remained for 15 minutes. A portion of the crude material, after evaporation, was dissolved in 0.1 N AcOH and subjected to gel filtration on a column (1.5 × 40 cm) of Sephadex G25 with 0.1 N AcOH. Cation exchange chromatography was done on a carboxymethyl cellulose column (Bio-Rad) eluted with 0.5 M ammonium acetate buffer (pH 7.0) solution. Analytical reverse phase HPLC of the product gave the following results: Retention time; 8.61 min, Purity; 91.1%, Fluent; 0.1 M NaH_2PO_4 (pH 6.9) in 25%MeCN/water, Amino Acid analysis; Ser 0.84 (1), Sar 0.96 (1), Pro 0.96 (1), Ala 1.04 (1), Val 0.90 (1), Tyr 1.82 (2), Phe 0.97 (1).

In conclusion, this type of reaction vessel for SPPS is proved to be another stationary reaction vessel which can be protected from atmospheric moisture. And, the vacuum applied in the reaction vessel can draw the next solvent or reagent into the vessel without inverting the reaction vessel[2,12], which allows for cooling the vessel with simple laboratory cooling system.

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Reaction of Thebaine with Trifluoromethyl Substituted Acetylenic Dienophiles

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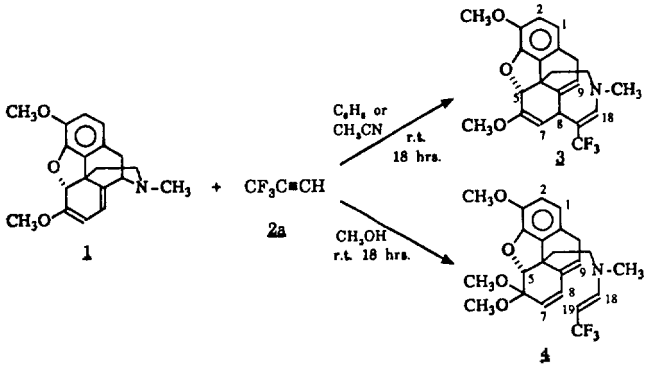
In the search for more potent analgesics, the chemical modification of thebaine **1**, which is too toxic to be used as an analgesic, has been widely performed as one of better approaches.[1] Since thebaine **1** has the electron-rich diene moiety in the cyclic system, especially, a number of Diels-Alder reaction of thebaine **1** with a variety of dienophiles and chemical transformations of the resulting adducts have been extensively studied for a long time. In contrast to the numerous studies on the Diels-Alder reaction of thebaine **1** with olefinic dienophiles,[2-7] there have been a few reports relating the reaction of thebaine **1** with acetylenic dienophiles.[8-10] Rapoport and Sheldrick[8] reported that reaction of thebaine **1** with dimethyl acetylenedicarboxylate (DMAD) in benzene at 50 °C provided the Diels-Alder adduct in 90% yield, while the similar reaction of ethyl propiolate (EP) afforded the Diels-Alder adduct in 6% yield. Recently, Kanematsu[9] and Archer[10] independently found that the addition reactions of thebaine **1** with acetylenic dienophiles remarkably depended on the solvent and provided new 1:1 addition products in polar solvents.

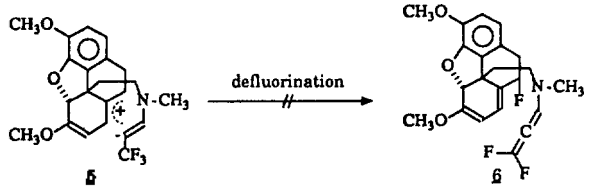
As one of our efforts to obtain morphine alkaloid of biological interest from thebaine **1**, we are interested in the introduction of trifluoromethyl group into the thebaine system *via* reactions of thebaine **1** with trifluoromethyl substituted acetylenic dienophiles because of unique nature of trifluoromethyl group for biological activities. It has been well known that the presence of trifluoromethyl moiety often confers unique properties to a molecule in terms of increased lipophilicity.[11] In this communication we address the reactions of thebaine **1** with trifluoromethyl substituted acetylenic dienophiles **2a-b**, which are easily prepared from the previous methods,[12,13] in nonpolar and polar solvents and also examine the effect of trifluoromethyl group in the reaction.

When thebaine **1** was allowed to react with trifluoropropyne **2a** in benzene at room temperature for 18 hours, only 1:1 addition adduct **3** was obtained in 34% yield: mp 79-80 °C; mass spectrum, *m/e* 405 (M^+); IR (KBr) 1670, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (m, 2H, H-15), 2.94 (s, 3H, NCH_3), 3.19-3.28 (m, 4H, H-10, H-16), 3.57 (s, 3H, 6-OCH_3), 3.84 (s, 3H, 3-OCH_3), 4.52 (d, 1H, H-8, J = 5.0 Hz), 5.00 (s, 1H, H-5), 5.15 (d, 1H, H-7, J = 4.9 Hz), 5.94 (d, 1H, H-9, J = 5.2 Hz), 6.66 (d, 1H, H-1, J = 8.0 Hz), 6.69 (d, 1H, H-2, J = 8.0 Hz) 7.35 (s, 1H, H-18); ^{19}F NMR ($CHCl_3$) -65.52(s). No Diels-Alder adduct was obtained. However, remarkable increase of yield (~95%) for the addition adduct **3** was accomplished by using acetonitrile as a solvent in the reaction. When the same reaction was carried out in methanol as a solvent, methanol-addition adduct **4** was obtained in 60% yield: mp 56-58 °C; mass spectrum, *m/e* 437 (M^+); IR (KBr) 1675, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (m, 2H, H-15), 2.93 (s, 3H, NCH_3), 3.07-3.22 (m, 2H, H-16), 3.28 (dd, 1H, H-10α, J = 6.3, 20.0 Hz), 3.44 (d, 1H, H-10β, J = 19.4 Hz), 3.54 (s, 3H, 6-OCH_3), 3.64 (s, 3H, 6-OCH_3), 3.90 (s, 3H, 3-OCH_3), 4.43 (d, 1H, H-19, J = 12.9 Hz), 4.78 (s, 1H, H-5), 5.61 (d, 1H, H-7, J = 9.9 Hz), 5.95 (d, 1H, H-9, J = 5.0 Hz), 6.61 (d, 1H, H-8, J = 9.9 Hz), 6.66 (d, 1H, H-1, J = 8.1 Hz), 6.70 (d, 1H, H-2, J = 8.1 Hz), 7.34 (d, 1H, H-18, J = 12.9 Hz). ^{19}F NMR spectrum was not taken because the adduct **4** was easily decomposed at room temperature in 24 hours. The coupling constant of the H-18 and H-19 protons (J = 12.9 Hz) indicates that the stereochemistry of double

bond is trans.[14] All reactions were carried out in sealed tube and excess trifluoropropyne was used. Typical reaction procedure is as follow; The heavy wall tube was charged with thebaine (1 g, 3.2 mmol) and solvent such as benzene, acetonitrile or methanol. Excess of trifluoropropyne (bp −40 °C) generated from the reaction of activated zinc (3.6 g, 50 mmol) with 1,1,2-trichloro-3,3,3-trifluoropropene (5 g, 25 mmol)[12] in the presence of zinc chloride (0.34 g, 2.4 mmol) was directly condensed into the heavy wall tube *via* Dry-Ice/Isopropanol condenser. After addition of trifluoropropyne, the heavy wall tube was sealed and the mixture was stirred at room temperature for 18 hours. Removal of solvent, followed by separation *via* chromatotrun or MPLC (hexane: ethyl acetate = 4:1) provided the final product **3** or **4**.

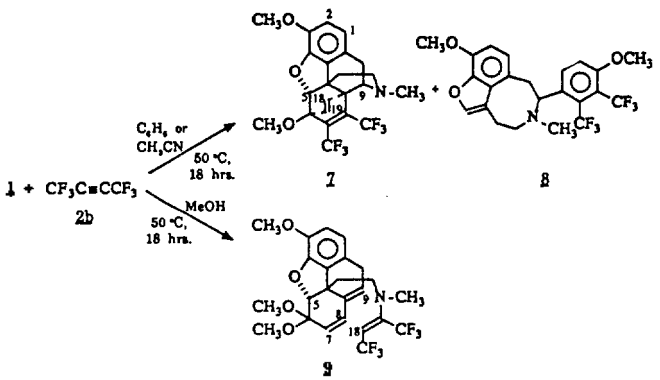


The formation of addition adducts **3** and **4** can be explained by the step-wise mechanism involving ionic species **5** which type of intermediate was suggested by Kanematsu[9b] in the reaction of thebaine with methyl propiolate. Only different thing is that the formed zwitterionic species **5** may undergo cyclization to give **3** or defluorination[15] to give difluoroallene **6**. But the latter was not detected in this reaction.



When thebaine **1** was treated with hexafluoro-2-butyne **2b** in benzene at 50 °C for 18 hours, Diels-Alder adduct **7**, mp 119–121 °C, and retro Diels-Alder adduct **8**, mp 164 °C, were obtained in 38% and 39% yields, respectively, based on the 52% conversion of thebaine **1**. However, the same reaction in acetonitrile provided adducts **7** and **8** in 16% and 24% yields, respectively, based on the 75% conversion of thebaine **1**. The structure of **7** was determined on the basis of its spectroscopic data. The MS spectrum showed an intense molecular ion peak at *m/e* 473 and IR (KBr) spectrum showed absorption at 1630, 1680 cm^{-1}. The ^1H NMR ($CDCl_3$) spectrum exhibited signals at δ 1.78–1.98 (m, 2H, H-15), 2.39 (s, 3H, NCH_3), 2.47–2.57 (m, 3H, H-10 , H-16), 3.30 (d, 1H, H-10β, J = 18.9 Hz), 3.71 (s, 3H, 6-OCH_3), 3.84 (s, 3H, 3-OCH_3), 3.98 (d, 1H, H-9, J = 6.6 Hz), 4.56 (d, 1H, H-5, J = 0.9 Hz), 5.60 (d, 1H, H-18, J = 7.9 Hz), 6.33 (dd, 1H, H-19, J = 1.1, 7.9 Hz), 6.57 (d, 1H, H-1, J = 8.1 Hz), and 6.68 (d, 1H, H-2, J = 8.1 Hz). The ^{19}F NMR ($CHCl_3$) spectrum showed two sets of signals at δ −63.81 (q, J = 13.6 Hz) and −65.09 (q, J = 13.6 Hz), which coupling constant is due to the *cis* coupling between two trifluoromethyl groups attached on two vicinal olefin carbons.[16] The structure of **8** was also determined on the similar manner. The ^1H NMR ($CDCl_3$) spectrum showed signals at δ 1.92 (s, 3H, NCH_3), 2.94 (m, 1H, H-4α), 3.05–3.17 (m, 4H, H-3, H-7), 3.57 (m, 1H, H-4m), 3.89 (s, 3H, 10-OCH_3), 4.00 (s, 3H, 4′-OCH_3), 4.16 (bs, 1H, H-6), 6.44 (d, 1H, H-8, J = 7.9 Hz), 6.59 (d, 1H, H-9, J = 7.9 Hz), 6.97 (bs, 2H, H-2′, H-3′), and 7.42 (s, 1H, H-1). The MS spectrum showed an intense molecular ion peak at *m/e* 473 and IR (KBr) spectrum showed absorption at 1630 cm^{-1}. In the ^1H NMR ($CDCl_3$) spectrum of **8**, the signals for vinyl protons (δ 5.60 and 6.33) and H-5 proton (δ 4.56), observed in adduct **7**, were totally disappeared, while the signals at δ 6.97 and 7.42 were observed. These signals are supposed to be due to the aromatic two protons and α-proton of furan ring of the adduct **8**.[17] No formation of cyclization product in acetonitrile may be rationalize by the steric and electronic factors caused by the second trifluoromethyl group. Isolation of retro Diels-Alder adduct **8** indicates that Diels-Alder adduct **7** can be easily fragmented in nonpolar or polar solvent even at 50 °C. When Diels-Alder adduct **7** was allowed to reflux in benzene or toluene to examine the easy of fragmentation of **7**, conversion to retro Diels-Alder adduct **8** was completed in 30 min. From the fact that the fragmentation of Diels-Alder to retro Diels-Alder adduct usually occurs at high temperature,[8] it is suggested that the trifluoromethyl group plays an important role for the fragmentation of **7** to **8** under mild condition.

However, the use of methanol as a solvent in this reaction provided only methanol-addition adduct **9** in 61% yield based on 75% conversion of thebaine: oil; mass spectrum, *m/e* 505 (M^+); IR (neat) 1630, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 2H, H-15), 2.66 (s, 3H, NCH_3), 2.92 (s, 3H, 6-OCH_3), 3.00–3.25 (m, 2H, H-16), 3.27 (dd, 1H, H-10α, J = 6.2, 20.1 Hz), 3.41 (d, 1H, H-10β, J = 20.2 Hz), 3.54 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 3-OCH_3), 4.54 (q, 1H, H-19, J = 9.1 Hz), 4.76 (s, 1H, H-5), 5.60 (d, 1H, H-7, J = 9.9 Hz), 5.95 (d, 1H, H-9, J = 4.5 Hz), 6.61 (d, 1H, H-8, J = 9.9 Hz), 6.66 (d, 1H, H-1, J = 8.1 Hz), 6.70 (d, 1H, H-2, J = 8.1 Hz); ^{19}F NMR ($CHCl_3$) δ −60.11 (q, 18-CF_3, J = 12.5 Hz), −69.57 (m, 19-CF_3). The coupling constant (J = 12.5 Hz) between trifluoromethyl groups indicates that stereochemistry of double bond bearing two trifluoromethyl groups is *cis*.[16] Typical reaction procedure is same as that of reaction of thebaine **1** with trifluoropropyne. Hexafluorobutyne (bp −12 °C) was prepared from the reaction of 2,3-dichlorohexafluoro-2-butene (2.88



g, 20 mmol) with activated zinc (1.3 g, 20 mmol) in 10 ml of acetic anhydride.[13]

In conclusion, trifluoromethyl group can be easily introduced into thebaine system *via* addition or Diels–Alder reaction which depends on the solvent, and plays an important role for the formation of retro Diels–Alder adduct.

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Resonance Bond–Contraction Demonstrated by Cross-Interaction Constants

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The cross interaction constants ρ_{ij} in eq. (1) have been shown to be a very versatile tool for characterizing transition state (TS) structures, especially in S_N2 reactions.[1] We present here a novel application of the cross-interaction constants to demonstration of resonance contraction of a bond in the S_N2 TS.

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \tag{1}$$

The sign of ρ_{ij} provides criteria for predicting substituent effects on the TS variation in S_N2 reactions.[1c,e] For example, if ρ_{XZ} is negative (Scheme 1), a stronger nucleophile ($X = p$-OCH_3) as well as a stronger nucleofuge ($Z = p$-NO_2) leads to a later TS so that eqs. (2) apply, whereas if ρ_{XZ} is positive the

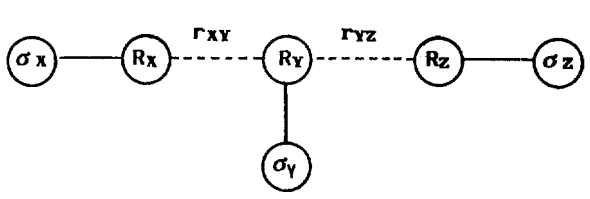
$$\left.\begin{aligned} \Delta r_{YZ} &= a\sigma_X \qquad a<0 \\ \Delta r_{XY} &= a'\sigma_Z \qquad a'<0 \end{aligned}\right\} \tag{2}$$

opposite effects are predicted so that the signs of a and a' in Eqs. (2) reverse to positive.[1c,e,2] On the other hand, the distance r_{ij} in Scheme 1 is shown to be a logarithmic inverse function of the magnitude of ρ_{ij}[2,3] so that another set of relations are obtained with positive constants, b and b', for

$$\left.\begin{aligned} \Delta\log|\rho_{YZ}| &= b\sigma_X \qquad b>0 \\ \Delta\log|\rho_{XY}| &= b'\sigma_Z \qquad b'>0 \end{aligned}\right\} \tag{3}$$

$\rho_{XZ}<0$, which reverse to negative (b, $b'<0$) for $\rho_{XZ}>0$.

In our previous works, it has been shown that the S_N2 reaction of anilines with benzyl benzenesulfonates, reaction (I)[4], belongs to the former category *i.e.*, $\rho_{XZ}<0$ with negative a (a') and positive b (b'), whereas that with phenacyl benzenesulfonates, reaction (II),[1c] belongs to the latter type, *i.e.*, $\rho_{XZ}>0$ with positive a (a') and negative b (b').



$i, j = X, Y$ or Z in eq. (1); $r_{XZ} + r_{YZ}$. σ_i and R_i are substituents and reaction centers in the nucleophile (X), substrate (Y) and leaving group (Z).

Scheme 1