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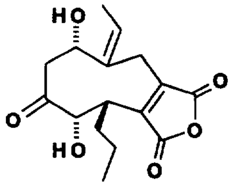
# Bis-Esters From Maleic Anhydrides Under Neutral Conditions: Protection of the Anhydride of the Natural Product Cornexistin

**Stephen C. Fields,* William H. Dent III, F. Richard Green III and Eric G. Tromiczak**

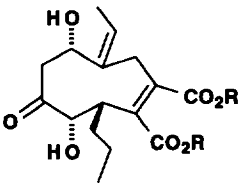
*Discovery Research, DowElanco, Dow Venture Center, 9330 Zionsville Road, Indianapolis, IN 46268-1054*

*Abstract:* Trimethylsilyldiazomethane converts maleic anhydride derivatives in alcoholic THF to bis-esters. The highly acid and base sensitive natural product cornexistin was converted to its bis-methyl ester in 70-75% yield and to the mixed benzyl/methyl ester in 61% yield. The mixed ester can be converted back to cornexistin via transfer hydrogenation.

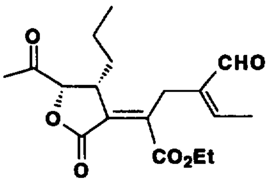
During the course of a structure-activity relationship study, we desired to protect the maleic anhydride of the herbicidally active natural product cornexistin[1] **1** as its bis-methyl ester **2**. The standard literature methods for converting anhydrides to bis-esters failed when applied to **1**. For example, heating **1** in ethanol for 2 hr with a catalytic amount of sulfuric acid[2] resulted in retro-aldol cleavage to form lactone **5** as the major product.[3,4] We also observed retro-aldol cleavage under basic conditions; thus, we required a set of neutral reaction conditions to achieve our desired transformation.



**1**



**2** $R^1 = R^2 = Me$
**3** $R^1 = R^2 = H$
**4 a** $R^1 = Me, R^2 = H$
**b** $R^1 = H, R^2 = Me$

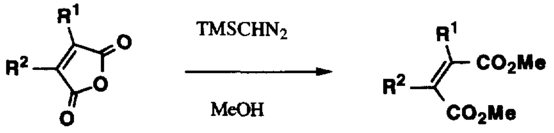


**5**

In contrast to other cyclic anhydrides, such as maleic anhydride,[5] cornexistin equilibrates under neutral conditions to a thermodynamic mixture of products *which favors the anhydride*. For example, we observed a 3:1:1 ratio of **1**/**4a**/**4b** at equilibrium in excess $CD_3OD$.[6] This mixture reverted back completely to **1** upon evaporation of solvent. This precluded the use of reagents such as diazomethane where the intermediate bis-carboxylic acids or mono-methyl ester/mono-carboxylic acids such as **3** and **4a**/**4b** are generally isolated.[7]

Because of the equilibrium phenomena, we sought an *in situ* esterification procedure. Trimethylsilyldiazomethane was a most attractive reagent owing to its commercial availability and its compatibility with methanol.[8] Thus, dissolving cornexistin in a 50% methanolic THF solution followed by addition of an excess of trimethylsilyldiazomethane ($TMSCHN_2$) afforded after 30 minutes complete conversion to a single product by HPLC. After acetic acid quench, aqueous workup and chromatography, the bis-methyl ester **2** was isolated in 70-75% yield.[9] A brief investigation of these conditions with some readily available maleic anhydride derivatives **6-8** showed that these conditions can be used for other maleic anhydrides (eq. 1, Table 1). The simplest example, maleic anhydride, gave a complex mixture of products which appear to arise from 1,3-dipolar addition of the reagent to the olefin bond.

**Table 1. Bis-methyl Esters from Maleic Anhydrides**



(1)

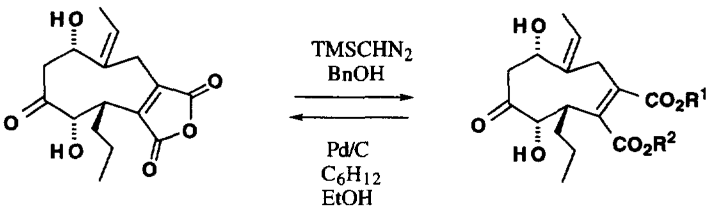
**6** $R^1 = R^2 = H$
**7** $R^1 = R^2 = (CH_2)_4$
**8** $R^1 = H$, $R^2 = Br$

**9** $R^1 = R^2 = H$
**10** $R^1 = R^2 = (CH_2)_4$
**11** $R^1 = H$ $R^2 = Br$

| Entry | Substrate | Product | Reaction time (hr) | %Yield |
|---|---|---|---|---|
| 1 | **1** | **2a** | 0.5 | 70-75 |
| 2 | **6** | **9** | 12 | <10[a] |
| 3 | **7** | **10** | 12 | 96 |
| 4 | **8** | **11** | 12 | 69 |

[a] complex mixture of products

Unfortunately, we were unable to reconvert bis-methyl ester **2** to the anhydride because retro-aldol cleavage occurs under the harsh conditions required to cleave the methyl esters. However, the mono-benzyl mono-methyl mixed bis-esters **12a**/**12b** (prepared in a 1.5:1 ratio by employing benzyl alcohol as the cosolvent in place of methanol in the trimethylsilyldiazomethane procedure)[10] can be cleanly debenzylated to **4a**/**4b** by phase-transfer hydrogenation[11] without any reduction of the exocyclic ethylidene or retro-aldol cleavage (eq 2). Cornexistin **1** is recovered as the sole product upon mild acidic workup.[12] Thus, a formal protecting sequence for the anhydride of cornexistin which is compatible with the molecule's sensitive functionality has been demonstrated.



(2)

1

**12a** $R^1$ = Bn, $R^2$ = Me
**b** $R^1$ = Me, $R^2$ = Bn

**Acknowledgement:** The authors would like to thank S. Thornburgh, G. Babbitt, P. Graupner and R. Hallberg for performing physical chemistry analysis.

## References and Notes

1. Nakajima, M.; Itoi, K.; Takamatsu, Y.; Sato, S.; Furukawa, Y.; Furuya, K.; Honma, T.; Kadotani, J.; Kozasa, M.; Haneishi, T. *J. Antibiotics* **1991**, *44*, 1065.

2. Eisner, U.; Elvidge, J. A.; Linstead, R. P. *J. Chem. Soc.* **1951**, 1501. Makowka, B. and Block, H. D. (Bayer Ag). United States Patent US 4,827,022; Date: 2 May 1989. CA: 88:287115141.

3. Write to the major author of this publication for a reprint of the poster entitled "Four Decomposition Products from the Natural Product Cornexistin", L. Bjelk, W. H. Dent III, R. J. Eilers, S. C. Fields, E. G. Tromiczak, S. S. Thornburgh, given at the CU-Hauser Symposium, May 26, 1995, Boulder, Colorado.

4. **3**: Analytical TLC on silica gel, 1:1 EtOAc/Hex, Rf=0.30. MS (EI) m/z (relative intensity) for $C_{18}H_{26}O_7$ = 332 (M+), 290, 247 (100), 219, 205, 91. IR ($CDCl_3$, $cm^{-1}$) 3400 (br), 2958, 1720, 1262. 300 MHz NMR ($CDCl_3$, ppm) 9.38 (s, 1H) 6.81 (q, 1 H, J = 8.7 Hz) 4.81 (d, 1 H, J = 7.2 Hz) 3.96 (m, 1 H) 3.74 (s, 3 H) 3.39 (d, 1 H, J = 14 Hz) 3.29 (d, 1 H, J = 14 Hz) 2.38 (s, 3 H) 2.02 (d, 1 H, J = 7.2 Hz) 1.65-1.20 (m, 4 H) 0.91 (t, 3 H, J = 7.0 Hz). 13C NMR (1H decoupled, CDCl3, ppm) 193.4, 167.7, 167.2, 152.5, 140.1, 138.4, 130.6, 83.4, 77.3, 52.6,41.9, 41.4, 28.4, 27.3, 19.9, 15.1, 14.2.

5. For example: Zilkha, A. and Bachi, M. D. *J. Org. Chem.* **1959**, *24*, 1096.

6. NMR tube experiment. Equilibrium measurements of **1** in anhydrous $CD_3OD$ were taken after 1 week. Partial 300 MHz NMR ($CD_3OD$, ppm) 5.85 (q, 0.6 H, J = 7.0 Hz) 5.70 (q, 0.2 H, J = 7.0 Hz) 5.52 (q, 0.2 H, J = 7.0 Hz) 5.02-4.92 (dd, 0.2 H, J = 5.0 Hz, 9.9 Hz) 4.90-4.80 (dd, 0.8 H, J = 5.2 Hz,

9.2 Hz) 4.07 (d, 0.2 H, J = 10.2 Hz) 3.99 (d, 0.2 H, J = 10.3 Hz) 3.76 (d, J = 0.6 H, J = 9.6 Hz) 1.75 (d, 2.4 H, J = 7.0 Hz) 1.70 (d, 0.3 H, J = 7.0 Hz) 1.69 (d, 0.3 H, J = 7.0 Hz). The structures of **4a** and **4b** were confirmed by characterization of their sodium salts.

7. For example: Oren, J.; Demuth, M.; Fuchs, B. *Synthesis* **1987**, 850.

8. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

9. **2**: MS (EI) m/z (relative intensity) for $C_{18}H_{26}O_7$ = 354 (M+, 5), 304 (10), 247 (80), 91 (90), 55 (100). IR ($CDCl_3$, cm$^{-1}$) 3440 (br), 2957, 2875, 1724, 1454, 1434, 1313, 1267, 1013. UV (EtOH, nm) l (e ) 542 (400), 366 (808), 260, (16253). 300 MHz NMR ($CDCl_3$, ppm) 5.62 (q, 1 H, J = 7.2 Hz) 4.88-4.75 (br m, 1 H) 4.68-4.55 (m, 1H) 4.25-4.15 (br m, 1 H) 3.77 (s, 3 H) 3.71 (s, 3 H) 3.30-3.00 (br m, 3 H) 2.90-2.65 (br m, 2 H) 2.10-1.95 (br m, 1 H) 1.70 (d, 3 H, J = 7.2 Hz) 1.50-1.10 (m, 4 H) 0.87 (t, 3 H, J = 7.2 Hz). $^{13}C$ NMR ($^1H$ decoupled, $CDCl_3$, ppm) 218.1, 168.2, 140.9, 136.0, 134.8, 131.9, 77.3, 76.3, 67.8, 52.3, 45.4, 42.7, 42.6, 34.9, 30.6, 20.8, 14.0, 13.7.

10. **12a/12b:** 1.5:1 ratio, 61% yield, 0.1 mmole scale. MS (DCI) m/z (relative intensity) for $C_{18}H_{26}O_7$ = 471(M+41), 459 (M+29), 431 (M+1), 399 (100). IR ($CDCl_3$, cm$^{-1}$) 3400 (br), 2958, 1720, 1262. 300 MHz NMR ($CDCl_3$, ppm) 7.35-7.25 (m, 5 H) 5.53 (q, 6 H, J = 7.0 Hz) 5.40 (d, 0.4 H, J = 7.0 Hz) 5.25-5.00 (m, 3 H) 4.80-4.72 (br m, 0.6H) 4.72-4.65 (br m, 0.4 H) 4.50-4.40 (br m, 1 H) 3.53 (s, 1.2 H) 4.24 (s, 1.8 H) 3.30-3.05 (br m, 3 H) 3.05-2.90 (br m, 1 H) 2.85-2.55 (br m, 2 H) 2.00-1.85 (br m, 1 H) 1.62 (d, 1.8 H, J = 7.0 Hz) 1.48 (d, 1.2 H, J = 7.0 Hz) 1.40-1.15 (m, 2 H) 1.15-0.95 (br m, 1 H) 0.79 (t, 1.8 H, J = 7.3 Hz) 0.71 (d, 1.2 H, J = 7.3 Hz).

11. Anantharamaiah, G. M. and Sivanandaiah, K. M. *J. Chem. Soc., Perkin Trans. I* **1977**, 490.

12. Conversion of **12a/12b to 1.** To a solution of **12a/12b** (10.0 mg) in EtOH (3 mL) was added cyclohexene (0.1 mL) and Pd/C (Aldrich; 10% Pd/C, 5 mg) and heated to reflux for 1 hour. Analysis by HPLC revealed the presence of only benzene and cornexistin **1**. The reaction was cooled and filtered through 1 g activated carbon and 1 g celite (washed with 5 mL EtOH and 5 mL 1 N HCl). The filtrate was concentrated *in vacuo* to give 5.1 mg cornexistin **1** (68% yield) which was pure by $^1H$ NMR.

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