desirable monomers in the semiconductor industry – for the production of optical lithography polymers [2–4], and in the preparation of fluorinated end-caps for use in high temperature polyimide polymers [5].

Fluorination of norbornene structure has been carried out with a variety of fluorinating agents, *inter alia* acids (e.g., HF [6]), covalent compounds (e.g., SF_4, XeF_2 [6,7]), ionic species (e.g., KF [8], Bu_4NHF_2 [8], $CsSO_4F$ [9]), or a combination of the above (e.g., $Pb(OAc)_4$/HF [10], XeF_2/HF [11], XeF_2/BF_3OEt_2 [12,13] or F-TEDA-BF_4 [14,15]). These fluorination reactions are slow processes, requiring elevated temperatures (>100 °C) and high pressure reactors and, in many cases, a specialized catalyst, as well. In addition the reagents are generally toxic or of a highly caustic nature, Moreover, when these methods were applied to the norbornene system, they were generally found to be neither regio- nor stereospecific. Additionally, a variety of products result, including those in which the double bond is attacked and converted to tetrahedral carbons. A synthetic strategy for the efficient mono- or difluorination of the C_7 carbon in norbornene system has yet to be reported [14].

We propose to accomplish this goal by beginning with 7-ketonorbornene derivatives which can be reduced if desired to the corresponding 7-hydroxy analog. The 7-hydroxy and 7-ketonorbornenes can be readily fluorinated with diethylaminosulfur trifluoride (DAST) [16–19] which is widely reported to convert alcohols to the analogous monofluoride and ketones into the corresponding geminal difluorides [6,19]. The key to the selectivity of DAST (and similar reagents) appears to stem from the fact that fluorine is delivered in its anionic form (F^-) as a nucleophile, rather than as the less selective fluoro radical ($F^\bullet$) [20]. The norbornene system is also particularly suited for gleaning information regarding the mechanism, stereoselectivity and regioselectivity of these DAST reactions [21].

2. Results and discussion

2.1. Stereospecific synthesis of anti-7-fluoronadic dimethyl ester (4)

Our synthetic approach to the preparation of 7-fluoro and 7,7-difluoronadic diesters (**4** and **7**) is shown in Scheme 1 and begins with the known 7-ketonadic anhydride (**1**) [22]. Overall, the preparation of the monofluoro analog **4** simply requires the hydride reduction of the 7-keto group to the related alcohol, and the conversion of the latter with DAST to the corresponding fluoride. Unfortunately, hydride reduction of cyclic anhydrides is reported to produce lactones [23]; hence, we first saponified 7-ketonadic anhydride **1** to the corresponding diacid *in situ*. Subsequent $NaBH_4$ reduction provides an 80% yield of the 7-hydroxynadic diacid (**2**) in an *anti* to *syn* ratio (with respect to the olefin linkage) of 93:7. These isomers were identified and fully

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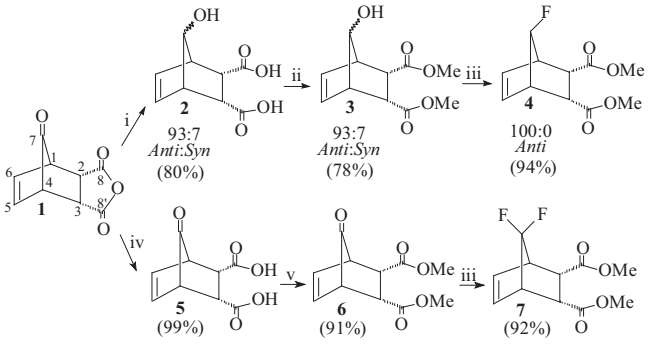


i. (1) $NaOH/H_2O$; (2) $NaBH_4$. **ii.** $MeOH/H_2SO_4$/))) or CH_2N_2/Et_2O.
iii. $DAST/CH_2Cl_2$. **iv.** $NaOH/H_2O$. **v.** CH_2N_2/Et_2O, 0 °C.

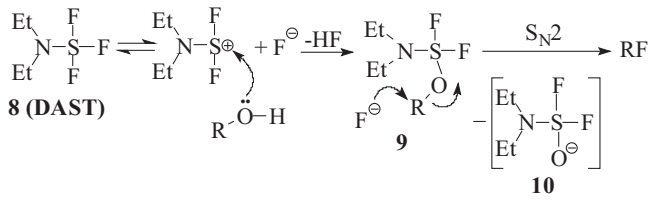
Scheme 1. Synthesis of 7-fluoronadic diester (4) and 7,7-difluoronadic diester (**7**).

characterized by NMR spectral analysis, as previously described [22]. The major **2**-*anti* product was purified via recrystallization (the mother liquor solution was enriched with the *syn* isomer, and yielded a sample of **2** in which the *anti*:*syn* ratio was 1:1 (*vide infra*)).

DAST reactions with carboxylic acids are known to give the corresponding acid fluorides [6,24] (the same is also expected in DAST reactions with anhydrides, since the HF generated *in situ* in DAST reactions catalyzes ring opening). Thus, as shown in Scheme 1, 7-hydroxydiacid **2** was first converted to the corresponding diester **3** via the Khurana procedure [25]. In this approach, the diacid is sonicated [symbolized by))))] in methanol in the presence of a catalytic amount of sulfuric acid. These esterification conditions are particularly mild, do not require elevated temperatures or concentrated acid, and yield pure 7-hydroxydiester **3** as a clean white solid in 78% yield. The 93:7 *anti* **3a** to *syn* **3b** ratio found in the preparation of **2** was maintained here as well. By comparison, the preparation of diester **3** via the diazotization [26] of hydroxydiacid **2** gave less pure product and in lower variable yields.

When 7-hydroxynadic dimethyl ester (**3**) was subsequently reacted with DAST in dichloromethane at −78 °C for 3 h, the desired product, 7-monofluoronadic dimethyl ester (**4**), was obtained in a 94% yield. With the olefinic linkage as the point of reference (as in nobornenes **1**–**3**), the monofluoro product **4** was identified and characterized by careful NMR spectral analysis (including NOE and 2D experiments) as the pure *anti* isomer **4a** (Fig. 1).

The exact configuration of the product was based on the following considerations. (a) Firstly, were the fluorine *syn* to the double bond (structure **4b** in Fig. 1), a long-range "W" type coupling ($^4J_{HH}$) might have been expected between the *anti* H_7 proton and the vinyl H_5 and H_6 hydrogens – but this was not the case. (b) Secondly, a small but considerable NOESY interaction was



Scheme 2. S_N2 mechanism of DAST reactions of alcohols.

found between the bridge hydrogen H_7 and the olefinic hydrogens H_5 and H_6. Since the hydroxyl group at C_7 in starting material **3** was also aligned *anti*, retention of configuration is being observed. (c) Finally, Adcock et al. [27] prepared a variety of *syn* and *anti* 7-fluoronorbornenes, and observed that the ^{19}F chemical shift of the *anti* isomers appears at *ca.* – 178 ppm, 23 ppm downfield of the *syn* isomer. The ^{19}F chemical shift of compound **4** also appears at a ^{19}F chemical shift of – 178.61 ppm – once again consistent with an *anti* assignment for the C_7 fluorine.

The exclusive formation of the *anti* isomer **4a** from a 93:7 *anti*:*syn* mixture of **3** is quite surprising, and this for two reasons. Firstly, the wrong isomer would seem to have predominated, since we would have expected the preferable formation of the *syn* isomer **4b**. As shown in Scheme 2, the mechanism for DAST reactions with alcohols involves a preliminary nucleophilic attack of the alcohol oxygen on the sulfur of DAST (**9**), which occurs with the loss of the elements of HF [6]. The resulting intermediate $ROSF_2NR_2$ is converted into the alkyl fluoride by S_N2 attack of fluoride ion on the carbon of the C–O. Overall, the displacement of the hydroxyl group by fluorine occurs with almost complete Walden inversion of configuration [28]. No stereo randomization is reported in many reactions involving carbohydrates and steroids [29,30] Moreover theoretical studies of DAST fluorination also predict that the carbon–fluoride bond formation should go through an S_N2 mechanism [31]. Thus, inversion of configuration should have converted 93:7 *anti*:*syn* alcohol **3** to a 93:7 *syn*:*anti* fluoride **4**.

Secondly, if for some reason configuration is retained in the nucleophilic substitution step, a 93:7 *anti*:*syn* mixture of starting material alcohol **3** should have yielded a 93:7 *anti*:*syn* mixture of fluoride **4**. Why do we obtain *anti* **4a** exclusively?

Further exploration of the literature revealed what seems to be an interesting resolution to this dilemma. The cases where DAST mediated fluorinations result in exclusive retention of configuration involve neighboring group participation [6]. This anchimeric assistance is generally observed with nucleophilic neighboring groups, like sulfur (R–S–R) [32], oxygen (–OMe) [33], nitrogen ($-N_3$) [33] and bromine (R–Br) [34], which are able to displace the OSF_2NEt_2 (**10**) leaving group. In addition, in one case, π-electrons of an adjacent double bond are also in position to displace this group [35]. In the norbornene system, anchimeric assistance has been invoked for leaving groups at C_7 aligned *anti* to the double bond [36,37]. Thus, putting the two pieces of the puzzle together,

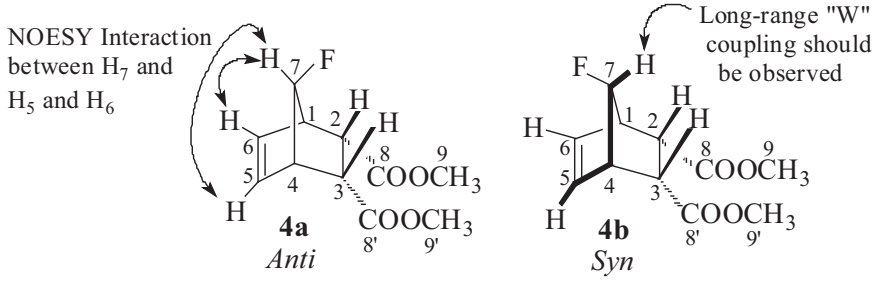
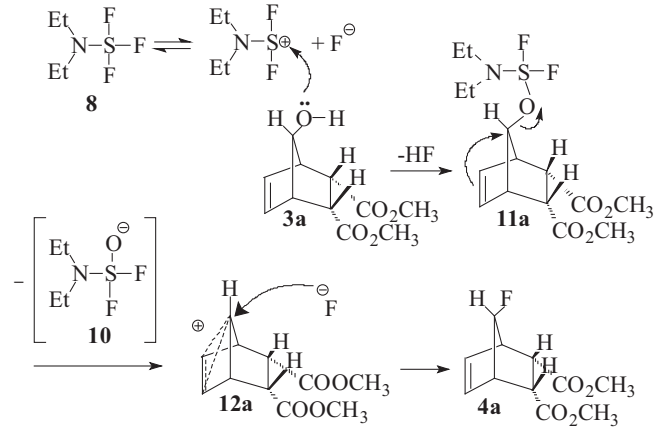
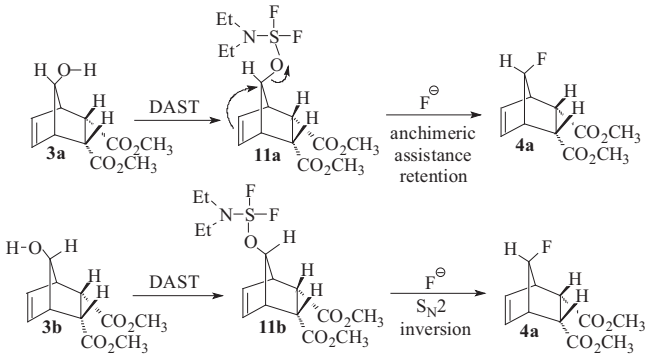


Fig. 1. *Anti* and *syn* 7-fluoronadic dimethyl ester **4a** and **4b**.



Scheme 3. Proposed anchimeric assistance in the fluorination of *anti*-7-hydroxynadic dimethyl ester (**3a**) with DAST (**8**).



Scheme 4. Proposed mechanism of the DAST-mediated fluorination of *anti* and *syn*-7-hydroxynadic dimethyl esters (**3a** and **3b**, respectively).

in the present fluorination of *anti* **3a**, anchimeric assistance by the norbornene double-bond is presumably also involved. As shown in Scheme 3, the interaction of the norbornene double bond with C_7 from the *syn* side of the ring directs the attacking fluoride ion specifically from the *anti* direction.

Scheme 4 presents a mechanistic comparison between the DAST reactions of *anti* and *syn* alcohols **3a** and **3b**, respectively. Anchimeric assistance of the norbornene double bond explains why *anti* alcohol **3a** is converted exclusively to *anti* fluoride **4a**. However, in the case of *syn* alcohol **3b**, anchimeric assistance is not available and the system perforce undergoes the typical S_N2 (Walden inversion) mechanism typical for DAST. Thus, *syn* alcohol **3b** also gives exclusively *anti* fluoride **4a**. Hence, our 93:7 *anti*/*syn* mixture of **3** reacts with DAST stereospecifically to give *anti*-7-fluoro **4a** as the sole product.[1] To prove this latter point further, a 1:1 mixture of *anti* and *syn* 7-hydroxynadic dimethyl ester (**3a** and **3b**) was reacted with DAST and the disappearance of starting material was followed by NMR. After 2.5 h of reaction, *anti*-epimer **3a** was completely consumed, while only 26% of *syn*-epimer **3b** reacted; nevertheless, *anti*-7-fluoro isomer **4a** was again the sole product.

2.2. Synthesis of 7,7-difluoronadic dimethyl ester (7)

We turn now to the synthesis of 7,7-difluoronadic dimethyl ester (**7**; Scheme 1), which was also synthesized from norbornen-7-one-2,3-dicarboxylic acid anhydride (**1**) [22]. Saponification of **1** with $NaOH/H_2O$ gave, following acidification and recrystallization, a nearly quantitative yield of the corresponding pure diacid **5**. The X-ray structure of diacid **5** is shown in Fig. 2 (the full X-ray analysis, performed as previously described [38], is available in Supporting Information).

As shown in Scheme 5, two different approaches were investigated for preparation of the desired diester **6**: (a) Khurana's acidic methanolic sonication (method i) [25], discussed above; and (b) diazotization (method ii) [26]. The former method indeed efficiently esterified diacid **5**. Surprisingly, however, the ketone at C_7 also reacted under these conditions to yield the corresponding dimethyl ketal **13**. The reactivity of the carbonyl presumably results from the angle strain at the C_7-carbonyl of the C_4–C_7–C_1 bridge. The observed angle in the crystal structure shown in Fig. 2 is *ca.* 97°, which is much smaller than the optimal 120°. Hence, the C_7-carbonyl undergoes facile ketal formation to give an sp^3 carbon at C_7, thereby reducing the angle strain substantially – from 23° down to 11°.

Diesterification of diacid **5** with diazomethane (method ii) is a very facile process [26]. As shown in Scheme 5, diazotization of diacid **5** at 0 °C for 5 min yielded a 93% yield of product mixture – which by NMR analysis proved to be 91% dimethyl ester **6** accompanied by a 2% yield of epoxide **14** (*vide infra*). At longer reaction times, secondary reactions on the C_7-carbonyl begin to take place. Thus, when the same diazotation of **5** was carried out for 4 h, only a small amount (4%) of 7-oxonadic diester (**6**) was obtained. Instead, the main product proved to be *anti* epoxide **14** (71%) accompanied by a 25% yield of the ring-expanded [2.2.2]bicyclooctenone **15** [39]. Our determination that the *anti* oxirane is formed is based on the previous report of Bly et al. [40] that the reaction of CH_2N_2 with 7-oxonorbornene (**18**) yields the spiro-*anti*-epoxide **19** and [2.2.2]bicyclooctenone (**20**) in a 4:3 ratio (Scheme 6).

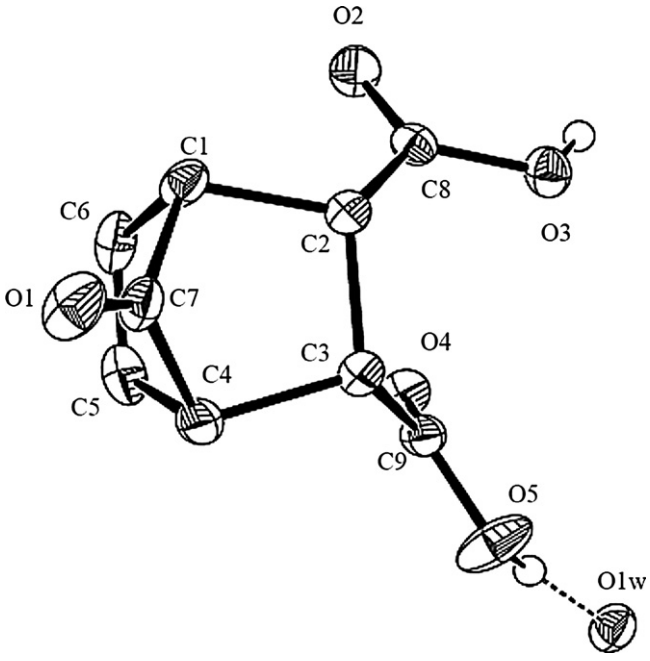
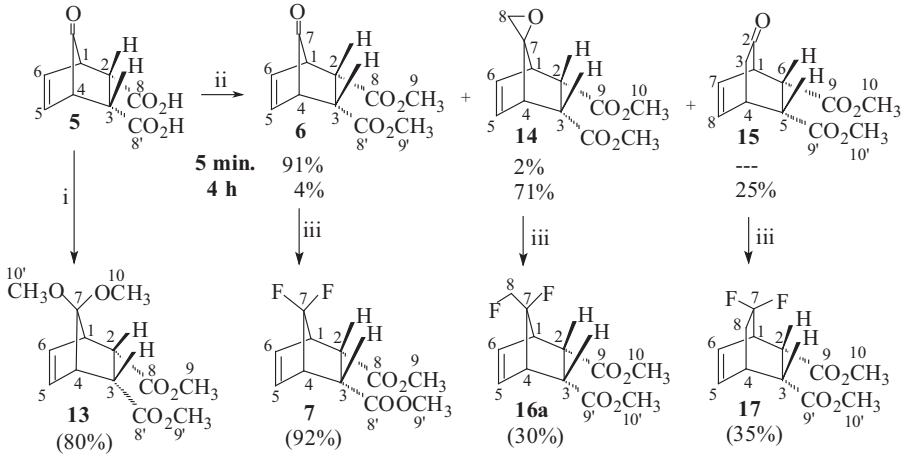


Fig. 2. X-ray structure of 7-oxonadic acid (**5**).

[1] Adcock et al. [27] briefly describe, in the experimental section of their article, the preparation of *anti*-**4a** using another fluorination agent, 2-chloro-1,1,2-trifluorotriethylamine (TCC). While they mention that the *anti*:*syn* ratio of the starting alcohol was *ca.* 90:10, they make no mention of whether the fluorination proceeded stereospecifically, nor do they suggest a mechanism if such was the case.



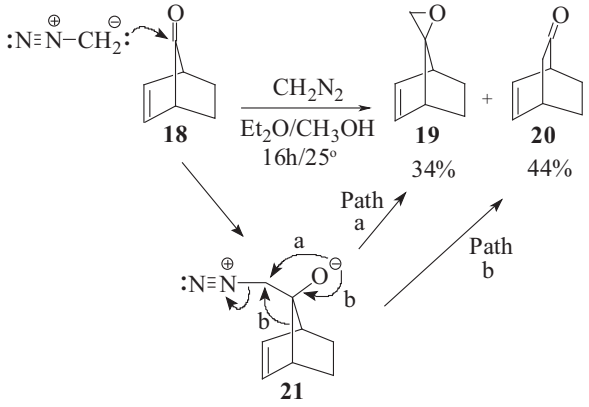
i. MeOH/H$^+$/))) **ii.** CH_2N_2/Et_2O, 0 °C. **iii.** DAST/CH_2Cl_2, –78 °C to rt 22Hr.

Scheme 5. Esterification of diacid **5**, and fluorination of the corresponding products.

Two brief comments should be made at this juncture. In the reaction of ketones with diazomethane, both the formation of epoxides as well as ketones with one more carbon (homologs) are well precedented [41]. The formation of the *anti*-oxirane exclusively results from the unhindered attack of the diazomethane from the double bond face forming intermediate **21**. The latter can generate both *anti*-epoxide **19** or ring expanded ketone **20**.

As shown in Scheme 5, the desired 7,7-difluoronadic ester **7** was obtained in a 92% yield from 7-oxonadic diester (**6**) upon treatment with DAST (containing a catalytic amount of HF, generated by the addition of EtOH) [6,19]. Similarly, when the same DAST reaction was performed on epoxide **14**, vicinal difluoride **16a** as the sole product (30% conversion; 100% yield). Finally, [2.2.2]bicyclooctenone **15** under the same conditions yielded the corresponding *gem*-difluoride **17** (35% conversion; 100% yield).

The structure of **16a** was determined to be *anti*-7-fluoro-*syn*-7-fluoromethyl, and not the epimeric *syn*-7-fluoro-*anti*-7-fluoromethyl **16b** (see Fig. 3), based on the following considerations: (a) Using a 700 MHz ^{1}H NMR instrument, weak – but not negligible – NOESY interactions were found between H_8 and H_5/H_6; this confirms that C_8 lies *syn*. (b) No NOE interaction was found between H_8 and H_2/H_3; this too confirms that C_8 does not lie *anti*. (c) As in the case of compound **4a**, ring carbons C_2 and C_3 are not W-split by F_7 – confirming that F_7 lies *anti*. By contrast, we found that C_2 and C_3 in 7,7-difluoronorbornene **7** were each split (d, J = 2.6 Hz) by the *syn*-fluorine.



Scheme 6. Diazotization of 7-ketonorbornene **18**.

Consistent with this *anti*-7-fluoro-*syn*-7-fluoromethyl assignment for **16**, is the intriguing ^{19}F NMR spectrum for the *anti*-F_7 of this compound (see Fig. 4). The C_7 fluorine resonates at −164.437 ppm and is split with three different coupling constants: by the H_8 methylene to a triplet ($^2J_{HF}$ = 24.5 Hz); by F_8 to a doublet ($^3J_{FF}$ = 15 Hz); and by H_1/H_4 and H_5/H_6 to quintet ($^3J_{HF}$ and $^4J_{HF}$ = 2 Hz), resulting in a very impressive "tdquint". By comparison, the fluorine at C_8 resonates at −228.450 ppm with a very clear td (see Supporting Information) produced by the H_8 methylene ($^2J_{HF}$ = 47 Hz) and F_7 ($^3J_{FF}$ = 15 Hz).

The reaction of oxiranes with DAST to yield vicinal difluorides has been reported by Hudlicky [42]. In light of the fact that the C_8-methylene in both the starting oxirane **14** and in the difluoro product **16** is *syn* to the double bond, the DAST reaction must have occurred with net retention around C_7. This is problematic since, as outlined in Scheme 7, the first step in the transformation of oxirane **14** to vicinal difluoride **16** is undoubtedly protonation of the epoxide by the catalytic HF present in the reaction mixture (see above). Fluoride attack should occur at the more substituted carbon C_7 from the back side of the oxirane, leading to fluorohydrin **23b** with the C_7 fluorine lying *syn* to the double bond and the C_8 alcohol *anti* to it. Upon reaction with DAST, **23b** would yield *syn*-7-

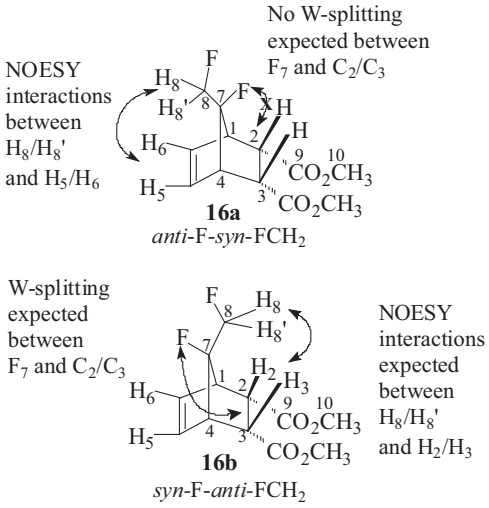


Fig. 3. 7-Fluoro-7-fluoromethylnadic dimethyl ester isomers **16a** and **16b**.

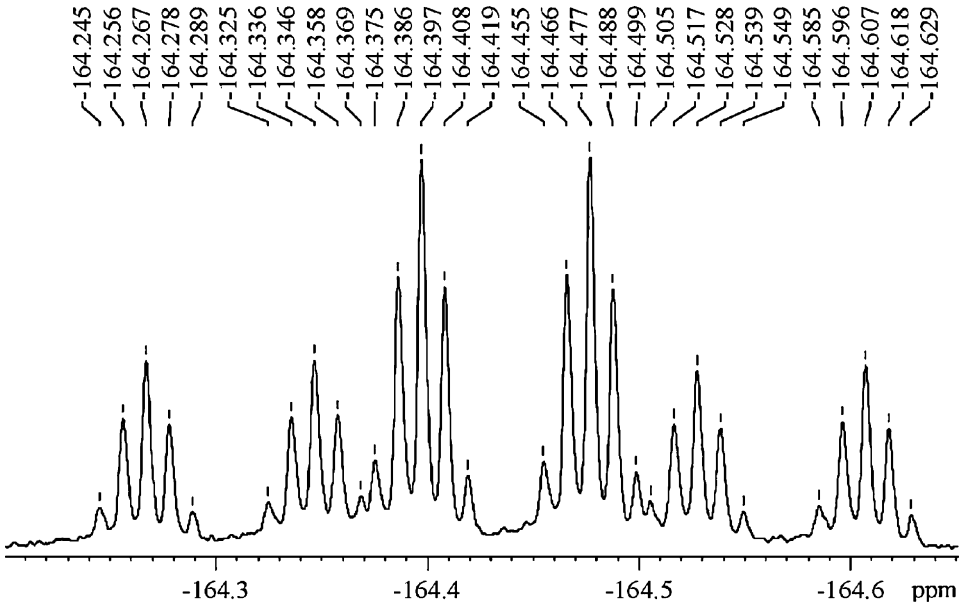


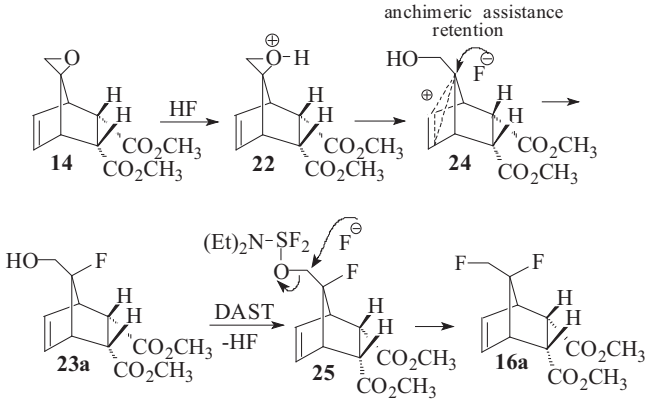
Fig. 4. ^{19}F NMR spectrum of *anti*-7-fluorine in nadic diester **16a**.

fluoro-*anti*-7-fluoromethyl **16b** – the epimeric difluoride with net inversion around C_7.

The net retention observed around C_7 in the DAST mediated fluorination of *anti*-epoxide **14**, as in the previous case of *anti*-7-alcohol **3a** (Scheme 3), results from anchimeric assistance [43] as outlined in Scheme 8. Following initial protonation of the oxirane, anchimeric assistance opens the oxirane from the back-side at the more substituted carbon C_7. This in turn directs fluoride attack from what was the front side of the oxirane. All this leads to fluorohydrin **23a**, with the C_7 fluorine lying *anti* to the double bond and the C_8 alcohol *syn* to it. Upon reaction with DAST, **23a** now yields *anti*-7-fluoro-*syn*-7-fluoromethyl **16a** with net inversion around C_7.

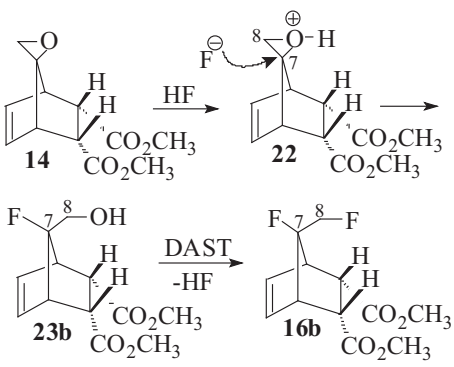
Finally, we turn briefly to the reaction of [2.2.2]bicyclooctenone **15** with DAST. Like other ketones, **15** reacts to yield *gem*-difluoride **17**; however, the reason for its slow reaction rate (35% conversion in 22 h) is unknown. It has been reported [6,19], however, that in the fluorination of ketones by DAST in the presence of catalytic HF, the acid initially adds to the carbonyl generating the corresponding α-fluoroalcohol. The latter then reacts with DAST yielding the observed α-difluoride.

We suggest that, in the case of 7-oxonadic ester **6**, anchimeric assistance transfers electron density from the norbornene double bond towards the 7-carbonyl carbon, which in turn pushes

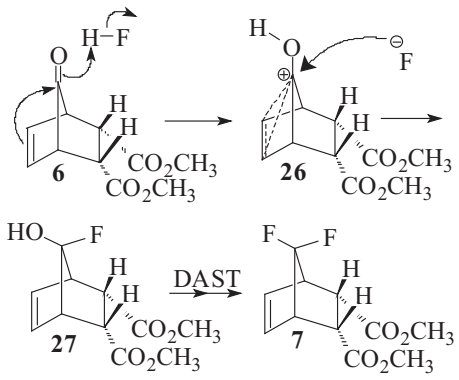


Scheme 8. Mechanism for the fluorination of *anti*-7-epoxynadic diester **14** with DAST.

electron density onto the carbonyl oxygen (Scheme 9). The latter becomes more nucleophilic towards HF and thereby increases the rate of α-fluoroalcohol **27** formation and ultimately difluorination to **7**. By contrast, in the case of the [2.2.2]bicyclooctenone **15**, the off-center alignment of the carbonyl renders the anchimeric



Scheme 7. Rejected mechanism for the DAST mediated fluorination of *anti*-7-epoxynadic diester **14**.



Scheme 9. Proposed anchimeric assistance in the fluorination of 7-ketonadic diester **6** by DAST.

assistance minimally present, with a concomitant drop in reaction rate.

3. Conclusions

The conversion of 7-ketonadic anhydride to the 7-fluoro and 7,7-difluoronadic methyl esters is a seemingly facile process. *En passant*, we have observed an important role for anchimeric assistance of the norbornene double bond, which guides the introduction of attacking fluorides *anti* to the olefinic linkage, and presumably hastens the reaction. This directing effect has a profound influence on the retention of configuration of the substituents about C_7 of the nadic system – as seen in the formation of specifically *anti*-fluorides **4a** and **16a** from the corresponding *anti* precursors **3a** and **14**, respectively.

4. Experimental

4.1. General remarks

Standard synthetic procedures and spectroscopic techniques were used and delineated in Supporting Information. ^{1}H and ^{13}C NMR chemical shifts are expressed in δ (ppm) relative to TMS (0 ppm) (in DMSO-d_6, acetone-d_6 or $CDCl_3$) as internal standard as reported by Gottlieb et al. [44]. The ^{19}F NMR chemical shifts are also expressed in δ (ppm), but relative to $CFCl_3$ (0 ppm). In the ^{1}H NMR data, "t," "q" and "quint" designates a second order triplet, quartet or quintet, respectively, caused by virtual and/or long-range coupling effects, which are widespread in the norbornene ring. The numbering of the various carbons and attached hydrogens appears in Schemes 1 and 5. X-ray spectroscopy was carried out as previously described [38] on a single crystal of the sample. Unless otherwise indicated, all the solvents and reagents were commercially available in high purity and used as received.

4.2. Synthesis of norbornen-7-one-2,3-dicarboxylic acid anhydride (1)

7-Ketonadic anhydride (**1**) was synthesized according to the previously published procedure [22], which was slightly modified in order to minimize the formation of the corresponding diacid. To this end, prior to the addition of the maleic anhydride to the pentane solutions of diethoxycyclopentadiene, the latter solutions were dried at 0 °C over $MgSO_4$ and filtered into a dry ice cooled (−78 °C) round-botom flask. The spectral data corresponded well to that previously published [22]; mp: 151 °C (lit. [45]: 152 °C); R_f (acetone): 0.66; R_f (Et_2O): 0.08.

4.3. Synthesis of anti- and syn-7-hydroxynadic acid (2a and 2b)

The titled compounds were synthesized from **1** following the published procedure of Meador et al. [22] The ratio of *anti*-**2a**:*syn*-**2b** based on ^{1}H NMR was 93:7, in agreement with previous reports [22]: mp: 168 °C. R_f (acetone): 0.135. R_f (Et_2O): 0.027. A pure sample of the *anti*-epimer **2a** was obtained via recrystalization from water. The mother liquor was enriched with the *syn* isomer, and yielded a sample of **2** in which the *anti*:*syn* (**2a**:**2b**) ratio was 1:1.

4.4. Synthesis of anti- and syn-7-hydroxynadic dimethyl ester (3a and 3b)

7-Hydroxynadic acid **2** (2.00 g, 10 mmol) was placed in a 20 mL vial and dissolved in 15 mL of methanol. To the vial was added 0.5 mL of 10 N H_2SO_4 and the resulting solution was corked and sonicated for 8 h. The mixture was poured into H_2O (25 mL) and extracted with dichloromethane (3× 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (2× 15 mL) and water (2× 15 mL) and then dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give 1.81 g (8 mmol, 78% yield) of the desired product **3** as a white solid. Based on ^{1}H NMR analysis, we determined that the ratio of *anti*-**3a**:*syn*-**3b** was identical to that of the starting material **2**. The physical and spectral data for **3a** were obtained for a pure sample of **3a** prepared from pure **2a**.

3a: mp: 63 °C. R_f (acetone): 0.72. R_f (Et_2O): 0.34. R_f (Et_2O/Hex, 1:1): 0.15. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.127 ("t", J = 1.8 Hz, 2H, H_5 and H_6), 3.642 (t, J = 1.8 Hz, 1H, H_7), 3.612 (s, 6H, H_9 and $H_{9'}$), 3.555 (m, 2H, H_2 and H_3), 3.534 (s, 1H, OH), 2.900 (m, 2H, H_1 and H_4). ^{1}H NMR (300 MHz, acetone-d_6): δ 6.040 ("t", J = 2.1 Hz, 2H, H_5 and H_6), 3.898 (bs, 1H, H_{10}), 3.565 (bs, 1H, H_7), 3.528 (s, 6H, H_9), 3.487 ("t", J = 2.1 Hz, 2H, H_2 and H_3), 2.800 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (C_8 and $C_{8'}$), 133.1 (C_5 and C_6), 82.0 (C_7), 51.4 (C_9 and $C_{9'}$), 49.9 (C_1 and C_4), 45.3 (C_2 and C_3). ^{13}C NMR (75 MHz, acetone-d_6): δ 173.4 (C_8), 134.0 (C_5 and C_6), 83.1 (C_7), 52.4 (C_9), 51.1(C_1 and C_4), 46.3 (C_2 and C_3). FTIR (KBr): 3572–3250 (bs, OH), 1743 (s, C=O), 1720 (s, C=O), 1642 (m, C=C) cm^{-1}. MS (DCI–CH_4) m/z: 227 (MH^+, 36%), 201 (MH^+–OH, 12%), 109 (MH^+–H_2O, 100%), 195 (MH^+–CH_3OH, 66%), 166 (M^+–CH_3OH–CO, 25%), 107 (MH^+–2CH_3OH–2CO, 39%). HRMS (DCI–CH_4) m/z: calcd for $C_{11}H_{14}O_5$ (MH^+), 227.0919; found: 227.0883. Anal. calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.06; H, 6.39.

3b: The NMR data was extracted from a 1:1 *syn*/*anti* mixture, prepared from 1:1 **2a**:**2b** mixture. ^{1}H NMR (300 MHz, acetone-d_6): δ 6.070 (m, 2H, H_5 and H_6), 4.617 (bs, 1H, H_{10}), 3.675 (bs, 1H, H_7), 3.528 (s, 6H, H_9), 3.350 ("t", J = 2.1 Hz, 2H, H_2 and H_3), 2.988 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, acetone-d_6): δ 172.4 (C_8), 131.9 (C_5 and C_6), 86.1 (C_7), 54.9 (C_9), 51.5 (C_1 and C_4), 46.1 (C_2 and C_3).

4.5. Synthesis of anti-7-fluoronadic dimethyl ester (4a)

A three-necked 500 mL r.b. flask was fitted with a magnetic stirring bar, a septum, and a pressure equalizing addition funnel containing 7-hydroxynadic dimethyl ester **3** (2.0 g, 8.8 mmol; *anti*:*syn* ratio 93:7) dissolved in 80 mL of dichloromethane. The reaction vessel was maintained under an argon atmosphere, charged with 80 mL of dichloromethane, and cooled to −78 °C in a dry-ice/acetone bath. Using a syringe, DAST (1.39 mL, 11 mmol) was added to the reaction flask through the septum. The 7-hydroxynadic diester **3** solution was added dropwise via the addition funnel over 30 min, and the reaction solution was then stirred for 2.5 h at −78 °C. The reaction mixture was poured into saturated $NaHCO_3$ solution (200 mL), and extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL) and then dried over anhydrous $MgSO_4$. The volatiles were concentrated *in vacuo* to give the desired product (1.89 g, 6.7 mmol, 94% yield) as a viscous colorless liquid. Often the product did not require further purification; however, when required, the product was purified by flash chromatography (hexane/Et_2O, 2:1). ^{1}H NMR showed the product to be the *anti* isomer **4a** exclusively (for discussion, see text).

4a: R_f (acetone): 0.69. R_f (Et_2O): 0.67. ^{1}H NMR (300 MHz, acetone-d_6): δ 6.154 (m, 2H, H_5 and H_6), 4.315 (dt, $^2J_{HF}$ = 58.8, $^3J_{HH}$ = 2.4 Hz, 1H, H_7), 3.643 (s, 6H, H_9 and $H_{9'}$), 3.514 ("quint", J = 1.8 Hz, 2H, H_2 and H_3), 3.129 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (C_8 and $C_{8'}$), 131.9 (d, $^3J_{CF}$ = 7.7 Hz, C_5 and C_6), 96.8 (d, $^1J_{CF}$ = 214.8 Hz, C_7), 51.6 (C_9 and $C_{9'}$), 48.1 (d, $^2J_{CF}$ = 16.4 Hz, C_1 and C_4), 45.0 (C_2 and C_3). ^{19}F NMR (188 MHz, $CDCl_3$): δ −178.78 (d, $^2J_{HF}$ = 58.9 Hz). FTIR (KBr): 1749 (s, C=O), 1734 (s, C=O ester), 1653 (m, C=C) cm^{-1}. MS (DCI–CH_4) m/z: 229 (MH^+, 38%), 228 (M^+, 50%), 209 (MH^+–HF, 68%), 197 (MH^+–CH_3OH,

100%), 169 (MH^+–CH_3OH–CO, 79%), 176 (M^+–CH_3OH–HF, 56%). HRMS (DCI–CH_4) *m/z*: calcd for $C_{11}H_{13}FO_4$ (M^+), 228.0798; found, 228.0835. Calcd for $C_{11}H_{14}FO_4$ (MH^+), 229.0876; found, 229.0879.

4.6. Synthesis of 7-oxonadic acid (5)

7-Oxonadic anhydride [22] (**1**) (4.0 g, 22 mmol) was suspended in 50 mL of distilled water containing 2.04 equiv. of NaOH (1.8 g, 45 mmol) and stirred at RT until the solid dissolved (*ca.* 1 h). The solution was acidified by the dropwise addition of conc. HCl (7.0 mL), and stirred for 15 min. The water was removed *in vacuo* and the resulting yellow solid product was dissolved in minimum amount of acetone and filtered. The mother liquor (acetone layer) was concentrated *in vacuo* to yield a light-brown solid. The latter was dissolved in a minimum amount of hot water, treated with activated carbon and filtered. The filtrate was allowed to recrystallize in the hood from the aqueous solution to give the desired pure ketodiacid **5** (4.36 g, 22 mmol, 99% yield). The FTIR and ^{1}H NMR spectral data in acetone-d_6 were essentially identical with those previously reported [22], though additional data is supplied below.

5: mp: 153 °C. R_f (acetone): 0.06. R_f (Et_2O): 0.03. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.290 (s, 2H, COOH), 6.555 ("t", J = 2.4 Hz, 2H, H_5 and H_6), 3.470 ("t", J = 1.5 Hz, 2H, H_2 and H_3), 3.145 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, DMSO-d_6): δ 199.0 (C_7), 171.5 (C_8 and $C_{8'}$), 131.1 (C_5 and C_6), 49.4 (C_2 and C_3), 43.3 (C_1 and C_4). MS (DCI–CH_4) *m/z*: 196 (M^+, 13%), 178 (M^+–H_2O, 51%), 168 (M^+–CO, 6%), 149 (M^+–H_2O–CO_2–H, 25%), 123 (M^+–COOH–CO, 18%), 77 ($C_6H_5^+$, 100%). HRMS (DCI–CH_4) *m/z*: calcd for $C_9H_8O_5$ (M^+), 196.0372; found, 196.0352. Anal. calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 54.91; H, 4.17.

4.7. Synthesis of 7-oxonadic dimethyl ester (6)

A solution of diazomethane in diethyl ether was prepared from N-methyl-N-nitrosourea according to the published procedure [26] with several modifications. To a 500 mL Erlenmeyer flask were added KOH (39.18 g, 0.70 mol) dissolved in water (60 mL) and ether (300 mL). The mixture was cooled to 0 °C, and N-methyl-N-nitrosourea (8.57 g, 0.083 mol) was added and stirred slowly for 10 min. The yellow ether layer was carefully decanted in one portion into 200 mL of chilled (0 °C) acetone containing 7-oxonadic acid (**5**) (2.00 g, 0.010 mol). A second portion of 300 mL of ether was added to the KOH/N-methyl-N-nitrosourea reaction flask, stirred briefly and poured into the reaction. The resulting solution was stirred for another 5 min at 0 °C, until no further N_2 evolved. Glacial acetic acid (8.0 mL) was carefully added to destroy the excess diazomethane. The mixture was partially concentrated *in vacuo* which aided in preventing the formation of emulsions. The mixture was poured into water (200 mL) and extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 200 mL), and brine (200 mL) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent, gave the desired product (2.13 g, 9.5 mmol, 93% yield) which was typically used without further purification. ^{1}H NMR and TLC analysis revealed the presence of small amounts (2% yield) of epoxide **14**. Analytically pure samples of ketone **6** were obtained via recrystallization from acetone/hexane.

6: mp: 82 °C. R_f (acetone): 0.70. R_f (Et_2O): 0.50. R_f (Et_2O, Hex 1:1): 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.643 ("t", J = 2.4 Hz, 2H, H_5 and H_6), 3.665 (s, 6H, H_9 and $H_{9'}$), 3.505 ("t", J = 1.8 Hz, 2H, H_2 and H_3), 3.271 (m, 2H, H_1 and H_4). ^{1}H NMR (300 MHz, acetone-d_6): δ 6.589 ("t", J = 2.4 Hz, 2H, H_5 and H_6), 3.633 (m, 2H, H_2 and H_3), 3.593 (s, 6H, H_9 and $H_{9'}$), 3.189 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.3 (C_7), 170.8 (C_8 and $C_{8'}$), 131.3 (C_5 and C_6), 52.2 (C_9 and $C_{9'}$), 49.8 (C_1 and C_4), 43.6 (C_2 and C_3). ^{13}C NMR (75 MHz, acetone-d_6): δ 198.5 (C_7), 171.3 (C_8 and $C_{8'}$), 132.2 (C_5 and C_6), 52.0 (C_9 and $C_{9'}$), 50.5 (C_1 and C_4), 44.3 (C_2 and C_3). FTIR (KBr): 1792 (s, C=O), 1737 (s, C=O) cm^{-1}. MS (DCI CH_4) *m/z*: 225 (MH^+, 36%), 197 (MH^+–CO, 4%), 196 (M^+–CO, 9%), 194 (MH^+–OCH_3, 11%), 193 (M^+–OCH_3, 100%), 165 (M^+–OCH_3–CO, 32%), 137 (M^+–CO_2CH_3–CO, 52%). HRMS (DCI–CH_4) *m/z*: calcd for $C_{11}H_{12}O_5$ (MH^+) 225.0763; found, 225.0735. Anal. calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.13; H, 5.46.

4.8. Synthesis of 7,7-difluoronadic dimethyl ester (7)

A 1 L 3-necked RB flask – fitted with a magnetic stirring bar, Ar bubbler and a septum – was charged with 7-oxonadic dimethyl ester (**6**, 64.00 g, 17.8 mmol) dissolved in dry dichloromethane (320 mL). The reaction mixture was stirred under an argon atmosphere and cooled to −78 °C in a dry ice/acetone bath. DAST (7.01 mL, 53.5 mmol, 3 equiv.) was added via syringe into the reaction flask through the septum, followed by 0.400 mL of ethanol (to generate a catalytic amount of HF). The solution was allowed to slowly come to room temperature overnight. The reaction mixture was then poured into 300 mL of saturated $NaHCO_3$ solution and extracted with dichloromethane (3× 300 mL). The combined organic extracts were washed with H_2O (400 mL) and brine (400 mL), and then dried over anhydrous $MgSO_4$. The volatiles were evaporated *in vacuo* and the residue (brown oil, 4.02 g, 16.4 mmol, 92% yield) was purified by flash column chromatography (hexane/Et_2O, 2:1) to give pure difluoride (2.21 g, 9.0 mmol, 50% yield).

7: R_f (acetone): 0.60. R_f (Et_2O): 0.62. R_f (Et_2O, Hex 1:1): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.322 ("q", J = 2.3 Hz, 2H, H_5 and H_6), 3.643 (s, 6H, H_9 and $H_{9'}$), 3.563 (m, 2H, H_2 and H_3), 3.233 (m, 2H, H_1 and H_4). ^{1}H NMR (300 MHz, acetone-d_6): δ 6.258 ("q", J = 2.3 Hz, 2H, H_5 and H_6), 3.579 (s, 6H, H_9 and $H_{9'}$), 3.573 (m, 2H, H_2 and H_3), 3.261 (m, 2H, H_1 and H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (C_8 and $C_{8'}$), 131.9 (d, $^3J_{CF}$ = 5.3 Hz, C_5 and C_6), 131.9 (dd, $^1J_{CF}$ = 265.4 Hz, $^1J_{CF}$ = 263.0 Hz, C_7 – note that we were unable to see the dd splitting because the central peak overlaps the C_5/C_6 peak; the $^1J_{CF}$ values are based on the acetone-d_6 spectrum below), 51.9, (C_9 and $C_{9'}$), 49.0 (t, $^2J_{CF}$ = 20.3 Hz, C_1 and C_4), 44.9 (d, $^3J_{CF}$ = 2.5 Hz, C_2 and C_3). ^{13}C NMR (75 MHz, acetone-d_6): δ 171.2 (C_8 and $C_{8'}$), 133.0 (dd, $^1J_{CF}$ = 265.4 Hz, $^1J_{CF}$ = 263.0 Hz, C_7), 132.6 (d, $^3J_{CF}$ = 5.4 Hz, C_5 and C_6), 52.0 (C_9 and $C_{9'}$), 49.6 (t, J = 20.3 Hz, C_1 and C_4), 45.6 (d, J = 2.6 Hz, C_2 and C_3). ^{19}F NMR (188 MHz, $CDCl_3$): δ −117.28 (d, $^2J_{FF}$ = 188 Hz), −138.47 (d, $^2J_{FF}$ = 188 Hz). ^{19}F NMR (188 MHz, acetone-d_6): δ −118.12 (d, $^2J_{FF}$ = 188 Hz), −138.80 (d, $^2J_{FF}$ = 188 Hz). FTIR (KBr): 1734 (s, C=O), 1717 (s, C=O) cm^{-1}. MS (DCI–CH_4) *m/z*: 247 (MH^+, 37%), 246 (M^+, 20%), 228 (MH^+–F, 14%), 227 (M^+–F, 71%), 215 (MH^+–CH_3OH, 100%), 197 (MH^+–OCH_3–F, 45%), 194 (M^+–CH_3OH–HF, 60%). HRMS (DCI–CH_4) *m/z*: calcd for $C_{11}H_{12}F_2O_4$ (MH^+), 247.0782; found, 247.0747. Calcd for $C_{11}H_{12}F_2O_4$ (M^+), 246.0704; found, 246.0743.

4.9. Synthesis of N-methyl-N-nitrosourea [$CH_3N(NO)CONH_2$]

The preparation of N-methyl-N-nitrosourea has been previously described [46] though only partial spectral data appears in the literature [47].

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (bs, 1H, NH), 7.81 (bs, 1H, NH), 3.08 (bs, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.0 (C=O), 26.4 (CH_3). MS (DCI–CH_4) *m/z*: 104 (MH^+, 36%), 73 (MH^+–CH_3–NH_2, 12%), 61 (MH^+–CH_3–NH_2, 26%), 60 (MH^+–NH_2–CO, 39%), 59 (MH^+–CH_3–NO, 100%), 58 (MH^+–NH_2–NO, 39%). HRMS (DCI–CH_4) *m/z*: calcd for $C_2H_5N_3O_2$ (MH^+) 104.0460; found, 104.0437.

4.10. Synthesis of 7,7-dimethoxynadic 2,3-dimethyl ester (13)

7-Oxonadic acid (**5**; 1.96 g, 10 mmol) dissolved in 15 mL of methanol was placed in a corked 20 mL vial. H_2SO_4 (0.5 mL of 10 N)

was added and the reaction mixture was sonicated for 4 h at room temperature. The mixture was poured into H_2O (25 mL) and extracted with dichloromethane (3× 25 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2× 15 mL) and H_2O (2× 15 mL), and then dried over anhydrous $MgSO_4$. The volatiles were evaporated, and the crude was dissolved in a minimum of acetone and placed in the freezer overnight to give crystals of ketal diester **13** (2.17 g, 8 mmol, 80% yield).

13: mp: 58 °C. R_f (acetone): 0.62. R_f (Et_2O): 0.51. ^1H NMR (600 MHz, $CDCl_3$): δ 6.275 (t, J = 2.1 Hz, 2H, H_5 and H_6), 3.619 (s, 6H, H_9 and $H_{9'}$), 3.494 (m, 2H, H_2 and H_3), 3.221 (s, 3H, H_{10}), 3.165 (m, 2H, H_1 and H_4), 3.151 (s, 3H, $H_{10'}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.4 (C_8 and $C_{8'}$), 132.4 (C_5 and C_6), 117.2 (C_7), 52.1 ($C_{10'}$), 51.6 (C_9 and $C_{9'}$), 50.0 (C_{10}), 48.4 (C_1 and C_4), 46.1 (C_2 and C_3). FTIR (KBr): 1747 (s, C=O), 1739 (s, C=O) cm^{-1}. MS (DCI–CH_4) m/z: 271 (MH^+, 22%), 239 (MH^+–CH_3OH, 100%), 211 (MH^+–CH_3OH–CO, 34%), 207 (MH^+–$C_2H_8O_2$, 15%). HRMS (DCI–CH_4) m/z: calcd for $C_{13}H_{18}O_6$ (MH^+), 271.1182; found, 271.1156. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.97; H, 6.84.

4.11. Synthesis of dimethyl spiro-[5-norbornene-anti-7,2′-oxacyclopropane]-endo-2,3-dicarboxylate (14) and dimethyl 5-oxobicyclo[2.2.2]oct-7-ene-endo-2,3-dicarboxylate (15)

A solution of diazomethane in diethyl ether was prepared as before and reacted with 7-oxonadic acid (**5**) (2.00 g, 0.010 mol) – as described above for the synthesis of ketone diester **6**. In this case, however, the reaction mixture was stirred not for 5 min, but for 4 h at 0 °C. The reaction mixture was worked up as before, and evaporation of the solvent yielded 1.83 g of the yellow oil crude. NMR analysis indicated the product mixture was comprised of **14** (71%), **15** (25%) and **6** (4%). The mixture was separated by flash column chromatography (Et_2O/Hex, 1:2–1:1) to give three pure products: **14** (0.63 g, 2.6 mmol, 26% yield), **15** (0.42 g, 1.8 mmol; 18% yield) and **6** (0.05 g, 0.2 mmol; 2% yield). Bicyclic ketone **15** is known [39], though only partial spectral data are reported.

14: colorless oil. R_f (Et_2O): 0.68. R_f (Et_2O/Hex 1:1): 0.25. ^1H NMR (300 MHz, $CDCl_3$): δ 6.339 ("t", J = 2.4 Hz, 2H, H_5 and H_6), 3.637 (s, 6H, H_{10} and $H_{10'}$), 3.589 (m, 2H, H_2 and H_3), 2.948 (s, 2H, H_8). 2.708 (m, 2H, H_1 and H_4). ^{13}C NMR (176 MHz, $CDCl_3$): δ 172.1 (C_9 and $C_{9'}$), 132.8 (C_5 and C_6), 76.1 (C_7), 51.7 (C_{10} and $C_{10'}$), 50.5 (C_8), 47.6 (C_1 and C_4), 47.0 (C_2 and C_3). FTIR (KBr) 1791 (s, C=O), 1733 (s, C=O) cm^{-1}. MS (DCI CH_4) m/z: 239 (MH^+, 13%), 113 ($C_6H_9O_2^+$, 33%), 207 (MH^+–OMe, 66%). HRMS (DCI–CH_4) m/z: calcd for $C_{12}H_{14}O_5$ (MH^+) 239.0919; found, 239.0924.

15: mp: 102 °C. R_f (Et_2O): 0.38. R_f (Et_2O/Hex 1:1): 0.11. ^1H NMR (300 MHz, $CDCl_3$): δ 6.565 (t, J = 7.2 Hz, 1H, H_8), 6.335 (t, J = 7.2 Hz, 1H, H_7), 3.654 (s, 3H, H_{10} or $H_{10'}$), 3.650 (s, 3H, H_{10} or $H_{10'}$), 3.480 (dt, J = 6.6, 1.2 Hz, 1H, H_1), 3.352 (m, 1H, H_4), 3.322 (bd, J = 1.5 Hz, 1H, H_6), 3.294 (bd, J = 2.1 Hz, 1H, H_5) 2.133 (bt, J = 3.3, Hz, 2H, H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5 (C_2), 172.1 ($C_{9'}$), 171.0 (C_9), 135.2 (C_8), 126.9 (C_7), 52.0 and 51.9 (C_{10} and $C_{10'}$), 50.6 (C_1), 46.6 (C_5), 43.3 (C_6), 39.1 (C_3), 35.4 (C_4). FTIR (KBr): 1745 (s, C=O), 1731 (s, C=O) cm^{-1}. MS (DCI CH_4) m/z: 239 (MH^+, 94%), 207 (M^+–OCH_3, 100%), 196 (M^+–CO–CH_2, 34%), 113 ($C_6H_9O_2^+$, 31%), HRMS (DCI–CH_4) m/z: calcd for $C_{12}H_{14}O_5$ (MH^+) 239.0919; found, 239.0918. Anal. calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92; O, 33.58. Found: C, 60.87; H, 6.07; O, 33.43.

4.12. Synthesis of anti-7-fluoro syn-7-fluoromethyl-nadic dimethyl ester (16a)

The title compound was synthesized from **14** (0.40 g, 1.68 mmol) following the same procedure described above for the preparation of compound **7**. NMR analysis of the reaction product showed it to be very clean **16a** (0.13 g, 0.5 mmol, 30% yield).

16a: Colorless oil, R_f (Et_2O): 0.60. R_f (Et_2O, Hex 1:1): 0.28. ^1H NMR (700 MHz, $CDCl_3$): δ 6.251 (q, J = 2.1 Hz, 2H, H_5 and H_6), 4.636 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 24.6 Hz, 2H, H_8), 3.658 (m, 2H, H_2 and H_3), 3.637 (s, 6H, H_{10} and $H_{10'}$), 3.176 (m, 2H, H_1 and H_4). ^{13}C NMR (176 MHz, $CDCl_3$): δ 171.9 (C_9 and $C_{9'}$), 133.3 (d, $^3J_{CF}$ = 5.5 Hz, C_5 and C_6), 108.9 (dd, $^1J_{CF}$ = 208.0 Hz, $^2J_{CF}$ = 19.4 Hz, C_7), 81.3 (dd, $^1J_{CF}$ = 172.3 Hz, $^2J_{CF}$ = 26.8 Hz, C_8), 51.9 (C_{10} and $C_{10'}$), 48.7 (dd, $^2J_{CF}$ = 17.4 Hz, $^3J_{CF}$ = 4.4 Hz, C_1 and C_4), 45.8 (C_2 and C_3). ^{19}F NMR (188 MHz, $CDCl_3$): δ −228.45 (td, $^2J_{HF}$ = 47 Hz, $^3J_{FF}$ = 15 Hz), −164.44 (tdquintet, $^2J_{HF}$ = 24.5 Hz, $^3J_{FF}$ = 15 Hz, $^3J_{HF}$ and $^4J_{HF}$ = 2 Hz). FTIR (KBr): 1792 (m, C=O), 1749 (s, C=O) cm^{-1}. MS (DCI CH_4) m/z: 261 (MH^+, 14%), 241 (M^+–F, 69%), 229 (M^+–OCH_3, 100%), 201 (M^+–CO_2CH_3, 15%). HRMS (DCI–CH_4) m/z: calcd for $C_{12}H_{15}F_2O_4$ (MH^+) 261.0941; found, 261.0938.

4.13. Synthesis of dimethyl 7,7-difluorobicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate (17)

The title compound was synthesized from 0.20 g (0.84 mmol) of **15** following the same procedure and amounts ratio as the beforementioned fluorination procedure used to synthesis compound **7**. The crude was identified – by NMR – as mixture of the product **17** (35%) and starting material **15** (65%). The desired product was isolated by a preparative plate runed on Et_2O to yield 0.02 g (0.077 mmol, 11% yield) of **17** as a clean colorless oil.

17: R_f (Et_2O): 0.57. ^1H NMR (700 MHz, $CDCl_3$): δ 6.443 (ddt, J = 8, 6, 1 Hz, 1H, H_5), 6.312 (dddd, J = 8, 7, 3.5, 1.5 Hz, 1H, H_6), 3.432 (dt, J = 10.5, 2 Hz, 1H, H_2), 3.275 (qm, J = 6 Hz, 1H, H_1), 3.153 (dd, J = 10.5, 2 Hz, 1H, H_3), 3.113 (m, 1H, H_4), 3.634 (s, 3H, H_{10} or $H_{10'}$), 3.632 (s, 3H, H_{10} or $H_{10'}$). 1.976 (tdd, J = 14.5, 7.5, 2.5 Hz, 1H, H_8 or $H_{8'}$), 1.900 (tdd, J = 14.5, 8.5, 3.5 Hz, 1H, H_8 or $H_{8'}$). ^{13}C NMR (176 MHz, $CDCl_3$): δ 172.4 ($C_{9'}$), 171.8 (C_9), 133.5 (C_5), 128.3 (d, $^3J_{CF}$ = 6.5 Hz, C_6), 125.6 (t, $^1J_{CF}$ = 221.5 Hz, C_7), 52.03 (C_{10} or $C_{10'}$), 52.00 (C_{10} or $C_{10'}$), 45.6 (C_3), 42.0 (d, $^3J_{CF}$ = 6 Hz, C_2), 41.7 (t, $^2J_{CF}$ = 24.5 Hz, C_1), 39.2 (t, $^2J_{CF}$ = 25 Hz, C_8), 34.0 (C_4). ^{19}F NMR (188 MHz, $CDCl_3$): δ −87.35 (dm, $^2J_{FF}$ = 230 Hz), −96.54 (dm, $^2J_{FF}$ = 230 Hz). FTIR (KBr): 1748 (s, C=O), 1212 (m), 1114 (m) cm^{-1}. MS (DCI CH_4) m/z: 261 (MH^+, 11%), 260 (M^+, 15%), 241 (M^+–F, 61%), 229 (M^+–OCH_3, 100%). HRMS (DCI–CH_4) m/z: calcd for $C_{12}H_{14}F_2O_4$ (M^+) 260.0860; found, 260.0857.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.03.009.

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