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THE SYNTHESIS OF NEOSPOROL: A TRICHOTHECENE IN SEARCH OF A NATURAL PRODUCT

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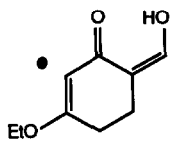
Abstract: The synthesis of neosporol **14**, a yet to be discovered trichothecene, is described. The critical reaction is a highly diastereoselective Claisen rearrangement that sets the C_5-C_6 stereochemistry.

In the preceding Letter, we provided ^{1}H NMR evidence supporting structure **14** as neosporol. Herein we detail the synthetic route, based upon previously reported model studies,[2] leading to neosporol.

The required, functionalized β-ketocyclohexylcarbonitrile **6** was prepared by the traditional base-catalyzed isoxazole cleavage.[3] Formylation (HCO_2Et, NaH; ether; reflux; 24h) of 3-ethoxycyclohexenone[4] afforded the hydroxymethylene ketone **1** (m.p.93-94°C (Et_2O/pentane); ^{1}H NMR: δ8.20 (1H, d, J=9.0 Hz); δ7.20 (1H, d, J=9.0 Hz))[5] in 95 % yield. Hydroxymethylene ketone **1**[3] was converted (NH_2OH·HCl, 1.1 equiv.; aq. EtOH, 1:1; reflux; 12h; 95%) into a 5:1 mixture of keto isoxazoles **2** (^{1}H NMR: δ8.17 (1H, s, aromatic)) and **3** (^{1}H NMR: δ8.11 (1H, s, aromatic)), respectively. Fractional distillation (b.p. 95-100°C, 0.2 Torr.) provided the pure, desired isoxazole **2** in 76% yield; ketalization (ethylene glycol, p-TsOH; benzene; reflux; 98%) gave **4** under standard conditions.



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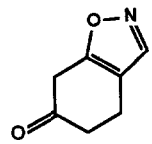

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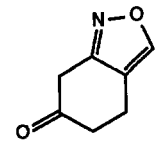

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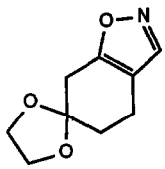

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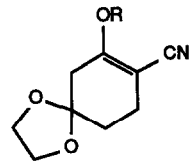
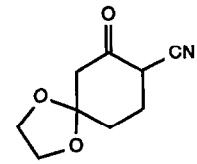


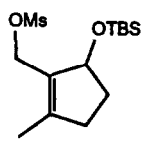
5a, R = H
b, R = K



6

Fragmentation (t-BuOK, HMPA, 0°C) of the isoxazole ring of **4** was complete within 2h, giving rise to a mixture of the enol **5a** (^{1}H NMR: δ6.05 (1H, s, exchanges with D_2O) and keto tautomer **6** (^{1}H NMR: δ3.47 (1H, dd, J=10.4, 5.7 Hz)). To the *in situ*-generated mesylate **7**, prepared at -25°C from its alcohol in THF as previously described[2] and maintained at -20°C, was added the potassium enolate **5b** (1.5 equiv.; from 3.0 equiv. t-BuOK[6]; 2.0 equiv. 18-crown-6[6]; HMPA; 0°C; 2h) over 10 min followed by stirring at 0°C for 3h. These conditions gave the O-alkylated nitrile **8** in 47% yield after flash chromatography; no C-alkylated product could be detected.

The success of the rearrangement of **8** was highly dependent upon the purity of the starting material. Trace impurities (TLC) increased the amount of elimination products; careful chromatography, the use of silylated glassware



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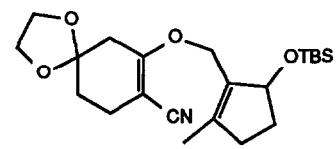

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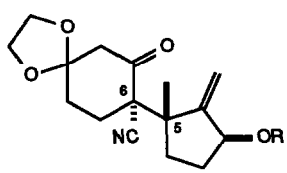

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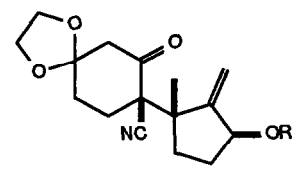
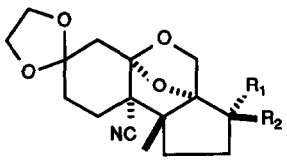
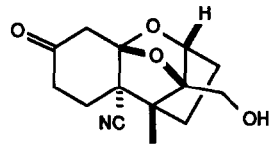


10

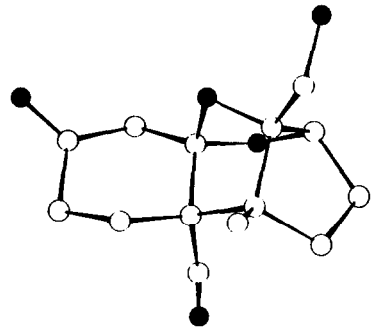
a, R = OTBS
b, R = H



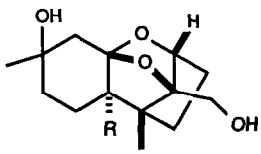
11a, R_1 = H, R_2 = OH
b, R_1, R_2 = O
c, R_1 = OH, R_2 = H



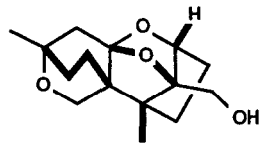
12



12 (URANUS PLOT, Hs omitted)



13a, R = CN
b, R = CHO
c, R = CH_2OH



14

(5% bis-(trimethylsilyl)acetamide (BSA)/pentane; reflux; 10h) as well as conducting the reaction under dilution conditions were all contributors to success. Accordingly, rearrangement was achieved (0.02M nonane; reflux (151°C; 4h) in 47% yield to give a 16:1 mixture of diastereomers. Although four diastereomers are possible, only ketonitrile **9a**, formed via a chairlike transition state with C_5-C_6 bond formation occurring trans to the O-silyl substituent, and **10a**, arising from a boatlike transition state with bond formation occurring trans to the O-silyl substituent, are reasonable.[2] Ketonitriles **9a** and **10a**[7] were shown to be stereoisomers at C_5-C_6 when they were independently desilylated (48% HF/CH_3CN, 1:20, 0°C, 2h; **9b** and **10b**, respectively) and oxidized under Swern conditions to give different exomethylene α,β-unsaturated ketones.[8]

Epoxidation of allylic alcohol **9b** (CF_3CO_3H, Na_2CO_3, CH_2Cl_2, 0°C, 45 min) effected ketal formation[9] (**11a**) and subsequent oxidation (Swern) realized the cyclopentanone **11b** (IR: ($CHCl_3$) 1754 cm^{-1}) in 39% overall yield. Selective exo-face reduction (LiAl(t-BuO)$_3$H, THF, 25°C, 5h; 90%) of the ketone afforded the α-alcohol **11c**, which, upon heating in 3N HCl/dioxane (1:2) for 2h, underwent exchange of the intramolecular ketals and hydrolysis of the ethylene glycol ketal to produce ketonitrile **12** (m.p. (EtOAc/hexane) 155-156°C; ^1H NMR: δ4.12 (1H, d, J=12.5 Hz); 3.71 (1H, dd, J=12.5, 7.4 Hz); IR: ($CHCl_3$) 3605, 1729 cm^{-1}) in 75% yield. The structure of ketonitrile **12** was fully confirmed by single crystal X-ray analysis.

Formation of the fifth ring was accomplished as follows. The carbonyl of ketonitrile **12** failed to undergo addition with methyllithium, and gave addition products and recovered starting material with methyl magnesium bromide; both

observations were ostensibly the result of facile enolization. However, the use of CH_3CeCl_2 (THF, 0°C, 3h; 57%))[10] proved successful, providing a 5:1 mixture of tertiary alcohols **13a** of undefined stereochemistry. The major alcohol was reduced ($LiAlH_4$, THF, reflux, 6h)[11] to the imine, hydrolyzed (5% aq. HOAc/MeOH, 1:1; 10h; 25°C) to aldehyde **13b**, and reduced ($LiAlH_4$, THF, reflux, 2h) to triol **13c**. Ring closure ($BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 ----> 25°C, 6h) to form neosporol **14**[12] (60% yield from **13a**) was accomplished using conditions under which the 1,3-dioxolane ring system is stable.[13]

Acknowledgments: This work was supported by grant CA-39976 from the National Cancer Institute.

References and Notes:

1. Author to whom inquires regarding X-ray data should be addressed.
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3. a) von Auwers, K.; Bahr, T.; Frese, E. *Justus Liebigs Ann. Chem.* **1925**, *441*, 54. b) Johnson, W. S.; Shelberg, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 1745.
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5. The proton at δ8.20 exchanged with D_2O; the doublet at δ7.20 collapsed to a singlet. The ^1H NMR spectrum indicated ~5% of the tautomeric aldehyde.
6. The stoichiometry was based upon mesylate. The excess base was used to neutralize triethylammonium methanesulfonate generated during the sulfonation of the alcohol.
7. Stereoisomer **10a** was accumulated from several experiments.
8. The boat-cis transition state, ostensibly the highest in energy of the four, can give the same enone as **10b**.
9. a) Demole, E.; Wuest, H. *Helv. Chim. Acta* **1967**, *50*, 1314. b) Wasserman, H. H.; Barber, E. H. *J. Am. Chem. Soc.* **1969**, *91*, 3674. c) Anderson, W.; Veysoglu, T. *J. Org. Chem.* **1978**, *43*, 2480.
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11. Stork, G.; Wakamatsu, S. U. T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945.
12. Neosporol **14**: ^1H NMR ($CDCl_3$, 250 MHz) δ4.27 (d, J =3.7 Hz, 1H), 4.07 (d, J=12.4 Hz, 1H), 3.91 (dd, J=8.1, 1.4 Hz, 1H), 3.75 (d, J=8.1 Hz, 1H), 3.72 (d, J=12.4 Hz, 1H), 2.09 (s, 2H), 2.00-1.85 (m, 2H), 1.85-1.45 (m, 7H), 1.21 (s, 3H), 0.99 (s, 3H); IR: ($CHCl_3$) 2961, 2930, 2878, 2857, 1466, 1385, 1031 cm-1; HRMS (EI) Calcd for $C_{15}H_{22}O_4$: 266.1518; Found: 266.1517.
13. These conditions had been employed previously to convert bis-dioxolane **11c** to a mixture of keto dioxolane **12** and its ethylene glycol ketal.

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