Tetrahedron Letters, Vol.32, No.30, pp 3635-3638, 1991
Printed in Great Britain

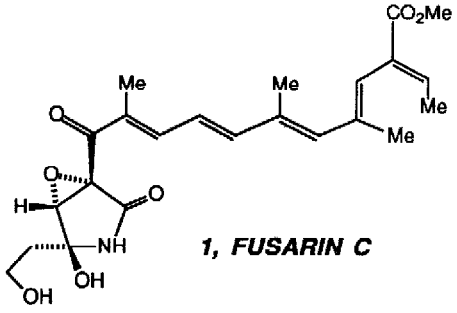
0040-4039/91 $3.00 + .00
Pergamon Press plc

# SYNTHESIS OF TRI-SUBSTITUTED FURANS: MILD Ti(IV)-MEDIATED COUPLINGS TO ACETALS. CONSTRUCTION OF THE EPOXY HEMI-AMIDO KETAL OF FUSARIN C+

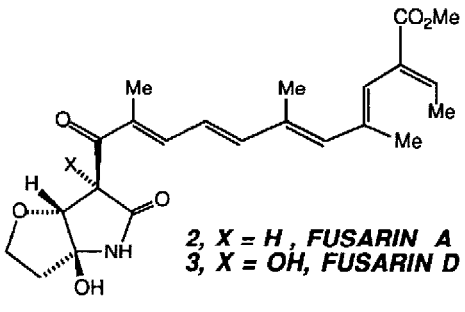
*Robert M. Williams* and Christopher S. Esslinger*
*Department of Chemistry, Colorado State University*
*Fort Collins, Colorado 80523*

**Summary:** *Coupling of β-keto amides and β-keto esters to 2-alkoxy methyl furanosides with $TiCl_4$ directly furnishes tri-substituted furans. The epoxy hemi-amido ketal ring system of fusarin C is constructed in two steps using this methodology.*

As part of a program directed toward the construction of the mutagenic mold metabolites fusarins A-D (**1-3**),[1] it was envisioned that coupling of β-ketoamide **4** with furanone **5** would yield after rearrangement (**6** → **7**), the key heterocycle[2] **8**. Oxidation of this system should provide access to the heterocyclic portions of **1** and **3** (**9** and **10** where X = OH) whereas, intramolecular conjugate addition should furnish the bicyclic heterocycle **10** (where X = H) corresponding to **2** (Scheme 1). As a direct result of investigating this strategy, we wish to report a mild and simple synthesis of tri-substituted furans *via* the direct coupling of β-keto esters and β-keto amides with acetals mediated by $TiCl_4$.




**1, FUSARIN C**

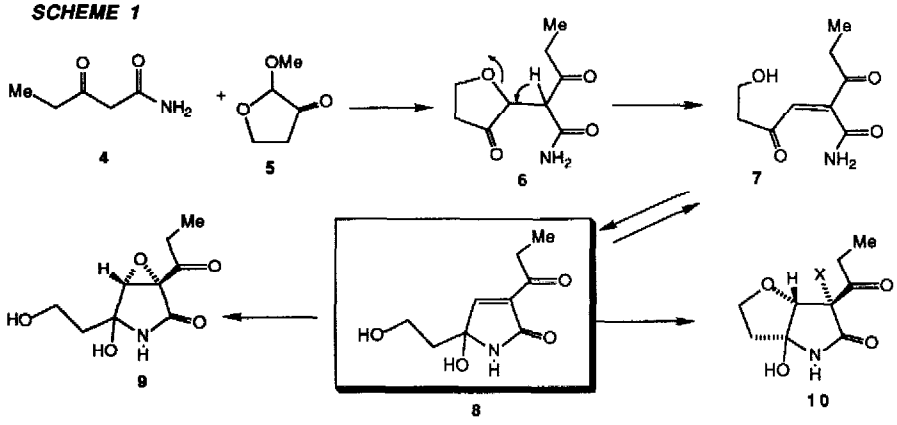



**2, X = H , FUSARIN A**
**3, X = OH, FUSARIN D**

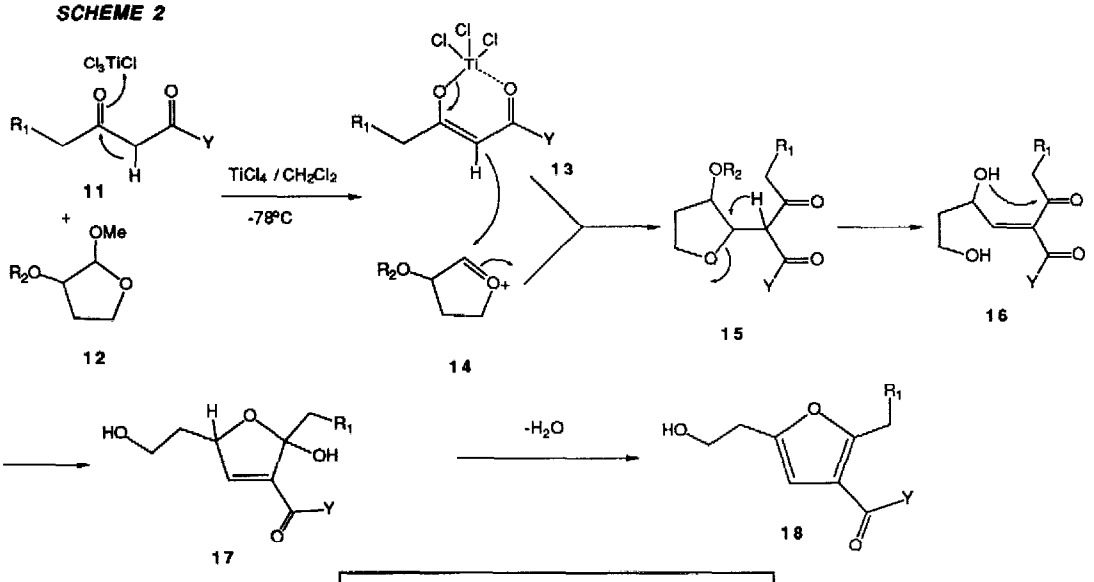
As shown in Scheme 2, coupling of the active methylene derivatives **11** with the cyclic methyl acetals **12** in $CH_2Cl_2$ at -78°C in the presence of $TiCl_4$[3] directly affords the furans **18** (Scheme 2).[4,5] It is quite reasonable[6] that substrates **11** complex with $TiCl_4$ with loss of HCl to generate the titanium enolates **13**. Concomitant Lewis acid activation of the acetals should generate the reactive oxonium species **14** which couple to **13** furnishing the initial adducts **15**. Lewis acid-assisted elimination of the β-alkoxy substituent from **15** furnishes enone **16** which cyclizes *via* the E-olefin geometry to **17**. It is not known if there is any stereocontrol with respect to the olefin geometry of incipient **16**; it is reasonable to expect however, that under the strongly Lewis-acidic coupling conditions, that any Z-olefin would isomerize to the E-isomer and immediately cyclize. Subsequent loss of water

+ This paper is dedicated to Professor Harry H. Wasserman on the occaision of his 70th birthday

**SCHEME 1**



**SCHEME 2**



| | $R_1$ | Y | $R_2$ (11) | 18 (% Yield) |
|---|---|---|---|---|
| a | H | $NH_2$ | $SiMe_2$t-Bu | 80 |
| b | Me | $NH_2$ | $SiMe_2$t-Bu | 84 |
| c | H | OEt | $SiMe_2$t-Bu | 59 |
| d | Me | OMe | H | 76 |
| e | H | OEt | H | 87 |

provides the observed furan products **18**. The structure of these materials were unambiguously corroborated through single crystal x-ray analysis of **18a** (where Y = $NH_2$ and $R_1$ = H).[8]

All of our attempts presently, to effect the direct coupling of furanone[7] **5** with **11** have produced products of undetermined structure. Utilizing the lower oxidation state inherent in **12** however, has allowed for the stepwise entry to the epoxy hemi-amido ketal ring system of fusarin C. Thus, oxidation of **18b** with m-CPBA in $CH_2Cl_2$

provides an equilibrium mixture of carbinolamines **20** and **21**[9] (2:1, 21% overall) presumably *via* **19**[10] (Scheme 3). Furthermore, **20** and **21** interconvert under the following conditions: pure **20** in $CDCl_3$, r.t., 2 weeks gives **20** : **21** in a 2:1 ratio; treatment of pure **21** with 10% aqueous $Na_2CO_3$, r.t., 30 min gave exclusively **20** (90% isolated); treatment of **20** with 0.5 M HCl followed by resilylation gave exclusively **21** (85% isolated).[11] The structures of **20** and **21** were confirmed by extensive 2D NMR, IR, elemental analysis and comparison of key spectroscopic data for compound **20** which correlate well with that reported for fusarin C (Table 1).[1a] The relative stereochemical assignments for **20** and **21** were made based on significant differences in the NOE behavior for the C-3 methine and C-4-OH group between these isomers .[11]Utilization of this heterocycle for the synthesis and biomechanistic studies on the mutagenicity of the fusarins is under study in these laboratories.

***SCHEME 3***

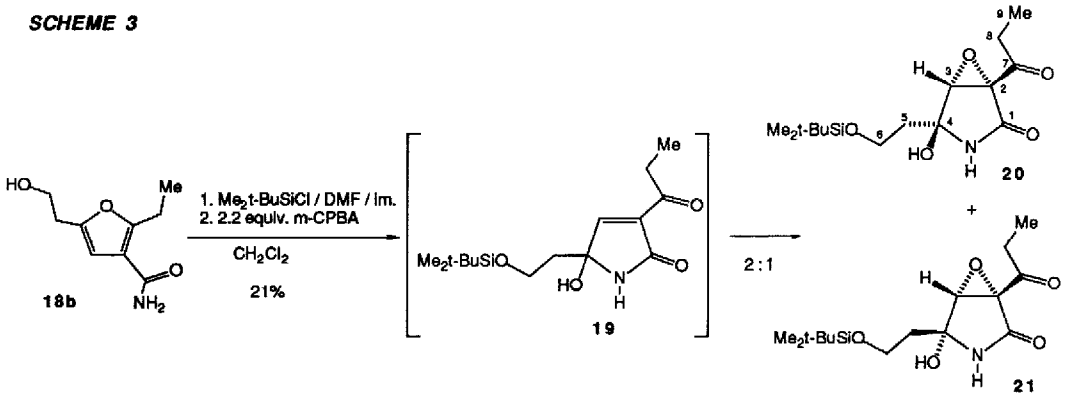



**Table 1.** NMR data[a] for **20** and related literature data for Fusarin C[1a]

| | **20** | | | | | **Fusarin C** | | | |
|---|---|---|---|---|---|---|---|---|---|
| Carbon atom[b] | δC[c]/ppm | $J(^{13}CH)$/Hz | δH[d]/ppm | $J$(HH)/Hz | Lit[1a] | δC/ppm | $J(^{13}CH)$/Hz | δH/ppm | $J$(HH)/Hz |
| 1 | 168.47Sd | --- | --- | --- | | 170.27S | --- | --- | --- |
| 2 | 60.70Sd | --- | --- | --- | | 62.17Sd | --- | --- | --- |
| 3 | 65.56Dd | 199.9 | 4.071d | 2.5 | | 64.15Dd | 197.1 | 4.061d | 2.1 |
| 4 | 84.76Sm | --- | --- | --- | | 85.92S | --- | --- | --- |
| 5 | 36.27Ts | 127.8 | 2.042ddd | 14.5, 5.0, 4.0 | | 36.27T | 128.5 | 2.113ddd | 14.6, 8.3, 4.1 |
| | | | 1.945ddd | 14.5, 6.0, 4.5 | | | | 2.059ddd | 14.6, 6.0, 3.7 |
| 6 | 59.01Ts | 143.5 | 3.985ddd | 11.5, 6.0, 4.0 | | 58.77Tt | 144.0 | 4.050ddd | 11.1, 8.3, 3.7 |
| | | | 3.891ddd | 11.5, 5.0, 4.5 | | | | 3.935ddd | 11.1, 6.0, 4.1 |
| 7 | 201.32Sd | --- | --- | --- | | 190.17Sm | --- | --- | --- |
| 8 | 32.90Td | 126.0 | 2.576q | 7.2 | | 133.90S | --- | --- | --- |
| 9 | 6.66Qd | 124.5 | 1.035t | 7.2 | | 11.55Qd | 128.6 | 1.981d | 1.3 |

[a] Recorded on a Bruker AC300P NMR spectrometer. [b] Numbering of carbon atoms for **21** and **1** are arbitrarily taken from that depicted for **21** in Scheme 3. [c] Relative to $CDCl_3$ δ 77.00. [d] Relative to $CDCl_3$ δ 7.240.

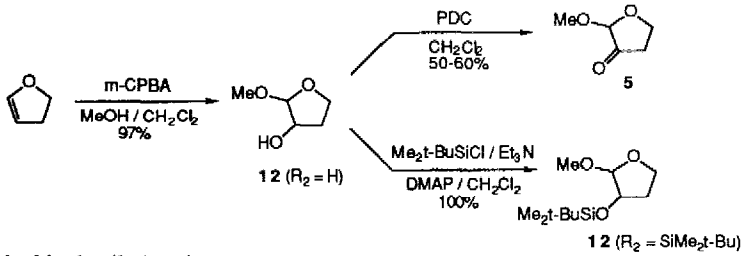
**Acknowledgement.** We are indebted to the Colorado State University Agricultural Experiment Station (part of Western Regional Project W-122) for financial support of this work. Professor Oren P. Anderson is acknowledged for solving the x-ray crystal structure. We also wish to thank Professor Raymond L. Funk for communicating similar Ti(IV) couplings prior to publication; see also ref. 3j.

## References and Footnotes

1. (a) Gelderblom, W.C.A.; Marasas, W.F.O.; Steyn, P.S.; Thiel, P.G.; van der Merwe, K.J.; van Rooyen, P.H.; Vleggaar, R.; Wessels, P.L. *J. Chem. Soc., Chem. Comm.* (1984) 122. (b) Gelderblom, W.C.A.; Thiel, P.G.; Marasas, W.F.O.; van der Merwe, K.J. *J. Agric. Food Chem.* (1984) **32**, 1064. (c)

Gaddamidi, V.; Bjeldanes, L.F.; Shoolery, J.N. *J. Agric. Food Chem.* (1985) **33**, 652. (d) Farbert, J.M.; Sanders, G.W. *J. Agric. Food Chem.* (1986) **34**, 963. (e) Thiel, P.G.; Gelderblom, W.C.A.; Marasas, W.F.O.; Nelson, P.E.; Wilson, T.M. *J. Agric. Food Chem.* (1986) **34**, 773.

2. For relevant synthetic work on a closely related heterocycle contained in cerulenin, see: (a) Corey, E.J.; Williams, D.R. *Tetrahedron Lett.* (1977) 3847. (b) Jakubowski, A.A.; Guziec, F.S.; Tishler, M. *Tetrahedron Lett.* (1977) 2399. (c) Boeckman, R.K.; Thomas, E.W. *J. Am. Chem. Soc.* (1977) **99**, 2805. (d) Pietraszkiewicz, M.; Sinay, P. *Tetrahedron Lett.* (1979) 4741. (e) Ohta, T.; Tsuchiyama, H.; Nozoe, S. *Heterocycles* (1986) **24**, 1137.
3. For related Lewis acid mediated couplings to acetals, see: (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* (1980) **102**, 3248. (b) Ishihara, K.; Yamamoto, H.; Heathcock, C.H. *Tetrahedron Lett.* (1989) **30**, 1825. (c) Lee, T.V.; Boucher, R.J.; Ellis, K.L.; Richardson, K.A. *Tetrahedron Lett.* (1988) **29**, 685. (d) Fleming, I.; Iqbal, J.; Krebs, E-P. *Tetrahedron* (1983) **39**, 841. (e) Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* (1988) **110**, 6556. (f) Stossel, D.; Chan, T.H. *J. Org. Chem.* (1988) **53**, 4901. (g) Heathcock, C.H.; Davidsen, S.K.; Hug, K.T.; Flippin, L.A. *J. Org. Chem.* (1986) **51**, 3027. (h) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chemistry Lett.* (1987) 491. (i) Kawai, M.; Onaka, M.; Izumi, Y. *Chemistry Lett.* (1986) 1581. (j) Funk, R.L.; Daily, W.J.; Olmstead, T.A.; Jellison, K.M. 1989 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December, 1989. Division of Organic Chemistry Abstract #0010.
4. General experimental procedure: A flame dried 50 mL round bottom flask equipped with magnetic stirring bar was charged with 225 mg (1.94 mmol, 1.1 equiv) propionylacetamide, 410 mg silyl furanol derivative (**12**, $R_2$ = $SiMe_2$t-Bu) (1.76 mmol, 1.0 equiv) and 25 mL dry $CH_2Cl_2$. The reaction mixture was chilled to -78°C under argon followed by addition of $TiCl_4$ (410 mg, 2.28 mmol, 1.3 equiv) *via* syringe. The reaction was stirred at -78°C for 1 h, then allowed to warm to room temperature over 1 h. The reaction was then quenched by addition of 15 mL MeOH and allowed to stir for another hour. The reaction mixture was concentrated *in vacuo* and chromatographed 3:1:4 EtOAc/MeOH/$CH_2Cl_2$ PTLC 20 cm x 20 cm x 2 mm to give 247 mg of **18** ($R_1$ = Me, Y = $NH_2$) as a white solid (84%) (Recryst. EtOAc/hexanes) m.p. 118°C (uncorrected).
5. All new compounds gave satisfactory $^1H$ NMR, IR, HRMS or combustion analytical data.
6. Antonioletti, R.; Bonadies, F.; Scettri, A. *J. Org. Chem.* (1988) **53**, 5540.
7. The synthesis of furanone **5** and substrates **12** is accomplished by oxidation of dihydrofuran in methanol with m-CPBA according to: Sweet, F.; Brown, R.K. *Can. J. Chem.* (1966) **44**, 1571 followed by PDC oxidation or silylation, respectively.




8. To be published in detail elsewhere.
9. See reference 2a. The equilibria favors **21** in acidic conditions and favors **20** in basic conditions, with slight preference for **20** in neutral conditions.
10. We do not have any direct evidence for **19**; however, epoxidation of a related electron-deficient double bond has been reported, see: Ohta, T.; Tsuchiyama, H.; Nozoe, S. *Heterocycles* (1986) **24**, 1137.
11. Compound **20** : elemental analysis calcd. for $C_{15}H_{27}NO_5Si$: C, 54.68; H, 8.26; N, 4.25. Found: C, 54.77; H, 8.14; N, 4.24. IR $cm^{-1}$ 3455, 3328, 2930, 1738, 1697, 1407, 1096. *m/e* ($NH_3CI$) 330, 329, 312, 287. NMR data for **21** $^{13}C$ (rel. $CDCl_3$ δ 77.0) [$J(^{13}CH)$Hz] 191.08, 167.86, 85.03, 65.15 [202], 60.35, 59.38 [145], 35.84 [126], 33.83 [122], 25.77 [126], 18.02, 6.79 [127], -5.59 [116]. $^1H$ (rel. $CDCl_3$ δ 7.24) [$J$(HH)Hz] 4.04 ddd [11.0, 7.0, 2.0], 4.00 d [2.5], 3.87 ddd [11.0, 5.5, 1.5], 2.68 dq [7.2, 1.6], 2.03 ddd [ 12.0, 5.5, 2.0], 1.99 ddd [12.0, 7.0, 1.5], 1.08 t [7.2]. NOE; irradiation on hydroxyl, enhancement of $C_3$ methine **20**, 4.64%; **21**, 0.01%. The antibiotic activities of **20/21** and derivatives will be described elsewhere.

(Received in USA 6 February 1991; accepted 29 April 1991)