Enantioselective Synthesis of Natural (−)-Austalide B, an Unusual Ortho Ester Metabolite Produced by Toxigenic Cultures of *Aspergillus ustus*

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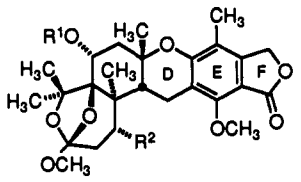
Austalides A–F (**1a–f**) comprise a group of meroterpenoid metabolites of considerable interest because of their production by a highly toxigenic strain of *Aspergillus ustus* found in dried fish routinely consumed in the Middle East.[1] The commendable



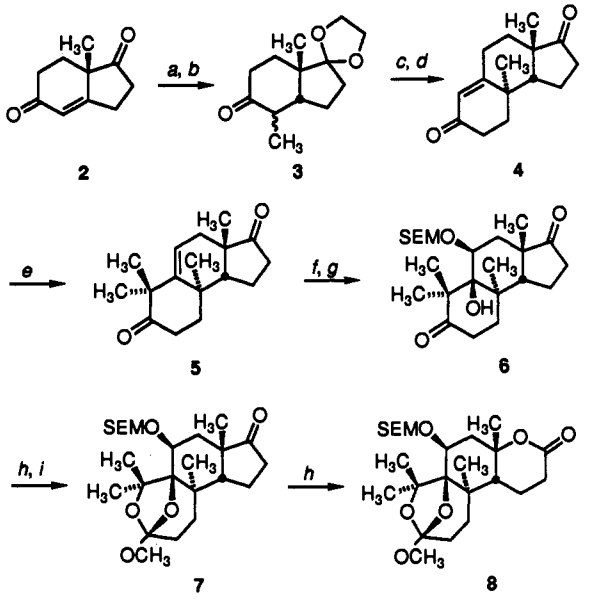
1a, $R^1 = COCH_3$, $R^2 = H$
b, $R^1 = R^2 = H$
c, $R^1 = COCH_3$, $R^2 = OCOCH_3$
d, $R^1 = H$, $R^2 = OCOCH_3$
e, $R^1 = COCH_3$, $R^2 = OH$
f, $R^1 = H$, $R^2 = OH$

effort expended by the CSIRO group in Pretoria resulted in structural elucidation of the members of this series by high-field ^1H and ^{13}C NMR spectroscopy,[1,2] in assignment of absolute configuration by means of X-ray crystallographic analysis,[3] and in definition of the probable pathway of austalide biosynthesis.[3,4] Central to the interesting molecular architecture of these mycotoxins are a bicyclic ortho ester subunit, a phthalide component reminiscent of that present in mycophenolic acid,[5] and the interlocking of these arrays via a cyclohexane ring having five contiguous stereogenic centers.

In this report, the experiments which have culminated in the first preparation of austalide B in its proper absolute configuration are described. We note in advance that the functional group diversity present in **1b** and its congeners causes these targets to be a useful forum for the development of new multiple annulation tactics.[6]

Retrosynthetic considerations involving the western sector led us back to the readily available diketone **2** (98% ee),[7] which was regioselectively ketalized[8] and subjected to dissolving metal reduction[9] followed by *in situ* methylation[10] to provide **3** (Scheme 1). Acid-catalyzed Robinson annulation involving the use of 4-chloro-2-butanone[11] was then found to proceed stereoselectively

Scheme 1



[a] $CH_3C(OCH_2CH_2O)CH_2CH_3$, TsOH. [b] Li, NH_3; MeI, ether. [c] H_3O^+. [d] $CH_3C(O)CH_2CH_2Cl$, TsOH, C_6H_6, Δ. [e] KO-*t*-Bu, *t*-BuOH, CH_3I. [f] OsO_4, NMO, aqueous acetone; $Na_2S_2O_4$. [g] SEMCl, $(i\text{-}Pr)_2NEt$. [h] MCPBA, $NaHCO_3$, CH_2Cl_2. [i] $Me_3O^+BF_4^-$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, room temperature.

to deliver **4** in low, but reproducible yield (30%).[12] On the other hand, this enedione proved conveniently amenable to regioselective dimethylation as in **5** (67%). The catalytic osmium tetraoxide-promoted dihydroxylation of **5** proceeded exclusively from the β-face,[14] thereby setting the stage for transient protection of the secondary carbinol as in **6** (80% for the two steps).

Further oxidation of both carbonyl groups was now required. Given their sterically congested environments and, most importantly, the close proximity of a hydroxyl group to the six-ring ketone, the requisite chemical transformations could be performed sequentially. In the event, treatment of **6** with excess MCPBA (and even trifluoroperacetic acid under more forcing conditions) resulted uniquely in Baeyer–Villiger oxidation within ring A (81%).[15] Formation of the ortho lactone was subsequently achieved by O-methylation of this intermediate with trimethyloxonium tetrafluoroborate[16] in the presence of 4-methyl-2,6-di-*tert*-butylpyridine (63%). At this juncture, oxidation of the cyclopentanone ring proceeded at a convenient rate under the predescribed peracid conditions to generate the pivotal intermediate **8** in good yield.

Attempts to take advantage of the known propensity of lactones to undergo enolization as the means to elaborate the eastern sector of the austalides were to no avail. The application of charge reversal by prior conversion of **8** to the dihydropyran and α-deprotonation of this vinyl ether likewise did not serve our purposes, nor did intramolecular Diels–Alder strategies prove viable. We then focused our attention on an alternative route involving Stille cross-coupling[17] of vinylstannane **12** to the enol

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(2) For the structure elucidation of austalides G–L, consult the following: Horak, R. M.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 363.

(3) Dillen, J. L. M.; Horak, R. M.; Maharaj, V. J.; Marais, S. F.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1989**, 393.

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(6) For alternative exploratory efforts aimed at elaboration of the phthalide subunit by this group, consult the following: (a) Paquette, L. A.; Schulze, M. M. *Heterocycles* **1993**, *35*, 585. (b) Paquette, L. A.; Sivik, M. R. *Synth. Commun.* **1991**, *21*, 467.

(7) Hajos, Z.; Parrish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 363.

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(9) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(10) Smith, H. A.; Huff, B. J. L.; Powers, W. J., III; Caine, D. *J. Org. Chem.* **1967**, *32*, 2851.

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(12) Base-promoted variants of the Robinson annulation fared no better. Recourse to methyl α-(trimethylsilyl)vinyl ketone[13a,b] and (*E*)-4-iodo-2-(trimethylsilyl)-2-butene[13c] did not improve matters.

(13) (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (c) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682.

(14) Sivik, M. R.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **1990**, *55*, 391.

(15) A modest amount (ca. 8%) of removal of the SEM group occurred during this reaction. Reprotection could be accomplished quantitatively.

(16) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.

(17) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

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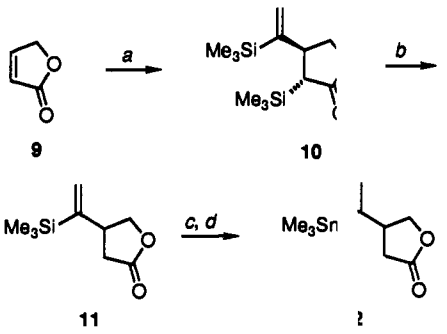
Scheme 2



[a] $Me_3SiC(=CH_2)MgBr$, $CuBr{\cdot}Me_2S$, Me_3SiC [b] HF, CH_3CN, H_2O. [c] Br_2; $Bu_4N^+F^-$. [d] $(Me_3Sn)_2$, $Pd(PPh_3)_4$.

triflate **13**. Thus, Cu(I)-catalyzed addition o 1-(trimethylsilyl)-vinyl)magnesium bromide to 5(2*H*)-furanon (**9**) *in the presence of chlorotrimethylsilane* gave rise to the C- lylated product **10** (Scheme 2). Failure to trap the initially fo ned enolate in this manner resulted chiefly in polymerization. Following chemoselective desilylation, **11** was transformed[18] v the vinyl bromide into the desired stannane **12**.

Following trial experiments that served to idicate the need to append an α-carbomethoxy group to **8** at the utset, C-acylation involving methyl cyanoformate[19] was effe ed in advance of O-triflation. We remain unaware of existing p cedent concerning the regioselectivity with which β-dicarbony compounds enter into reaction with *N*-phenyltriflimide. Proof hat **13a** had in fact been formed exclusively was gained by Diba H reduction of the product in CH_2Cl_2 at −78 °C to give enol tr late **13b** (Scheme 3).

It was soon determined that the successfu production of **13a** brought with it rate-retarding steric consequer ces not operational in the unsubstituted triflate, *viz.*, **13** (R = H). This was reflected, for example, in the quite inefficient conversio of **13a** to **14** when coupling was effected with $Pd(Ph_3P)_4$ and LiCl in THF at 60 °C. However, this complication could be nicely skir ted by substituting tri-2-furylphosphine[20] as a more suitable ligand for the palladium as $Pd_2(dba)_3$. The result was formation of 14 as a 1:1 mixture of two diastereomers in 71% yield.

Cyclization to form ring E was accomplish d by reaction with KHMDS in THF at −78 °C. Claisen conde nsation proceeded as expected to generate **15a** and **15b** (89% combined), which could be easily separated chromatographically. Neither of these dienyl ketones showed any tendency to aromatize when heated with $RhCl_3$, $Pd(OAc)_2$, or simply DBU in xylene or benzene. This lack of reactivity is attributed to conformational biases which serve to distort rings E and F substantially away from planarity, with concomitant stereoelectronic misalignment of the allylic proton. Confident that the positioning of an additional double bond in the interior of the six-membered ring would facilitate crafting of the benzene ring, we proceeded to O-methylate both

(18) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (b) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5911. (c) Chan, C.; Cox, P. B.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1988**, 971.
(19) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
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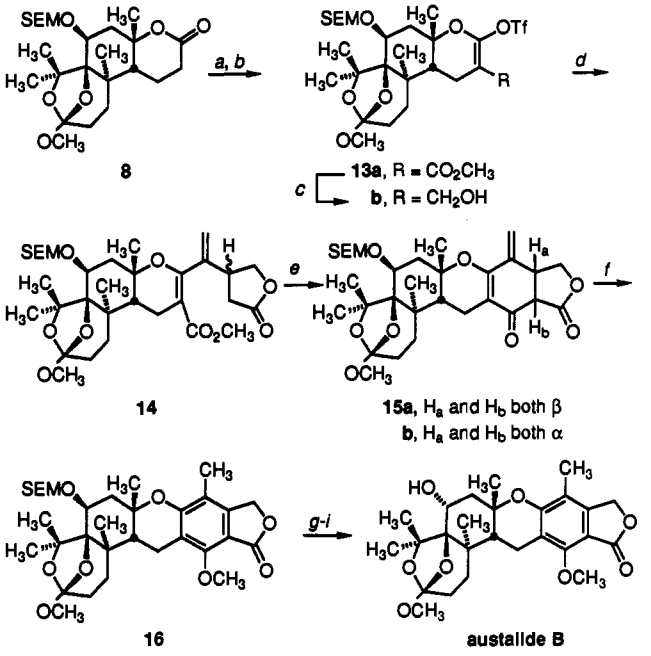
Scheme 3



[a] $LiN(i\text{-}Pr)_2$, $NCCO_2CH_3$, THF. [b] $KN(SiMe_3)_2$, THF; $PhNTf_2$. [c] Dibal-H. [d] **12**, $Pd_2(dba)_3$, $(furyl)_3P$, LiCl, THF, 60 °C. [e] $KN(SiMe_3)_2$, THF, −78 °C. [f] $KN(SiMe_3)_2$, HMPA, Me_2SO_4; C_6H_6, 80 °C. [g] $Bu_4N^+F^-$, HMPA, 45 °C. [h] TPAP, CH_2Cl_2, 0 °C. [i] $NaBH_4$, MeOH, 0 °C.

of these dienones and to effect [1,3] hydrogen sigmatropy by heating the diastereomeric ethers in benzene for 15 min. By this means, **16** was obtained in 46% overall yield. After cleavage of the SEM ether,[21] the configuration of the C-ring hydroxyl was inverted by sequential perruthenate oxidation[22] and sodium borohydride reduction to give austalide B (65% for the three steps), mp 241–243 °C; $[\alpha]^{22}_D$ −46.2° (*c* 0.9, $CHCl_3$), corresponding to >99% ee [lit.[1] mp 243–245 °C; $[\alpha]^{22}_D$ −46.2° (*c* 1.00, $CHCl_3$)]. Direct comparison of synthetic **1b** with the natural material showed them to be identical.

The asymmetric synthesis of natural austalide B outlined herein has been accomplished by means of a convergent approach involving 16 steps. The body of new chemistry developed *en route* to this target includes the stereocontrolled assembly of a cyclic ortho ester as well as a new method for elaborating a fully substituted and highly functionalized benzene ring. This technology should be applicable to the construction of various structurally related natural products.

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(21) Good temperature control is necessary. HMPA as solvent accelerates the rate of deprotection.
(22) Review: Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.