ORGANIC LETTERS

2003
Vol. 5, No. 1
89−92

Synthesis of the Carbocyclic Core of the Cornexistins by Ring-Closing Metathesis

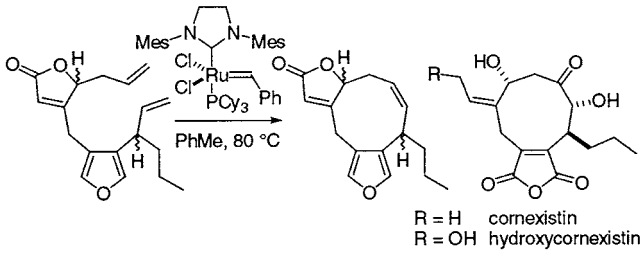
J. Stephen Clark,* Frederic Marlin, Bastien Nay, and Claire Wilson

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK

j.s.clark@nottingham.ac.uk

Received November 11, 2002

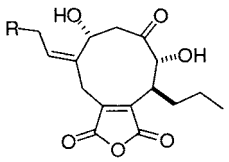
ABSTRACT

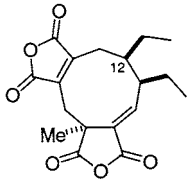


An advanced intermediate in the synthesis of the phytotoxins cornexistin and hydroxycornexistin has been synthesized. Sequential palladium-mediated sp^2–sp^3 fragment coupling and ring-closing diene metathesis have been used to construct the nine-membered carbocyclic core found in the natural products.

Cornexistin and hydroxycornexistin are phytotoxic members of the nonadride family of natural products.[1] The cornexistins contain a nine-membered carbocycle fused to a cyclic anhydride and are structurally related to several other natural products such as glaucanic acid, 12-epi-glaucanic acid,[2] CP-225,917, and CP-263,114.[3]

Cornexistin was first isolated from a culture of the fungus *Paecilomyces variotii* Bainier (strain SANK 21086) by researchers at Sankyo Co. in Japan in 1991, and its structure was elucidated using NMR spectroscopy and X-ray crystallography.[1a] This compound has attracted considerable attention in the agrochemical industry because it displays potent herbicidal activity against many grasses and broadleaf weeds but is well tolerated by maize plants.





The related compound hydroxycornexistin was isolated from the same strain of *P. variotii* by workers at DowElanco in the USA.[1b] This compound has even greater herbicidal activity than cornexistin against many broadleaf weeds, including several very aggressive varieties.

The selective and potent herbicidal activity of cornexistin and hydroxycornexistin combined with their novel mode of action makes them important lead compounds in the search for new herbicides for post-emergence weed control in crop production.[4]

Our interest in cornexistin and hydroxycornexistin as synthetic targets was aroused by the synthetic challenges these compounds present coupled with their potent bioac-

(1) (a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Sato, S.; Furukawa, Y.; Furuya, K.; Honma, T.; Kadotani, J.; Kozasa, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 1065. (b) Fields, S. C.; Mireles-Lo, L.; Gerwick, B. C. *J. Nat. Prod.* **1996**, *59*, 698.

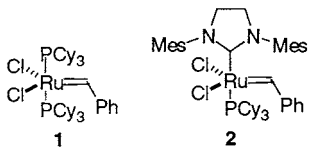
(2) Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1769.

(3) (a) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

10.1021/ol027265y CCC: $25.00
Published on Web 12/11/2002

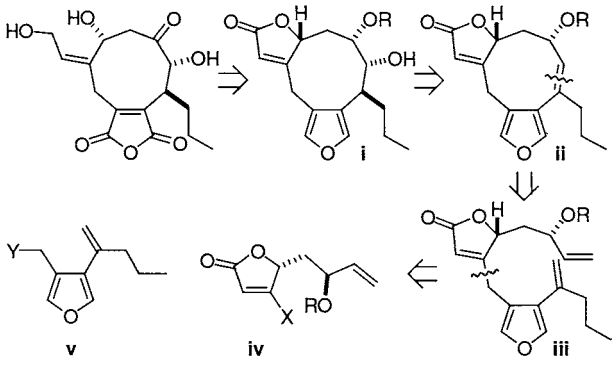
tivity. Both compounds possess a nine-membered carbocycle fused to a highly reactive cyclic anhydride, a combination of structural features that constitutes a significant obstacle to conventional methods of ring construction. In addition, the cornexistins present several problems with regard to stereocontrol; control of the exocyclic alkene configuration is especially problematic.

At the outset, we identified ring-closing metathesis (RCM) as the most promising reaction for construction of the nine-membered ring.[5] We[6] had already prepared a variety of medium-ring ethers using diene RCM reactions promoted by the ruthenium complexes **1** and **2**,[7] and other workers had used RCM to prepare medium-sized carbocycles. However, there were no literature examples involving direct construction of nine-membered carbocycles using RCM.[8]



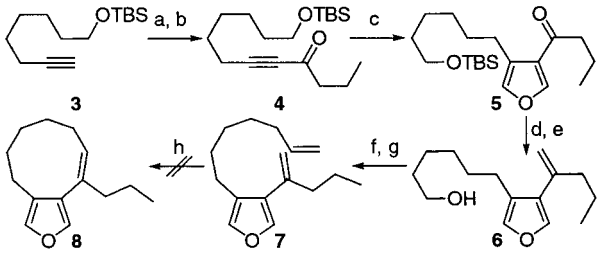
In our original retrosynthetic analysis of hydroxycornexistin, functional group interconversion (FGI) suggested the tricyclic furan **i** as a late-stage intermediate (Scheme 1). Further FGI gave the cyclononene **ii**, and disconnection of the alkene revealed the diene **iii**. Bond disconnection between the butenolide and furan portions of the diene **iii** resulted in lactone **iv** and the 3,4-dialkylfuran **v** as intermediates. This retrosynthetic analysis implies that the synthesis will involve coupling of fragments corresponding to the chiral lactone **iv** and the achiral furan **v**, followed by RCM of the diene **iii** and stereoselective hydroboration of the resulting trisubstituted alkene. Subsequent reduction of the lactone, adjustment of oxidation levels and removal of protecting groups would then deliver hydroxycornexistin.

Scheme 1



To explore the key RCM reaction, diene **7** was prepared from TBS-protected 7-octyn-1-ol (**3**) (Scheme 2). Reaction of butanal with the lithium acetylide derived from alkyne **3** and immediate oxidation of the resulting alcohol using catalytic TPAP[9] afforded ketone **4**. Subsequent reaction with 4-phenyloxazole[10] at 200 °C resulted in Diels−Alder reaction, and immediate retrocycloaddition to give furan **5**.[11] The ketone was then methylenated using Nysted reagent and titanium(IV) chloride,[12] and the protecting group was then removed to deliver alcohol **6**. Swern oxidation and Wittig methylenation of the resulting aldehyde delivered precursor **7** required for the anticipated RCM reaction.

Scheme 2[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF; (ii) *n*-PrCHO, THF, −78 °C → rt; (b) TPAP, NMO, CH_2Cl_2, rt, 66% (two steps); (c) 4-Phenyloxazole, 200 °C, 70%; (d) $Zn(CH_2ZnBr)_2$·THF, $TiCl_4$, THF, 0 °C → rt, 89%; (e) TBAF, THF, rt, 99%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −60 °C → rt, 91%; (g) Ph_3PCH_2, THF, rt, 85%; (h) **1** or **2** CH_2Cl_2, rt or reflux.

Unfortunately, all attempts to effect ring closure by RCM failed to deliver the required carbocyclic product **8**. The failure of the reaction was attributed to difficulties in forming a nine-membered ring and a conjugated trisubstituted alkene during metathesis. To circumvent these problems, we altered our retrosynthetic analysis to give key disconnection of the nine-membered carbocycle at a different position (Scheme 3). In this retrosynthetic analysis, FGI of hydroxycornexistin suggests the diol **vi** as a late-stage intermediate. Recognition that the syn 1,2-diol implies an alkene then leads to cyclononene **vii**, and this can be disconnected to give diene **viii**. Further disconnection at one of the C−C bonds connecting the two rings leads to butenolide **ix** and 3,4-

(4) (a) Haneishi, T.; Nakajima, M.; Koi, K.; Furuya, K.; Iwado, S.; Sato, S. U.S. Patent 4 897 104, 1990. (b) Haneishi, T.; Nakajima, M.; Koi, K.; Furuya, K.; Iwado, S.; Sato, S. U.S. Patent 4 990 178, 1991. (c) Fields, S. C.; Gerwick, B. C.; Mireles-Lo, L. U.S. Patent 5 424 278, 1995.

(5) For reviews concerning RCM reactions, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 371. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Fürstner A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

(6) (a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (c) Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321. (d) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231. (e) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372.

(7) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(8) For preparation of a related eight-membered carbocyclic system, see: Efremov, I.; Paquette, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 9324.

(9) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

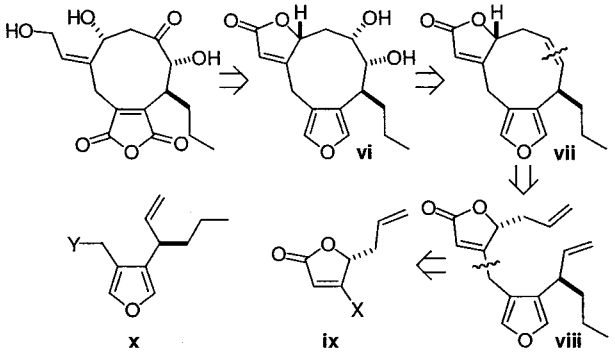
(10) Whitney, S. E.; Winters, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 929.

(11) Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* **1979**, *9*, 789.

(12) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313.

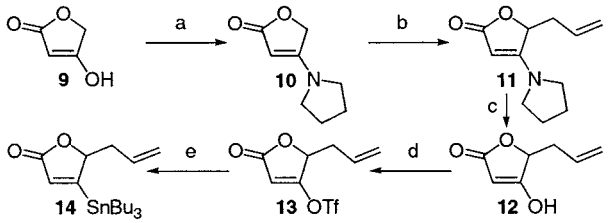
disubstituted furan **x** bearing suitable substituents (X and Y) for a metal-mediated sp^2-sp^3 coupling reaction.[13] This retrosynthetic plan has the advantage that RCM of a substrate possessing two terminal alkenes is implicit.

Scheme 3



The precursors required for implementation of the synthetic plan suggested in Scheme 3 were prepared by the routes shown in Schemes 4 and 5. The readily available starting material tetronic acid (**9**) was first converted into the vinylogous amide **10** in high yield by reaction with pyrrolidine (Scheme 4).[14] Deprotonation with *t*-butyllithium and treatment of the resulting anion with allyl bromide then afforded alkylated product **11**.[15] Acid-catalyzed hydrolysis of the compound delivered tetronic acid derivative **12**, and this was then converted into triflate **13**. The stannane (**14**) required for the sp^2-sp^3 coupling reaction was obtained by the palladium-catalyzed reaction of triflate **13** with hexabutylditin.[16]

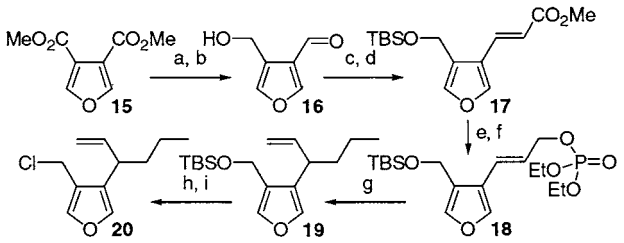
Scheme 4[a]



[a] Reagents and conditions: (a) pyrrolidine, heat, 94%; (b) *t*-BuLi, CH_2CHCH_2Br, THF, −78 °C → rt, 70%; (c) aqueous HCl, 60 °C, 81%; (d) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 89%; (e) $(Bu_3Sn)_2$, LiCl, $Pd(PPh_3)_4$, THF, reflux, 75%.

The synthesis of the second coupling partner commenced from commercially available dimethyl 3,4-furandicarboxylate (**15**) (Scheme 5). Complete reduction of the diester followed by selective mono-oxidation of the resulting diol with manganese dioxide afforded aldehyde **16**.[17] Protection of the remaining hydroxyl group as the TBS ether followed by Wittig reaction of the aldehyde with methyl (triphenylphosphoranylidene)acetate delivered alkene **17** in high yield. The ester was then reduced with lithium aluminum hydride, and the resulting allylic alcohol was treated with diethyl chlorophosphate to give allylic phosphate **18**. The side chain was installed by copper-catalyzed S_N2' displacement of the allylic phosphate with *n*-propylmagnesium chloride, following the procedure of Yamamoto and co-workers, to give alkene **19**.[18] Cleavage of the TBS ether and conversion of the resulting primary alcohol into the corresponding chloride via the mesylate, using the procedure described by Tanis for the synthesis of related chlorides,[19] afforded the second coupling partner **20**.

Scheme 5[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, −78 °C → rt; (b) MnO_2, CH_2Cl_2, rt; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 73% (over three steps); (d) $Ph_3P{=}CHCO_2Et$, THF, rt, 98%; (e) $LiAlH_4$, THF, −78 °C → rt, 98%; (f) $P(O)(OEt)_2Cl$, pyridine, DMAP, CH_2Cl_2, rt; (g) *n*-PrMgCl, CuCN (10 mol %), LiCl (30 mol %), THF, −78 °C, 63% (over two steps); (h) TBAF, THF, rt, 82%; (i) $MeSO_2Cl$, LiCl, collidine, DMF, 0 °C, 90%.

The precursor required for the RCM reaction was prepared by sp^2-sp^3 coupling of vinylic stannane **14** and chloride **20**. Coupled product **21** was obtained in 60% yield (1:1 mixture of diastereoisomers) upon treatment with $Pd_2(dba)_3$ and triphenylarsine in THF at reflux (Scheme 6).[20] This compound was then subjected to RCM using ruthenium complex **2** in toluene at 80 °C. The reaction was complete in 3 h, and tricyclic product **22** was obtained as a separable mixture of diastereoisomers (**a** and **b**) in 61% yield. When the RCM reaction was performed using ruthenium complex **1** in dichloromethane at reflux, the reaction took 60 h and alkene **22a**/**b** was obtained in 70% yield.

(13) For reviews of the Stille reaction, see: (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1999.

(14) Momose, T.; Toyooka, N.; Nishi, T.; Takeuchi, Y. *Heterocycles* **1988**, *27*, 1907.

(15) For the alkylation of a related tetronic acid derivative, see: Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *Tetrahedron Lett.* **1988**, *29*, 1489.

(16) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

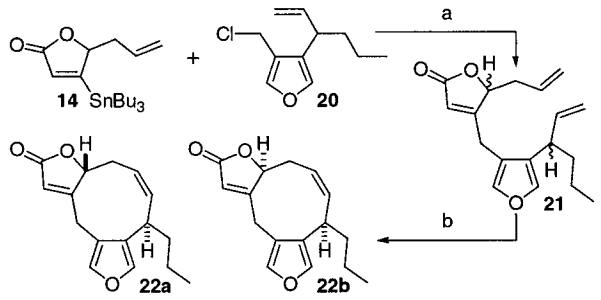
(17) Cook, M. J.; Forbes, E. J. *Tetrahedron* **1968**, *24*, 4501.

(18) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689.

(19) Tanis, S. P. *Tetrahedron Lett.* **1982**, *23*, 3115.

(20) For examples of related palladium-mediated sp^2-sp^3 coupling reactions, see: (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739. (b) Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583. (c) Takeda, T.; Kabasawa, Y.; Fujiwara, T. *Tetrahedron* **1995**, *51*, 2515.

Scheme 6[a]



[a] Reagents and conditions: (a) $Pd_2(dba)_3$, $AsPh_3$, THF, reflux, 60%; (b) **2**, PhMe, 80 °C, 3 h, 61% or **1**, CH_2Cl_2, rt, 3 d, 70%.

The more polar diastereoisomer was obtained as a crystalline solid, and subsequent recrystallization from dichloromethane−petroleum ether gave crystals suitable for X-ray analysis.[21] This revealed the more polar isomer to be the unnatural diastereoisomer **22b** (Figure 1).

In summary, we have constructed the core of the cornexistins by employing a concise 11-step route in which the novel sequence of palladium-catalyzed sp^2-sp^3 fragment coupling followed by RCM is used. This is the first synthesis of the core of the cornexistins. In addition, we believe that this is the first example of direct construction of a nine-membered carbocycle using RCM.

(21) Crystallographic data (excluding structure factors) for compound **22b** have been deposited (CCDC 196700) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, upon application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax, +44 (0)1223 336033; e-mail, deposit@ccdc.cam.ac.uk).

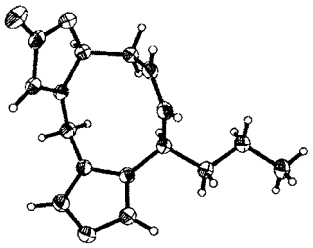


Figure 1. X-ray crystal structure of compound **22b**.

The preparation of fragments **13** and **20** as single enantiomers and completion of the total syntheses of cornexistin and hydroxycornexistin are in progress. Results of this work will be reported in due course.

Acknowledgment. We thank the EPSRC (Grant GR/N63666) for financial support and for the provision of a Bruker SMART1000 CCD X-ray diffractometer (Grant GR/M54728). We also thank Dr. John Clough (Syngenta, Jealott's Hill Research Station, Bracknell, Berks., UK) for helpful discussions regarding aspects of this work.

Supporting Information Available: Spectroscopic and other data for compounds **14**, **20**, **21**, **22a**, **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027265Y