The Stereochemical Course of Nucleophilic Additions of 2-Trialkylsiloxyfurans to Cyclic *N*-Acyliminium Ions

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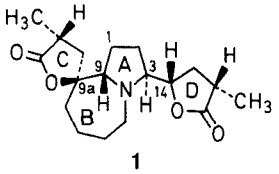
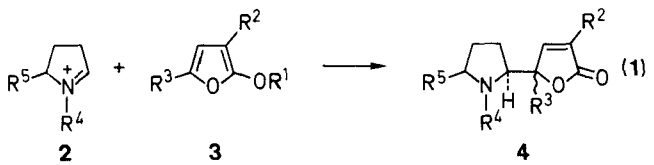
The additions of 2-(trimethylsiloxy)furan **(5)** and 2-(*tert*-butyldimethylsiloxy)-3-methylfuran **(6)** to the cyclic *N*-acyliminium ion generated upon treatment of 1-benzyloxycarbonyl-2-ethoxypyrrolidine **(7)** with diethyl ether–boron trifluoride complex afforded mixtures of adducts *threo*-**8**/*erythro*-**8** and *threo*-**9**/*erythro*-**9**, respectively, in which the threo diastereoisomers dominated by ratios of 8.5–6:1.

The Mannich reaction together with its numerous variants involves the nucleophilic addition of electron-rich olefins to *N*-acyl(alkyl)iminium salts and as such constitutes a powerful and broadly exploited tactic for the construction of new carbon–carbon bonds alpha to a nitrogen atom.[1] As part of a program directed toward the total synthesis of croomine **(1)**,[2] which is a representative member of the *Stemona* family of alkaloids, it occurred to us that the nucleophilic additions of substituted furans **3** to cyclic acyliminium ions **2** to give adducts **4** according to eq. 1 might constitute an efficacious solution to the problem of rapidly assembling the array of A, C, and D rings of croomine. Although the union of the A and D rings would entail a bimolecular process for the construction of the C(3)–C(14) bond, the C(9)–C(9a) bond could be formed by either an inter- or intramolecular reaction. Examination of the literature provided a measure of confidence that the addition reaction itself was feasible.[3–6] However, since the relative stereochemical outcome at the two newly constructed centers could not be confidently predicted on the basis of extant knowledge, we embarked on a simple model study to address this issue. We now report the results of these initial investigations.



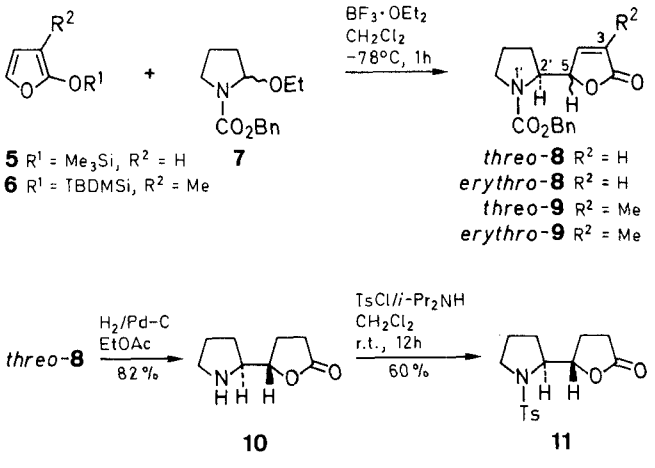
1



2 **3** **4** (1)

The addition of 2-(trimethylsiloxy)furan **5** to the acyliminium ion generated in situ from the reaction of 1-benzyloxycarbonyl-2-ethoxypyrrolidine[7] **(7)** with diethyl ether–boron trifluoride complex ($BF_3 \cdot OEt_2$) at −78 °C proceeded smoothly to give a separable mixture (5:1) of the adducts *threo*-**8** and *erythro*-**8** in 79% isolated yield (Scheme). The diastereoisomeric ratios were determined by integration of peaks in the ^1H NMR, since equilibration of the adducts occurred upon separation by capillary gas chromatography. For example, integration of the peaks obtained by capillary GLC analysis of *threo*-**8** that was homogeneous by ^1H NMR gave an "apparent" ratio of *threo*-**8**/*erythro*-**8** of 1.9:1. To ensure that the adducts *threo*-**8** and *erythro*-**8** did not equilibrate under the conditions of the reaction, they were independently exposed to $BF_3 \cdot OEt_2$ in dichloromethane at −78 °C in the presence of added chlorotrimethylsilane; there was no evidence of interconversion. On the other hand, equilibration of *threo*-**8**- and *erythro*-**8** could be induced upon treatment with triethylamine and 4-dimethylaminopyridine in dichloromethane.

Although there were features in the ^1H and ^{13}C NMR spectra of *threo*-**8** and *erythro*-**8** that would ultimately prove diagnostic in making structural assignments of related compounds (*vide infra*), it was not possible to use these data alone to firmly establish their respective structures. Therefore, the assignment of relative stereochemistry of the major adduct *threo*-**8** was unequivocally established by transformation into the crystalline sulfonamide derivative **11** by reduction by catalytic hydrogenation to afford **10** followed by *N*-tosylation. X-ray crystallographic analysis of **11** then established the threo-relationship between the two newly created stereogenic centers.[8] It is relevant to recognize that the relative stereochemistry between C(3) and C(14) and also between C(9) and C(9a) in croomine is also threo.



5 R^1 = Me_3Si, R^2 = H
6 R^1 = TBDMSi, R^2 = Me
7
threo-**8** R^2 = H
erythro-**8** R^2 = H
threo-**9** R^2 = Me
erythro-**9** R^2 = Me

10 **11**

Scheme

Since croomine possesses methyl groups on each of the C and D lactone rings, we were interested to see whether 2-(*tert*-butyldimethylsiloxy)-3-methylfuran[9] **(6)** would add to the *N*-acyliminium salt derived from **7** with similarly high stereoselectivity. In the event, reaction of **6** and **7** in the presence of $BF_3 \cdot OEt_2$ furnished an inseparable mixture (6:1) of *threo*-**9** and *erythro*-**9** in 76% yield; no reaction occurred in the absence of Lewis acid. The

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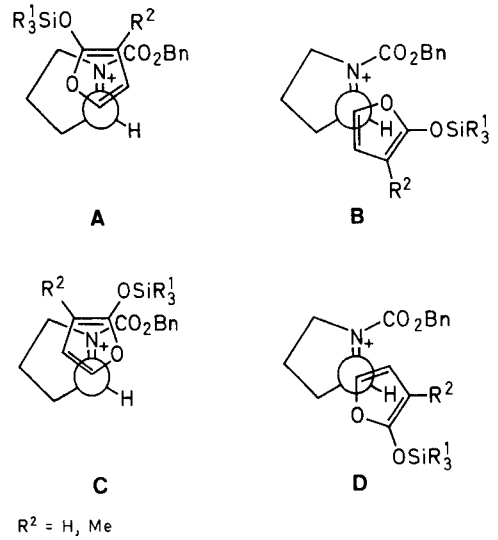
relative stereochemistry assigned to adducts *threo*-**9** and *erythro*-**9** was based upon comparison of their ^1H and ^{13}C NMR spectra with those of compounds *threo*-**8** and *erythro*-**8**. Specifically, there appears to be a trend in which the ^{13}C chemical shifts of C-5 are further downfield in the threo-adducts than in the corresponding erythro-adducts, whereas the ^{13}C chemical shift of C-2′ is further upfield in the threo-adduct. Also, the ^1H chemical shift of the proton on C-2′ is further downfield in the threo-adducts than in the erythro-adducts.

The observed diastereoselectively in the nucleophilic additions of **5** and **6** to the *N*-acycliminium salt generated from **7** is consistent with that observed in other acid-catalyzed additions of 2-trialkylsiloxyfurans to various electrophiles to give preferentially threo-adducts.[3-6] Formation of the major products *threo*-**8** and *threo*-**9** from the addition of siloxyfurans **5** and **6** to the acyl iminium salt derived from **7** can arise from either transition state **A** or **B**, whereas the minor products *erythro*-**8** and *erythro*-**9** would be produced via the alternative transition states **C** or **D**. For related reactions, it has been suggested that transition state **A** should be preferred since it is "Diels–Alder like" with the silyoxyfuran having favorable orbtal overlap with the π-system of the acyliminium ion.[10] However, antiperiplanar transition states such as **B** have also been favorably considered in Lewis acid catalyzed additions to aldehydes and imines,[11] and it is not presently possible to distinguish between these two explanations. Studies are in progress in an effort to clarify the origins of the observed diastereoselectivity in the additions of 2-trialkylsiloxyfurans to cyclic acyl iminium salts.



Having thus established that the addition of 2-trialkylsiloxyfurans **5** and **6** to five-membered, cyclic *N*-acyliminium ions occurs with a significant degree of diastereoselection to give threo-adducts, it remains to apply this discovery to the formulation of a novel entry to alkaloids of the *Stemona* family. The results of these investigations will be reported in due course.

***rel*-(*S*)-5-[(*S*)- and *rel*-(*R*)-5-[(*S*)-1′-Benzyloxycarbonyl-2′-pyrrolidinyl]furan-2(5*H*)-one [*threo*- and *erythro*-1-Benzyloxycarbonyl-2-(2,5-dihydro-5-oxo-2-furyl)pyrrolidine] (*threo*- and *erythro*-8):**

To a solution of 7[7] (0.99 g, 4.0 mmol) in dry CH_2Cl_2 (8 mL) at −78 °C was sequentially added 2-trimethylsiloxyfuran (**5**, 0.75 g, 4.8 mmol) and then $BF_3 \cdot OEt_2$ (0.57 g, 0.49 mL, 4.0 mmol). The clear, yellow solution was stirred for 1 h at −78 °C, whereupon the reaction was quenched at −78 °C by the addition of sat. aq $NaHCO_3$ (5 mL). The cooling bath was removed, and the reaction was allowed to warm to r.t.. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. aq $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The clear yellow oil was filtered through a short plug of silica gel to remove polar impurities (40% EtOAc in hexane) to afford 0.91 g (79%) of a mixture (8.5:1) containing only the adducts *threo*-**8** and *erythro*-**8** as a colorless oil. Analytical samples of each diastereomer were obtained by preparative HPLC (30% EtOAc in hexane) using four 30 cm Porasil A columns.

rel-(S)-1-Benzyloxycarbonyl-2-[(S)-2,5-dihydro-5-oxo-2-furyl]pyrrolidine (threo-8):

^1H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, J = 5.6 Hz, 1 H, C(4)H),7.25–7.50 (complex, 5 H, C(4″)H, C(5″)H, and C(6″)H), 5.97 (dd, J = 5.6, 2.0 Hz, 1 H, C(3)H), 5.15–5.23 (m, 1 H, C(5)H), 5.02–5.08 (complex, 2 H, C(3″)H), 4.32–4.34 (br d, 1 H, C(2′)H), 3.33–3.56 (complex, 2 H, C(5′)H), 1.95–2.08 (complex, 2 H, C(4′)H and C(3′)H), 1.76–1.92 (complex, 2 H, C(3′)H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0 (C(2)), 155.5 (C(1″)), 154.6 (C(4)), 136.4 (C(3a″)), 128.6 (C(6″)), 128.4 (C(4″)), 127.6 (C(5″)), 120.9 (C(3)), 85.1 (C(5)), 66.9 (C(3″)), 58.0 (C(2′)), 47.1 (C(5′)), 27.4 (C(3′)), 24.1 (C(4′)).

IR (neat): ν = 3500, 2970, 2900, 1760, 1700 cm^{-1}.

MS: (CI): m/z = 288, 204 (base), 175, 160.

HRMS: m/z (M^+) calcd for $C_{16}H_{18}NO_4$ 288.1236, found 288.1254.

rel-(S)-1-Benzyloxycarbonyl-2-[(R)-2,5-dihydro-5-oxo-5-furyl]pyrrolidine (erythro-8):

^1H NMR (250 MHz, $CDCl_3$): δ = 7.48 (d, J = 5.8 Hz, 1 H, C(4)H), 7.32–7.36 (complex, 5 H, C(4″)H, C(5″)H, and C(6″)H), 6.17 (d, J = 5.8 Hz, 1 H, C(3)H), 5.45 (br s, 1 H, C(5)H), 5.08–5.26 (complex, 2 H, C(3″)H), 4.05–4.09 (m, 1 H, C(2′)H), 3.48–3.52 (complex, 2 H, C(5′)H), 1.60–2.04 (complex, 4 H, C(4′)H and C(3′)H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.7 (C(2)), 155.0 (C(1″)), 154.8 (C(4)), 128.8 (C(3a″)), 128.6 (C(6″)), 128.1 (C(4″)), 127.9 (C(5″)), 122.1 (C(3)), 83.2 (C(5)), 67.1 (C(3″)), 59.0 (C(2′)), 46.7 (C(5′)), 25.1 (C(3′)), 24.2 (C(4′)).

MS (CI): m/z = 288, (base), 204.

HRMS: m/z (M^+) calcd for $C_{16}H_{18}NO_4$ 288.1236, found 288.1246.

***rel*-(*S*)-5-[(*S*)- and *rel*-5-[(*S*)-1′-Benzyloxycarbonyl-2′-pyrrolidinyl]-3-methylfuran-2(5*H*)-one [*threo*- and *erythro*-1-Benzyloxycarbonyl-2-(2,5-dihydro-4-methyl-5-oxo-2-furyl)pyrrolidine] (*threo*- and *erythro*- 9):**

To a solution of **7** (0.32 g, 1.3 mmol) in dry CH_2Cl_2 (1.5 mL) at −78 °C was added sequentially furan **6** (0.33 g, 1.55 mmol) and then $BF_3 \cdot OEt_2$ (0.18 g, 0.16 mL, 1.3 mmol). After 1 h at −78 °C, the reaction was quenched and worked up as above to give 0.30 g (76%) of a mixture (6:1) of the adducts *threo*-**9** and *erythro*-**9** as a colorless oil. These diastereomers could not be separated by HPLC chromatography.

rel-(S)-1-Benzyloxycarbonyl-2-[(S)- and rel-(S)-1-Benzyloxycarbonyl-2-[(R)-2,5-dihydro-4-methyl-5-oxo-2-furyl]pyrrolidine (threo-9 and erythro-9):

^1H NMR (500 MHz, DMSO-d_6, 100 °C): δ = 7.19–7.44 (complex, 6.0 H, C(5)H, C(4′)H, C(5′)H, and C(6′)H), 5.03–5.18 (complex, 3.0 H, C(3′)H and C(4b)H), 4.25 (dt, J = 8.4, 3.3 Hz, 0.7 H, C(4a)H), 4.04–4.06 (m, 0.1 H, C(4a)H), 3.41–3.49 (m, 1.0 H, C(2)H), 3.24–3.36 (m, 1.1 H, C(2)H), 1.95–2.08 (m, 0.9 H, C(4)H), 1.67–1.89 (complex, 5.3 H, C(3)H, C(4)H, and C(6)-CH_3).

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^{13}C NMR for *threo*-**9** (125 MHz, DMSO-d_6, 100°C): δ = 172.6 (C(7)), 153.9 (C(1')), 147.0 (C(5)), 136.4 (C(3a')), 128.2 (C(6)), 127.8 (C(6')), 127.2 (C(4')), 126.9 (C(5')), 81.3 (C(4b)), 65.7 (C(3')), 57.3 (C(4a)), 46.3 (C(2)), 25.9 (C(4)), 23.0 (C(3)), 9.3 (C(6)-CH_3); ^{13}C-NMR for *erythro*-**9** (125 MHz, DMSO-d_6, 100°C): δ = 172.8 (C(7)), 153.7 (C(1')), 147.3 (C(5)), 136.4 (C(3a')), 128.6 (C(6)), 127.7 (C(6')), 127.3 (C(4')), 126.8 (C(5')), 80.3 (C(4b)), 65.2 (C(3')), 58.2 (C(4a)), 46.1 (C(2)), 26.0 (C(4)), 22.9 (C(3)), 9.5 (C(6)-CH_3).

IR (neat): ν = 3480, 2940, 1750, 1680 cm^{-1}.

MS (CI): m/z = 302 (base), 204, 160.

HRMS: m/z (M^+) calcd for $C_{17}H_{20}NO_4$ 302.1392, found 302.1378.

rel-(*S*)-2-[(*S*)-Tetrahydro-5-oxo-2-furyl]pyrrolidine (10):
A solution of *threo*-**8** (75 mg, 0.26 mmol) in EtOAc (3 mL) containing 10% Pd-C (28 mg) was stirred under H_2 (1 atm) overnight (2 h). The catalyst was removed by filtration through Celite, and the filter pad was washed with MeOH (30 mL). The combined filtrates were concentrated under reduced pressure to afford an oil which solidified under high vacuum to yield 18 mg (82%) of **10** as a white solid; mp 87–89°C.

^{1}H NMR (500 MHz, DMSO-d_6/$CDCl_3$ (1:1)): δ = 4.01 (dt, J = 4.1, 3.8, 2.2 Hz, 1 H, C(5)H), 3.27–3.44 (complex, 3 H, C(5')H, C(2')H), 2.36–2.45 (m, 1 H, C(3)H), 2.13–2.23 (m, 1 H, C(3)H), 1.93–1.99 (m, 1 H, C(4)H), 1.70–1.90 (complex, 4 H, C(6)H, C(5)H, C(4)H), 1.61–1.67 (m, 1 H, C(4')H).

^{13}C NMR (90.8 MHz, $CDCl_3$): δ = 169.0 (C(2)), 63.6 (C(5)), 62.5 (C(2')), 45.3 (C(5')), 28.4 (C(4)), 27.6 (C(3')), 26.1 (C(3)), 22.0 (C(4')).

MS (CI): m/z = 156 (base)

HRMS: m/z (M^+) calcd for $C_8H_{13}NO_2$ 155.0946, found: 155.0946.

rel-(*S*)-2-[(*S*)-Tetrahydro-5-oxo-2-furyl]-1-tosylpyrrolidine (11):
A solution of **10** (41 mg, 0.26 mmol) in anhydr. CH_2Cl_2 (2 mL) containing diisopropylethylamine (41 mg, 55 µL, 0.31 mmol) and TsCl (59 mg, 0.31 mmol) was stirred overnight (12 h). The mixture was diluted with CH_2Cl_2 (30 mL), and the organic phase was washed with sat. aq $NaHCO_3$ (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow oil which was purified by flash chromatography (50% EtOAc in hexane) to afford 48 mg (60%) of **11** as a while solid; mp 103–105°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.1 Hz, 2 H, C(aromatic) H), 7.31 (d, J = 8.1 Hz, 2 H, C(aromatic)H), 4.67–4.70 (m, 1 H, C(5')H), 3.94 (dt, J = 8.8, 3.5 Hz, 1 H, C(2)H), 3.29–3.34 (complex, 2 H, C(5)H), 2.65–2.70 (m, 1 H, C(3')H), 2.44–2.54 (complex, 2 H, C(4')H and C(3')H), 2.41 (s, 3 H, N(1)$SO_2C_6H_5CH_3$), 2.27–2.33 (m, 1 H, C(4')H), 1.81–1.88 (m, 1 H, C(4)H), 1.73–1.80 (m, 1 H, C(3)H), 1.55–1.63 (m, 1 H, C(3)H), 1.28–1.34 (m, 1 H, C(4)H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1 (C(2')), 144.0 (C(aromatic)CH_3), 134.1 (C(aromatic)SO_2N(1')), 129.9 (C(aromatic)), 127.6 (C(aromatic), 82.5 (C(5')), 61.7 (C(2')), 50.0 (C(5)), 28.3 (C(3')), 28.0 (C(3)), 24.3 (C(4)), 23.8 (C(4')), 21.5 (N(1')$SO_2C_6H_5CH_3$).

MS (CI): m/z = 310 (base), 224154.

HRMS: m/z (M^+) calcd for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1113.

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(8) Compound **11** formed orthorhombic crystals, Pca2^1 [a = 25.62(4); b = 6.168(3); c = 19.328(8)]. The final R value was 0.0473 for 1547 reflections [$F_0 \geq 6(\sigma(F_0)$]. Further details will be published independently. See: Lynch, V.M.; Corbett, J.W.; Martin, S.F.; Davis, B.E. *Acta Cryst.* submitted.
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