

perature under argon and added into degassed 5 ml of CDCl_3 (Fluka 31330 or Aldrich 23, 691-8) under argon in darkness and filtered off after 24 hours.

7. CDCl_3 was treated with molecular sieves in the same manner as described in reference 6 except that it was decanted (not filtered). Very small particles of molecular sieves were seen in decanted CDCl_3 .

Unexpected Effect of Fluorine in Diels-Alder Reaction of 2-Fluoroacrolein with Thebaine

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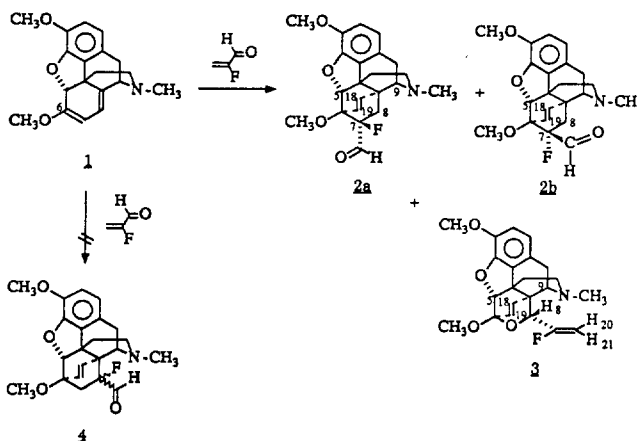
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Although a number of Diels-Alder reactions of thebaine 1 with dienophilic monosubstituted¹⁻³ and 1,2-disubstituted^{4,5} ethylenes have been previously studied, the fact that 7 α -(1-hydroxy-1-methylalkyl)-6,14-endo-ethenotetrahydrooripavines⁶ obtained *via* the chemical transformation of the Diels-Alder adduct prepared from the reaction of thebaine 1 with methyl vinyl ketone have shown the remarkable opioid agonist/antagonist properties has stimulated studies on the Diels-Alder reaction of thebaine 1 with 1,1-disubstituted ethylenes.⁷ However, there has been no report concerning the reaction of thebaine 1 with fluoro-substituted ethylene, which should be convenient tool for the introduction of fluorine into the specific site of thebaine system.

As one of our efforts to obtain morphine alkaloid of biological interest from thebaine 1, we are interested in the introduction of fluorine into thebaine system because fluorine can have profound and unexpected results on biological activity.⁸ Fluorine is the only element which can replace hydrogen without notable steric consequences. Once introduced, carbon-fluorine bond energy renders the substituent relatively resistant to metabolic transformations, and electronegativity of fluorine can have pronounced effects on the electron distribution in molecule, which cause different reaction between nonfluorinated and fluorinated compound.⁹ In this communication we address the fluorine introduction into thebaine system *via* Diels-Alder reaction of thebaine 1 with 2-fluoroacrolein and effect of fluorine in that reaction.

When thebaine 1 was allowed to react with 2-fluoroacrolein (2 eq.), which is prepared from the previous method,¹⁰ in benzene at 50°C for 18 hours, Diels-Alder adduct 2, mp 98-99°C, and hetero Diels-Alder adduct 3, mp 109-109°C, were obtained in 75% and 11% yields, respectively. However, the reaction in acetonitrile resulted in the formation of adducts 2 and 3 in 25% and 15% yields, respectively. There was no formation of regioisomer 4. Diels-Alder adduct 2 is a

88:12 mixture of 7 β -fluorine (2a)/7 α -fluorine (2b) stereoisomers which can not be separated by MPLC or HPLC. Thus, the ratio of these isomers was determined by integration ratio of aldehyde protons of two isomers in ¹H NMR spectrum. The decrease of stereoselectivity in the formation of adduct 2, as compared to that in the reaction of thebaine 1 with acrolein¹, can be rationalized by 1,3-diaxial interaction between C-5 hydrogen and C-7 fluorine atom. The absence of the regioisomeric aldehyde adduct 4 is presumably a result of a combination of steric and electronic effects. C-6 Methoxy polarization of the diene system results in formation of only the C-7 regioisomer 2. One important feature in this reaction is the formation of hetero Diels-Alder adduct 3 which is totally unexpected product.



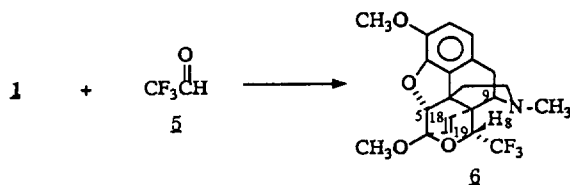
Since the adducts 2a and 2b can not be separated by MPLC or HPLC, the structures of 2a and 2b were also determined on the basis of spectroscopic data of the mixture of stereo-isomers. The MS spectrum showed an intense molecular ion peak at m/e 385 and IR spectrum showed characteristic absorptions at 2750 and 2850 cm^{-1} for aldehyde C-H and 1740 cm^{-1} for C=O group. The ¹H NMR (CDCl_3) spectrum of 2a exhibited characteristic signals of H-5 proton at δ 5.22 (d, $J = 1.0$ Hz), two H-8 protons at δ 1.92 (dd, $J = 21.2, 14.6$ Hz, H-8 α) and 2.91 (dd, $J = 31.7, 14.6$ Hz, H-8 β), H-9 proton at δ 3.23 (d, $J = 4.9$ Hz), two vinyl protons at δ 5.60 (d, $J = 8.7$ Hz, H-18) and 5.78 (ddd, $J = 8.7, 4.5, 1.1$ Hz, H-19), and aldehyde proton at δ 9.52 (d, $J = 8.2$ Hz). The assignment of adduct 2a as the C-7 β fluorine compound rests on the coupling constant between C-8 β proton and C-7 β fluorine, since this type of coupling constant between C-8 β proton and C-7 β fluorine, since this type of coupling constant is usually larger than that between C-8 β proton and C-7 β fluorine ($J_{H\alpha F\beta} = 31.7$ Hz *vs.* $J_{H\alpha F\alpha} = 21.2$ Hz).¹¹ Since C-8 β proton is shifted downfield due to the deshielding effect of the tertiary amine,¹¹ especially, the stereochemistry of adduct 2a can be easily determined. Zigzag coupling ($J = 4.5$ Hz) between H-19 proton and fluorine also indicates that fluorine should be oriented at β -position. The ¹H NMR (CDCl_3) spectrum of 2b also exhibited characteristic signals of H-5 proton at δ 4.69(s), H-8 α proton at δ 1.53 (dd, $J = 31.9, 14.5$ Hz), two vinyl protons at δ 5.61 (d, $J = 8.8$ Hz, H-18) and 6.05 (d, $J = 8.8$ Hz, H-19), and aldehyde proton at δ 9.98 (d, $J = 3.0$ Hz). Other characteristic signals (H-8 β and H-9 proton) of adduct can not be identified because of overlapping with signals of adduct 2a. Upfield shift of signal for

H-5 proton of adduct **2b**, as compared to chemical shift of H-5 proton of adduct **2a**, can be explained by anisotropic shielding effect of carbonyl group, which indicates that aldehyde group on C-7 carbon should be oriented at β -position. This explanation can be reinforced by coupling constant between H-8 proton and C-7 α fluorine ($J_{\text{H}\alpha\text{F}\beta} = 31.9$ Hz). The ^{19}F NMR (CHCl_3) spectrum exhibited signals of C-7 fluorine compound **2b** at $\delta -71.90$ (ddd, $J = 33.8, 19.3, 2.4$ Hz) and C-7 fluorine compound **2a** at $\delta -86.47$ (overlapped ddd), and showed that the integration ratio of their signals (**2a:2b**) was 88:12.

Since there has been no report concerning the hetero Diels-Alder reaction of thebaine **1** with α, β -unsaturated aldehydes or ketones, it is postulated that fluorine plays an important role in the formation of hetero Diels-Alder adduct **3**. Fluorine in 2-fluoroacrolein system probably lowers the energies of the frontier orbitals of the carbonyl group because of electron-withdrawing effect of fluorine and causes to reduce the energy difference between the HOMO of diene and the LUMO of carbonyl dienophile. On the other hand, the energy difference between the HOMO of diene and the LUMO of olefin dienophile is relatively increased because of the mesomeric effect¹² of fluorine toward olefin group. Thus, it is suggested that the opposite effect of fluorine toward two functional groups results in the formation of adduct **3**. The structural proof of the novel adduct **3** was based on the spectroscopic data. The MS spectrum showed an intense molecular ion peak at m/e 385, and IR spectrum showed characteristic absorptions at 1674 and 1628 cm^{-1} for $>\text{C}=\text{C}<$ groups and no absorption for $>\text{C}=\text{O}$ group. The ^1H NMR (CDCl_3) spectrum of **3** showed characteristic signals of H-5 proton at $\delta 4.58$ (d, $J = 1.0$ Hz), two vicinal vinyl protons at $\delta 5.51$ (d, $J = 8.7$ Hz, H-18) and 6.09 (dd, $J = 8.8, 1.2$ Hz, H-19), two geminal vinyl protons at $\delta 4.40$ (ddd, $J = 50.1, 2.8, 1.2$ Hz, H-20) and 4.65 (ddd, $J = 18.5, 2.8, 0.7$ Hz, H-21), H-8 proton at $\delta 5.38$ (d, $J = 4.9$ Hz), and H-9 proton at $\delta 3.54$ (d, $J = 5.0$ Hz). The chemical shifts of the protons at C-8 and C-9 appear to be diagnostic of the stereochemistry of the C-8 substituent in adduct **3** and the regiochemistry of adduct **3**. The down-field shift of H-8 proton ($\delta 5.38$), which is due to deshielding effect of the tertiary amine¹¹, indicates that the proton on C-8 of adduct **3** should be oriented at m -position. The proton on C-9 also is shifted downfield ($\delta 3.54$) due to the deshielding effect of the vinyl group.¹³ The large coupling constant ($J = 50.1$ Hz) of H-20 proton is due to the trans H-F coupling, and relatively small coupling constant ($J = 18.5$ Hz) of H-21 proton is due to the cis H-F coupling.

The isolation of hetero Diels-Alder adduct **3** prompted us to perform the reaction of thebaine **1** with trifluoroacetaldehyde¹⁴ in order to clarify the effect of fluorine in the formation of hetero Diels-Alder adduct **3**. Thus, the reaction of thebaine **1** with trifluoroacetaldehyde **5** (~ 10 eq) in benzene at 50°C for 24 hours provided hetero Diels-Alder adduct **6** in 91% yield. The stereochemistry and regiochemistry of adduct **6** were determined by similar manner as shown in adduct **3**. The ^1H NMR (CDCl_3) spectrum of **6** showed char-

acteristic signals of H-5 proton at $\delta 4.57$ (d, $J = 1.1$ Hz), two vicinal vinyl protons at $\delta 5.60$ (d, $J = 8.8$ Hz, H-18) and 6.15 (d, $J = 8.7$ Hz, H-19), H-8 proton at $\delta 5.23$ (q, $J = 7.7$ Hz), and H-9 proton at $\delta 3.60$ (d, $J = 6.7$ Hz). The ^{19}F NMR (CHCl_3) spectrum of **6** showed one doublet signal ($J = 7.7$ Hz) at $\delta -51.40$ which is due to the coupling between CF_3 group and H-8 proton.



In conclusion, fluorine in the reaction of thebaine with 2-fluoroacrolein affected on distribution of stereoisomers of Diels-Alder adduct and derived a new type of hetero Diels-Alder reaction which was not detected in the reaction of thebaine **1** with acrolein.¹

Further studies on the expansion of the reaction of the reaction of thebaine **1** with fluorinated aldehydes are currently underway.

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