Synthetic Study on Ecteinascidin 743 Starting from D-Glucose

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Abstract: During the course of synthetic study on ecteinascidin 743 (**1**), key intermediate **5** was prepared. Stereocontrolled synthesis of **5** from D-glucose was accomplished using incorporation of two nitrogen atoms and stereoselective addition of a phenol to an imine as key steps.

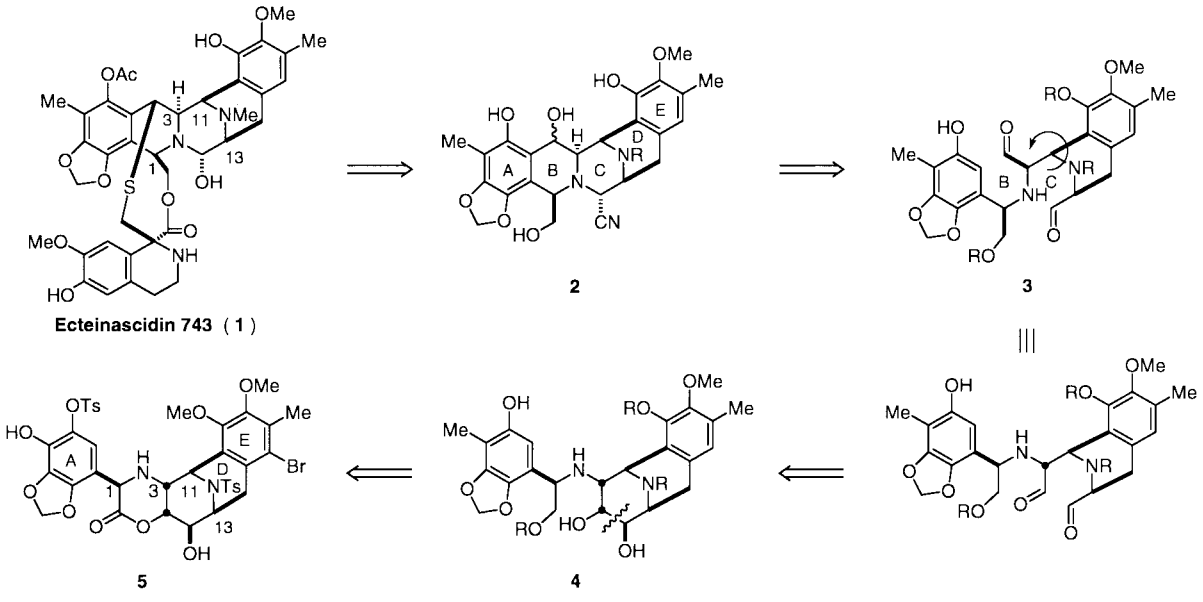
Key words: ecteinascidin 743, D-glucose, bicyclo [3.3.1] system, imine

The ecteinascidins were isolated by Rinehart and coworkers from the marine tunicate *Ecteinascidia turbinata*.[1,2] Their novel structure and extremely potent antitumor activities have promoted extensive studies.[3,4,5] The first of these compounds to advance to clinical trials was ecteinascidin 743 (**1**). In this communication, we report our synthetic approach to **1**. We plan to construct this compound from the pentacyclic framework **2**, which is common to all ecteinascidins (Scheme 1). An intramolecular *ortho*-addition of the phenol to an aldehyde will provide the B-ring of **2**.[6] The C-ring should be accessible from amino aldehyde **3**, since a similar ring closure was demonstrated in our total synthesis of saframycin A.[7] The dialdehyde **3** will be prepared by oxidative cleavage of the diol **4**, which should be readily derived from **5**. The pentacycle **5** bears four chiral centers at C_1, C_3, C_{11}, and C_{13} as well as the aromatic A- and E-rings of **1**. Described herein is a stereoselective synthesis of this key intermediate, employing the incorporation of two nitrogen atoms into D-glucose and the addition of phenol to an imine.

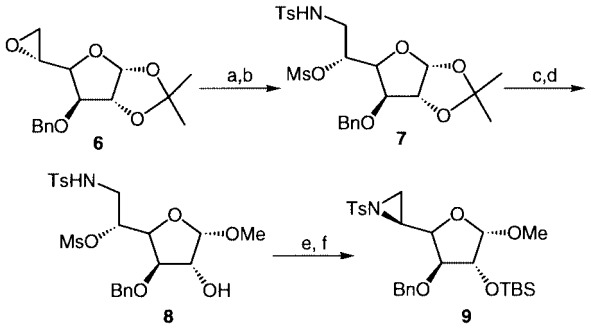
Our synthesis began with epoxide **6**, available on multigram scale from inexpensive D-glucose in five steps (Scheme 2).[8] Upon treatment with *p*-toluenesulfonamide and Cs_2CO_3, epoxide **6** underwent smooth ring opening followed by mesylation to give **7**. Acidic hydrolysis of acetonide **7** afforded a 3:2 mixture of diastereomers at the anomeric position. Subsequent treatment with $SnCl_4$ furnished the desired α-isomer **8**.[9] Base-induced ring closure of mesylate **8** and subsequent protection as a TBS ether provided aziridine **9**.

The Grignard reagent **13**, precursor for the E-ring, was prepared from 3-methylcatechol (**10**) in six steps (Scheme 3). Selective protection of **10** by TsCl, bromination of the resulting phenol, and methylation gave bromide **11**. After the phenol protecting group of **11** was changed from the tosylate to a MOM ether, the bromide **12** was converted to Grignard reagent **13** by treatment with Mg in THF.

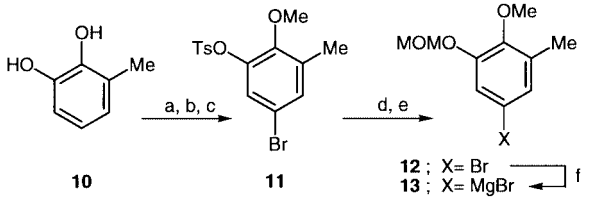
A copper-catalyzed ring opening of the aziridine **9** by freshly prepared **13** gave **14** (Scheme 4). Following protection of sulfonamide **14** with the Boc group and cleavage of the TBS ether, the second nitrogen atom was incorporated by conversion of the alcohol to a triflate and



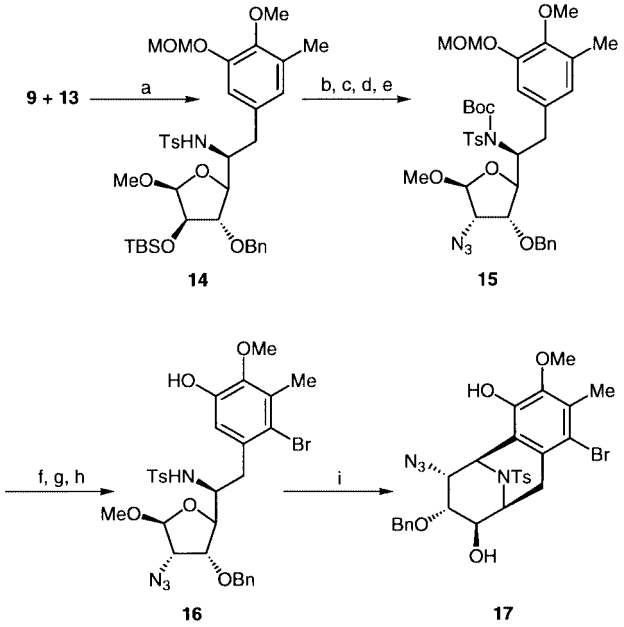
Scheme 1



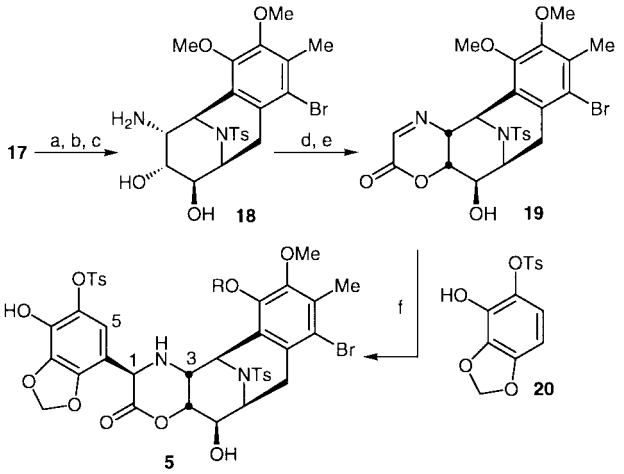
Scheme 2: (a) $TsNH_2$, Cs_2CO_3 , DMF, 80 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C (2 steps, 96%); (c) HCl, MeOH, reflux (99%); (d) $SnCl_4$, CH_2Cl_2, rt (88%); (e) NaOH, MeOH, rt (91%); (f) TBSCl, imidazole, DMF, rt (98%).



Scheme 3: (a) TsCl, TEA, CH_2Cl_2, 0 °C (83%); (b) Br_2, AcOH, CH_2Cl_2, rt (97%); (c) MeI, K_2CO_3, acetone, reflux (96%); (d) NaOH, EtOH-H_2O, reflux (97%); (e) MOMCl, iPr_2NEt, CH_2Cl_2, rt (97%); (f) Mg, THF, rt.



Scheme 4: (a) CuI, THF, 0 °C to rt (91% from **9**); (b) $(Boc)_2O$, DMAP, CH_3CN, rt (96%); (c) TBAF, THF, rt (98%); (d) Tf_2O, Py, CH_2Cl_2, 0 °C; (e) LiN_3, DMF, 80 °C (2 steps, 90%); (f) TMSBr, CH_2Cl_2, rt; (g) TFA, CH_2Cl_2, rt (2 steps, 97%); (h) $PyHBr_3$, CH_2Cl_2, rt (89%); (i) TFA, H_2O, 70 °C (88%).



Scheme 5: (a) MeI, K_2CO_3, acetone, reflux (89%); (b) BCl_3, CH_2Cl_2, -78 °C to 0 °C (87%); (c) Rh/C, H_2, EtOAc, rt (82%); (d) $BrCH_2CO_2Ph$, MS 4A, propylene oxide, CH_3CN, 80°C (92%); (e) $Pb(OAc)_4$, benzene, 80 °C (80%); (f) TFA, CH_2Cl_2, 0°C (89%).

treatment with lithium azide, to yield **15**. This displacement did not proceed in the case of the β-anomer.[10] After sequential removal of the MOM ether and the BOC group, regioselective bromination of the phenol provided *p*-bromide **16**. This bromide prevented any formation of the unwanted tetrahydroisoquinoline isomer in the next step. The bicyclo [3.3.1] system was constructed by treating the methoxy acetal **16** with TFA-H_2O. The cyclization proceeded through an iminium-ion intermediate to afford **17** as a single isomer.[11]

Conversion of **17** into amino diol **18** was accomplished by a three-step sequence involving protection of the phenol as a methyl ether, deprotection of the benzyl ether, and hydrogenolysis of the azide group. The dehydrooxazinone ring was introduced into **18** by regioselective aminolactonization and subsequent $Pb(OAc)_4$ oxidation of the amine to provide acylimine **19**. A TFA-induced intermolecular addition of phenol **20**[12] to **19** provided **5**. The reaction occurred at the sterically less hindered convex face of the tetracyclic imine **19** with complete diastereoselectivity. The stereochemistry at C_1 of **5** was confirmed by 2D NOESY spectroscopy. The strong NOE observed between the C_3 and C_5 protons proves that the E-ring must occupy the β-face of the tetracyclic system. Therefore, **5** possesses the desired *R* configuration at C_1 (Scheme 5).

In summary, we have successfully synthesized the key intermediate **5** from D-glucose with complete stereoselectivty at four chiral centers.

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(12) We prepared phenol **20** from 3,4-(methylenedioxy)phenol in four steps: i) MOMCl, iPr_2NEt, CH_2Cl_2, (91%); ii) *n*-BuLi, $(MeO)_3B$, THF; H_2O_2, (92%); iii) TMSCl, NaI, CH_3CN, (86%); iv) TsCl, iPr_2NEt, CH_2Cl_2, (56%).

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