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Total Synthesis of Ambruticin**

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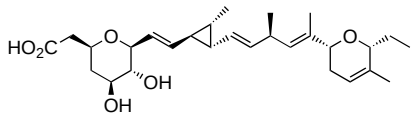
Ambruticin (**1**) was isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum* var. *fulvum*. It is an orally active antifungal agent showing in vitro and in vivo activity against a variety of pathogenic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitides*, as well as the dermatophytic filamentous fungi.[1] Ambruticin features unique *cis*-2,6-disubstituted tetrahydropyran and dihydropyran ring systems together with a methylcyclopropane moiety. In spite of considerable interest



1 (+)-Ambruticin

in the preparation of **1**,[2] we found in the literature only one total synthesis, reported by Kende in 1990,[3] and the difficulty in designing a stereoselective total synthesis is manifested in recent reports dealing with partial syntheses of the molecule.[4] In our continuing search for new applications of stereoselective radical cyclization reactions of β-alkoxyacrylates,[5] we examined the efficacy of these reactions in a stereocontrolled synthesis of **1**.

In our retrosynthetic analysis, the tetrahydropyran aldehyde **B** was to be prepared from a β-alkoxyacrylate precursor **C**, which may be obtained from L-arabinose (**2**). The dihydropyran derivative **E** was envisaged to arise from the diene **F** by olefin metathesis.[6] Connection of the parts **A** and **D** by Julia-type olefination would then complete the construction of the carbon framework (Scheme 1).

Selective acetonide protection of the dithioacetal derivative of L-arabinose (**2**) and benzylation of the remaining hydroxy groups gave the acetonide **4** (Scheme 2).[2a] The β-alkoxyacrylate **5** was obtained from **4** by acetonide deprotection, regioselective TBS protection of the primary hydroxy group, and reaction with methyl propiolate. The aldehyde group generated from the dithioacetal moiety in **5** was reduced with $NaBH_4$, and bromide substitution led to the primary bromide **6**, which was then stereoselectively transformed into the

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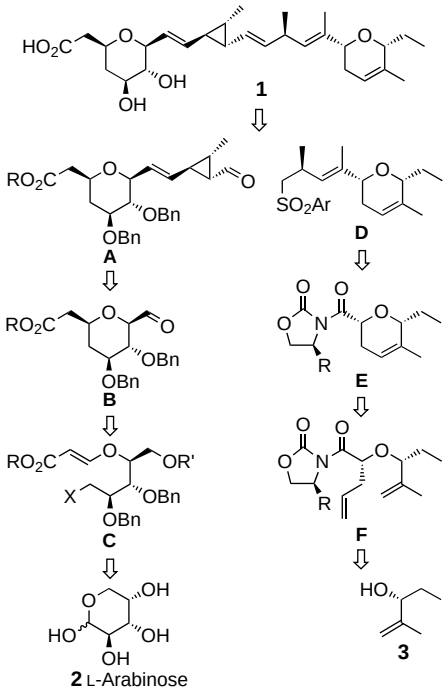
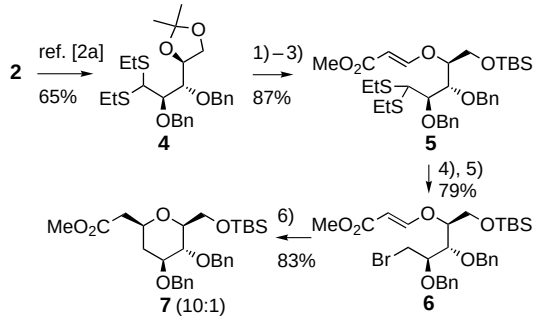


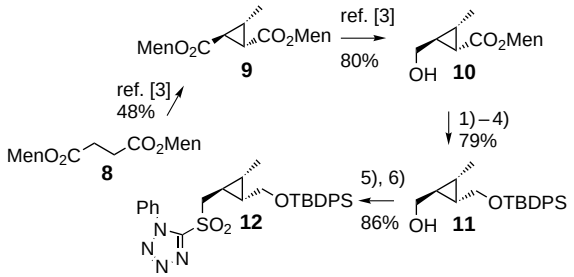
Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. 1) Cat. HCl, MeOH, 0 °C→RT, 8 h. 2) 1.05 equiv TBSCl, 2.0 equiv imidazole, CH_2Cl_2, RT, 10 min. 3) 1.1 equiv HC≡CCO_2Me, 0.2 equiv NMM, CH_2Cl_2, RT, 2 h. 4) 1.5 equiv $PhI(TFA)_2$, 3.0 equiv $NaHCO_3$, MeCN/H_2O (9:1), 0 °C, 5 min; 1.0 equiv $NaBH_4$, 0 °C, 30 min. 5) 1.5 equiv CBr_4, 1.2 equiv Ph_3P, 3.0 equiv NEt_3, CH_2Cl_2, 0 °C→RT, 2 h. 6) 1.2 equiv Bu_3SnH, 0.2 equiv AIBN, benzene (0.005 M), reflux, 2 h, (syringe pump, 1 h). AIBN = azobisisobutyronitrile, NMM = *N*-methylmorpholine, TBS = *tert*-butyldimethylsilyl.

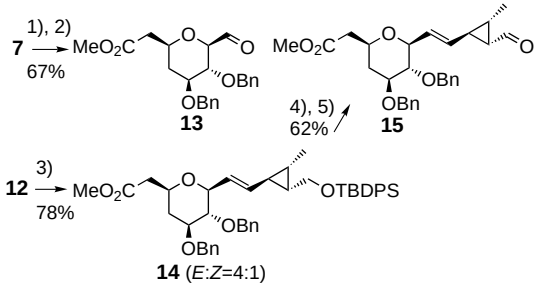
desired tetrahydropyran derivative **7** (2,6-*cis*:*trans* = 10:1) under the standard high-dilution radical-generating conditions in the presence of tributylstannane and AIBN.

Preparation of the primary alcohol **10** from dimenthyl succinate (**8**) was achieved by following the Kende protocol,[3] which involves stereoselective double alkylation with 1-bromo-1-chloroethane, selective hydrolysis of the sterically less hindered ester moiety of the diester **9**, and borane reduction (Scheme 3). Conversion of **10** into the TBDPS ether **11** was then effected by TBS protection, $LiAlH_4$ reduction, TBDPS protection, and TBS deprotection. Mitsunobu-type reaction of **11** with 1-phenyl-1*H*-tetrazole-5-thiol proceeded efficiently to provide the expected sulfide, which was converted into the sulfone **12** by oxidation with MCPBA.



Scheme 3. 1) 1.1 equiv TBSCl, 2.0 equiv imidazole, CH_2Cl_2, RT, 30 min. 2) 1.5 equiv $LiAlH_4$, Et_2O, 0 °C, 1 h. 3) 1.1 equiv TBDPSCl, 2.0 equiv imidazole, CH_2Cl_2, RT, 1 h. 4) 0.1 equiv CSA, MeOH, 0 °C, 40 min. 5) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph_3P, THF, 0 °C, 5 min. 6) 2.0 equiv MCPBA, CH_2Cl_2, 0 °C, 30 min. DIAD = diisopropyl azodicarboxylate, MCPBA = *m*-chloroperbenzoic acid, Men = menthyl, TBDPS = *tert*-butyldiphenylsilyl.

The aldehyde **13** was obtained from the TBS ether **7** by deprotection, separation of diastereomers, and Swern oxidation (Scheme 4). Construction of the *trans*-disubstituted double bond at C8–C9 was problematic. Classical Julia



Scheme 4. 1) Cat. HCl, MeOH, 0 °C→RT, 30 min. 2) 2.2 equiv $(COCl)_2$, 4.0 equiv DMSO, CH_2Cl_2, −78 °C, 1 h; 5.0 equiv NEt_3, −78 °C, 7 h. 3) 2.0 equiv NaHDMS, THF/HMPA (4:1), −78 °C, 5 min; 2.0 equiv **13**, −78 °C→RT, 3 h. 4) Cat. HCl, MeOH, RT, 1 h. 5) 2.2 equiv $(COCl)_2$, 4.0 equiv DMSO, CH_2Cl_2, −78 °C, 30 min; 5.0 equiv NEt_3, −78 °C→RT. HMPA = hexamethylphosphoramide, NaHDMS = sodium hexamethyldisilazide.

reactions employing the aldehyde **13** did not work, but after considerable experimentation, the Kocienski–Julia reaction proved fruitful.[7] The olefin **14** (*E*:*Z* = 4:1) was obtained in 78% yield by deprotonation of the sulfone **12** by two equivalents of sodium hexamethyldisilazide and subsequent addition of two equivalents of the aldehyde **13** in the presence of HMPA. Use of lithium hexamethyldisilazide gave **14** with better selectivity (*E*:*Z* = 9:1) but lower yield (63%), and the reaction became essentially nonstereoselective when potassium hexamethyldisilazide was employed (63% yield, *E*:*Z* = 1:1). The required aldehyde **15** was prepared from **14** by deprotection of the TBDPS group under acidic conditions, separation of the geometric isomers, and Swern oxidation.

Synthesis of the right-hand half of ambruticin (**1**) commenced with (*R*)-3-hydroxy-2-methylpent-1-ene (**3**),[8] which was converted to the ether **16** by reaction with sodium bromoacetate (Scheme 5). The sodium enolate of the corresponding imide **17** reacted with allyl iodide to yield the diene **18** in a stereoselective manner. Olefin metathesis of the diene **18** proceeded uneventfully with the Grubbs catalyst[9] to give the dihydropyran imide **19** in excellent yield.

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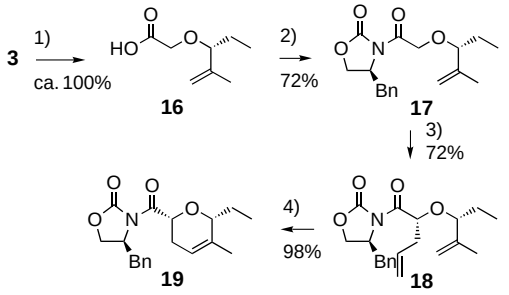
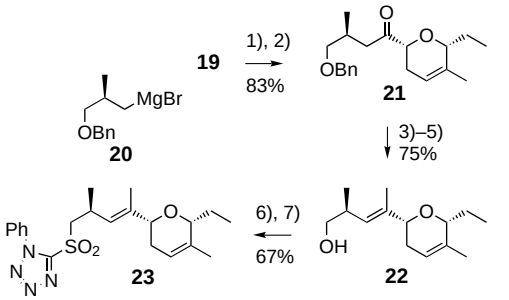


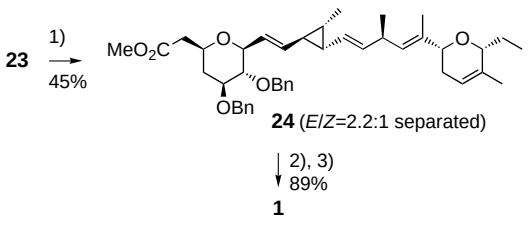
Scheme 5. 1) 1.0 equiv NaH, $BrCH_2CO_2Na$, RT, 8 h (reverse addition). 2) 1.0 equiv PivCl, 1.1 equiv NEt_3, Et_2O, $-78\rightarrow0\,^{\circ}C$; 1.0 equiv X_c-Li, THF, $-78\,^{\circ}C$, 8 h. 3) 1.2 equiv NaHDMS, 5.0 equiv H_2CCHCH_2I, THF, $-78\rightarrow-45\,^{\circ}C$, 5 h. 4) 0.05 equiv $[RhCl_2(CHPh)(PCy_3)_2]$, CH_2Cl_2 (0.005 M), reflux, 3 h; 0.075 equiv $Pb(OAc)_4$. Piv = pivaloyl.

Conversion of **19** to the corresponding Weinreb amide and subsequent reaction with the Grignard reagent **20**[10] led to the ketone **21** (Scheme 6). The trisubstituted olefin **22** was obtained by regioselective enol triflate formation and reaction with lithium dimethylcuprate[11] followed by lithium/ammonia debenzylation. Mitsunobu-type reaction of **22** with 1-phenyl-1*H*-tetrazole-5-thiol and selective oxidation with ammonium heptamolybdate and hydrogen peroxide[12] provided the sulfone **23** in reasonable yield.



Scheme 6. 1) 3.5 equiv $MeNH(OMe)\cdot HCl$, 3.5 equiv Me_3Al, THF, $0\,^{\circ}C$, 3 h. 2) 3.0 equiv **20**, $40\,^{\circ}C$, THF, 8 h. 3) 1.25 equiv LiHMDS, 1.5 equiv $PhNTf_2$, THF/HMPA (4:1), $-78\,^{\circ}C$, 30 min. 4) 3.0 equiv Me_2CuLi, Et_2O, $-78\,^{\circ}C$, 1 h. 5) 10 equiv Li ($\times3$), NH_3(l)/EtOH (5:1), $-78\,^{\circ}C$, 10 min. 6) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph_3P, THF, $0\,^{\circ}C$, 30 min. 7) 2.0 equiv $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, $0\,^{\circ}C$, 3 h.

The final coupling reaction was performed by treating the sulfone **23** with sodium hexamethyldisilazide in the presence of HMPA, and then with 1.5 equivalents of the aldehyde **15** (Scheme 7). Thus, 45% of the desired (*E*)-olefin **24** was obtained directly along with the (*Z*)-isomer, which was isolated in 21% yield. Use of potassium hexamethyldisilazide resulted in higher stereoselectivity ($E:Z = 6:1$), but the yield was low (15%). Ambruticin (**1**) was obtained from **24** by basic hydrolysis and lithium/ammonia debenzylation.



Scheme 7. 1) 1.2 equiv NaHMDS, THF/HMPA (4:1), $-60\,^{\circ}C$, 30 min; 1.5 equiv **15**, $-60\rightarrow0\,^{\circ}C$, 3 h. 2) 0.5 N LiOH, THF/H_2O (3:1), RT, 8 h. 3) 10 equiv Li ($\times3$), NH_3(l)/EtOH (5:1), $-78\,^{\circ}C$, 10 min.

In summary, oxacyclic building blocks were prepared by using highly stereoselective radical cyclization and olefin metathesis reactions. The convergent strategy featuring the Kocienski–Julia reaction may be easily adapted to the synthesis of ambruticin analogues for the evaluation of bioactivities.

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